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Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors

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Abstract

***Objective*—To assess the risk of death associated with various patterns of alcohol consumption.**

***Design*—Prospective study of mortality in relation to alcohol drinking habits in 1978, with causes of death sought over the next 13 years (to 1991).**

***Subjects*—12 321 British male doctors born between 1900 and 1930 (mean 1916) who replied to a postal questionnaire in 1978. Those written to in 1978 were the survivors of a long running prospective study of the effects of smoking that had begun in 1951 and was still continuing.**

***Results*—Men were divided on the basis of their response to the 1978 questionnaire into two groups according to whether or not they had ever had any type of vascular disease, diabetes, or "life threatening disease" and into seven groups according to the amount of alcohol they drank. By 1991 almost a third had died. All statistical analyses of mortality were standardised for age, calendar year, and smoking habit. There was a U shaped relation between all cause mortality and the average amount of alcohol reportedly drunk; those who reported drinking 8-14 units of alcohol a week (corresponding to an average of one to two units a day) had the lowest risks. The causes of death were grouped into three main categories: "alcohol augmented" causes (6% of all deaths: cirrhosis, liver cancer, upper aerodigestive (mouth, oesophagus, larynx, and pharynx) cancer, alcoholism, poisoning, or injury), ischaemic heart disease (33% of all deaths), and other causes. The few deaths from alcohol augmented causes showed, at least among regular drinkers, a progressive trend, with the risk increasing with dose. In contrast, the many deaths from ischaemic heart disease showed no significant trend among regular drinkers, but there were significantly lower rates in regular drinkers than in non-drinkers. The aggregate of all other causes showed a U shaped dose-response relation similar to that for all cause mortality. Similar differences persisted irrespective of a history of previous disease, age (under 75 or 75 and older), and period of follow up (first five and last eight years). Some, but apparently not much, of the excess mortality in non-drinkers could be attributed to the inclusion among them of a small proportion of former drinkers.**

***Conclusion*—The consumption of alcohol appeared to reduce the risk of ischaemic heart disease, largely irrespective of amount. Among regular drinkers mortality from all causes combined increased progressively with amount drunk above 21 units a week. Among British men in middle or older age the consumption of an average of one or two units of alcohol a day is associated with significantly lower all cause mortality than is the consumption of no alcohol, or the consumption of substantial amounts. Above about three units (two American units) of alcohol a day, progressively greater levels of consumption are associated with progressively higher all cause mortality.**

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Introduction

It has long been recognised that alcohol can cause death acutely, from poisoning, accidents, or violence, and that long term use can increase the incidence of cirrhosis and of certain types of cancer. In recent years, however, evidence has emerged that the regular consumption of small to moderate amounts of alcohol can also reduce the risk of ischaemic heart disease.[1] We now need reasonably quantitative information about both the increases and the decreases in mortality that are produced by various patterns of alcohol consumption and about the ways in which these vary with sex, age, and the existence of other predisposing or protective factors.

Reliable quantitative evidence is, however, difficult to obtain. Information about usual drinking habits has to be obtained not from direct measurement but from answers provided by individual people about themselves or their close relatives and friends. Unless the amount usually drunk is close to zero it is intrinsically difficult to describe, and the description is peculiarly liable to bias. For many people, the consumption of alcohol has emotional and moral overtones, and

respondents may underestimate the amount drunk from feelings of guilt or, perhaps less often, exaggerate it out of bravado. Moreover, the amount that a person normally drinks may vary substantially from one period to another, affecting the relevance of answers at one time to subsequent mortality. Despite these difficulties, prospective studies of alcohol use and subsequent mortality can still yield useful results, at least among people in middle or old age with long established habits.

Information about use of alcohol and of tobacco was obtained in 1978 from a group of male British doctors born between 1900 and 1930. Their deaths during 1978-91 were then monitored and related to their replies in 1978. The chief purpose of writing to these doctors in 1978 was to ask them to volunteer for a study of the prophylactic value of aspirin against the development of ischaemic heart disease.[2] Alcohol use was not the central point of that study, the alcohol questions were not particularly emphasised, and in consequence the replies may have been subject to relatively little bias. The present results are of special interest in that they refer to a population that is older than in most other studies, with about half the deaths being of men in their 80s or late 70s. However, the findings may not apply quantitatively to young people or to women (in whom breast cancer is a major cause of death). Moreover, doctors differ in many ways from the general male population. Hence, although the quantitative evidence about chronic hazards may be of general relevance to other populations with high rates of ischaemic heart disease and low rates of cancers of the liver and the mouth, oesophagus, larynx, and pharynx (upper aerodigestive tract), the quantitative evidence about acute hazards may be of more limited relevance.

Subjects and methods

POPULATION STUDIED

In 1951, 34439 male British doctors replied to a questionnaire about their smoking habits that marked the start of a prospective study of smoking and mortality that has continued for 40 years,[3] with further questionnaires every few years about the smoking habits of the survivors. In 1978 a special questionnaire sought information about several other matters, including alcohol consumption. Doctors were excluded from the 1978 inquiry only if their addresses were not recorded in the 1977 *Medical Directory* as being in the United Kingdom, if they had previously been withdrawn from the study of the effects of smoking,[3] or if they had been born before 1 January 1900. Of 18408 questionnaires that were sent out, 13479 (73%) were returned (after, if needed, one reminder). Of these, 89 were from doctors written to in error who did not meet our entry criteria, 45 were from doctors who died before 1 November 1978 (when follow up for the present study of alcohol began), 734 lacked replies to crucial questions about past health, and a further 290 did not contain adequate answers to the questions about alcohol. The remaining 12321 provided the basic material for the present 13 year prospective study.

INITIAL, INTERIM, AND FINAL QUESTIONNAIRES: 1978, 1989, AND 1990-1

The 1978 questionnaire sought information about the doctors' current smoking and drinking habits and about their past health. Inquiry about drinking habits was limited to asking whether alcohol was taken "never or almost never," "less often than weekly," "in most weeks, but less often than daily," or "on most days." If the reply was at least in most weeks the respondents were further asked to say how much they drank in an average week in terms of glasses of beer, cider, lager, etc (counting one pint as two glasses and one glass as one unit); glasses of wine, sherry, port, etc (counting a bottle of wine as seven glasses; a bottle of sherry, port, etc, as 14 glasses; and one glass as one unit); and glasses of spirits or liqueurs (counting a double measure of spirits in a public house as one glass and a full size, 0·7 litre bottle of spirits or liqueurs as 14 glasses and one such glass as two units). In the hope of avoiding misleading reports, we invited those who did not say how much they drank to say that they drank "less often than weekly." This unfortunately annoyed some doctors who did drink less often than weekly and who wrote to say so, and this means that the data for occasional drinkers cannot be used for quantitative comparisons. Of the respondents who took alcohol "never, or almost never," 43 mentioned spontaneously on their 1978 form that they had previously drunk alcohol regularly, and these men were removed from the group of non-drinkers.

Inquiry about past health in 1978 concentrated on vascular disease, as the chief object of the 1978 questionnaire was to start a study of the value of aspirin in men who had not had overt vascular disease. The doctors were therefore specifically asked at the start of the study to say if they had ever had a myocardial infarction, any other heart disease, a transient ischaemic attack, any other form of cerebral vascular disease, hypertension requiring treatment, angina, intermittent claudication, or any other vascular disease or disorder of coagulation. For non-vascular diseases the questions about medical histories were less detailed, and the participants were asked only if they had had diabetes or any other life threatening or disabling disease. Altogether, 5402 reported that they had had some previous disease (vascular or other), and 6919 reported that they had not.

In April 1989 an interim inquiry was made of the 849 doctors who were not known to have died and who had said in 1978 that they took alcohol never or almost never. They were asked whether they had ever taken alcohol "at least as often as most weeks" in the past and, if so, when they started and stopped and, when they drank most, how much they used to drink. Eight were too ill to reply, 23 were not traced, and adequate replies were received from 797 (97% of the remainder). The replies to this interim questionnaire were used not to predict individual outcome but only to characterise the average previous habits of those who had described themselves in 1978 as non-drinkers and, in particular, to determine the proportion of former drinkers.

Further inquiry about changes in drinking and smoking habits, the use of aspirin, and the occurrence of any vascular condition was made of the surviving doctors in the course of the final follow up in the early 1990s. Replies were received from 8421 (96% of those believed to have been alive at the time). These too were used not to predict outcome but to characterise the average subsequent habits of the various categories of 1978 respondents.

FOLLOW UP OF MORTALITY: 1978-91

Participants have been followed from 1 November 1978 to 31 October 1991 in several overlapping ways.[3] On this evidence 3846 were known to have died before 1 November 1991, 8459 were believed to have been alive on that date (8220 who replied to our questionnaire after 1 November 1990 and were not found to have died before 1 November 1991 and 239 who had not replied to the questionnaire but were identified as alive after the follow up), and 16 (0·1% of the study population) were not traced and were included in the mortality analyses only until the last date that they were known to have been alive.

CAUSES OF DEATH

For nearly all deaths, including many of those that occurred abroad, information about the underlying cause was obtained from official death certificates. In a few cases, when no official information could be obtained, the cause was given in an obituary or described by a relative. In 78 the cause remained unknown, commonly because the death occurred in a country in which information about the medical cause of death was not publicly available. Causes were classified according to the *International Classification of Disease*, ninth revision (ICD-9).

STATISTICAL METHODS

Mortality was calculated separately according to the number of units of alcohol consumed a week reported in 1978: none, undefined, 1-7, 8-14, 15-21, 22-28, 29-42, or ≥43. (The undefined category included those who drank sometimes but less often than weekly, those who drank but preferred not to state the weekly amount, and those who were not drinking alcohol in 1978 but spontaneously mentioned that they had previously done so.) In some analyses the last six groups were reduced to three (1-14, 15-28, and ≥29 units).

In each alcohol category the observed number of deaths (O) was compared with the expected number (E). These expected numbers were estimated in the usual way by multiplying the numbers of man years observed in each single year of attained age (from 50 to 91) in each of the separate 13 years of observation (from 1 November 1978 to 31 October 1991) by the mortality observed for all men irrespective of drinking habit in the same age group and period and summing over all ages and periods. To standardise for smoking, the same procedure was followed after dividing each age and period category into six smoking categories: lifelong non-smokers; current smokers of only cigarettes smoking 1-14, 15-24, or 25 or more a day; other current smokers; and former smokers.[3] Analyses were carried out separately for men who reported some previous relevant disease and for men who did not.

The next step in the analysis, having calculated the ratio of the observed to the expected number of deaths in a particular category of reported alcohol consumption (O/E), was to multiply it by the overall death rate per 1000 years (R). This gave a useful approximation to the standardised rate. For the sole purpose of comparing different categories of alcohol intake, the standard deviation of this quantity was about $R\sqrt{O/E}$. In our study slightly better approximations involving "floating absolute risks" have been used,[4] and these are described in the appendix. (In principle these floating absolute risks are preferable, but in practice they gave answers that differed little from the results of the simpler approximations described above.)

TABLE I—*Smoking habits of 12321 doctors in relation to alcohol consumption (responses to 1978 questionnaire). Values are numbers (percentages) of doctors*

Alcohol consumption	Lifelong non-smoker	Former smoker	Current smokers: Smoking only cigarettes (No smoked a day) 1-14	15-24	≥25	Other smokers	Smoking habits unspecified or unclear	Total
Non-drinker*	502	428	42	39	36	126	29	1 202 (10)
Former drinker*	6	23	0	0	4	10	0	43 (0·3)
Less than weekly or preferred not to state	513	678	41	75	34	220	22	1 584 (13)
Units consumed a week:								
1-14	1158	2223	162	183	83	846	66	4 721 (38)
15-28	359	1398	110	136	97	671	23	2 794 (23)
29-42	102	571	48	77	59	286	9	1 152 (9)
≥43	55	388	27	60	79	211	5	825 (7)
Total	2695 (22)	5709 (46)	430 (3)	570 (5)	392 (3)	2370 (19)	155 (1)	12 321 (100)

*Questionnaire asked only about current alcohol use, but those who reported that they used alcohol "never, or hardly ever" were divided into former drinkers and non-drinkers depending on whether or not they spontaneously mentioned past alcohol use.

TABLE II—*Alcohol consumption of 8421* doctors who answered questionnaires in 1978 and 1990-1. Values are numbers (percentages) of doctors*

Alcohol consumption in 1978	Alcohol consumption in 1990-1: Non-drinker	Less than weekly or preferred not to state	Weekly but no amount stated	Units consumed a week: 1-14	15-28	29-42	≥43	Total
Non-drinker†	530	89	3	73	7	2	3	707 (8)
Former drinker†	15	1	0	4	1	1	0	22 (0·3)
Less than weekly or preferred not to state	229	419	16	349	30	9	8	1060 (13)
Units consumed a week:								
1-14	172	295	50	2292	541	82	12	3444 (41)
15-28	46	44	23	723	847	250	45	1978 (23)
29-42	21	16	4	104	261	250	76	732 (9)
≥43	14	10	7	31	120	154	142	478 (6)
Total	1027 (12)	874 (10)	103 (1)	3576 (42)	1807 (21)	748 (9)	286 (3)	8421 (100)

*8220 believed to be alive on 1 November 1991 and 201 who died before that date after completing the questionnaire.
†See table I for definitions.

Results

CORRELATION BETWEEN DRINKING AND SMOKING

Drinking and smoking habits tend to be correlated[5] so that any estimate of the medical effects of one needs to take account of the effects of the other. Of the doctors who replied in 1978 and who therefore formed the basis of our present study, most had been lifelong non-smokers or had given up smoking before 1978. Nevertheless, a close correlation between drinking and smoking habits persisted, as shown in table I, which shows the numbers of men smoking different amounts in 1978 according to the amount drunk. Among non-drinkers the proportion of lifelong non-smokers was six times higher than among men who drank more than 42 units of alcohol a week (502/1202 (42%) *v* 55/825 (7%)), while the proportion smoking 25 or more cigarettes a day was three times lower (36/1202 (3%) *v* 79/825 (10%)).

CONSISTENCY OF SELF REPORTED DRINKING HABITS

The responses of the 8421 men who described their habits in 1978 and in 1990-1 are compared in table II. For the 81% of respondents who described their habits adequately in both questionnaires (that is, excluding all those who said they drank less than weekly, who preferred not to state the amount in either questionnaire, or who replied that they drank regularly without stating the amount in response to the 1990-1 questionnaire) the average amount drunk in 1990-1 was similar to that in 1978: about 60% reported drinking about the same, 24% reported a decreased amount, and 16% reported an increased amount. For the 707 who reported themselves in 1978 to be non-drinkers, their replies in 1990-1 indicated that only 12% were drinking alcohol weekly and only 2% had taken to drinking 15 or more units a week.

Just as a minority of the 1978 "non-drinkers" reported subsequently that they were taking some alcohol, some reported in response to the special questionnaire in 1989 that they had drunk alcohol in the past, but the proportion was again small. Of the 797 non-drinkers in 1978 who replied adequately to the 1989 questionnaire about whether they had ever drunk alcohol more than occasionally, 635 (80%) had not, 80 (10%) had drunk 1-14 units a week at some time, and only 42 (5%) said they had ever drunk more than 42 units a week. As might have been expected, those who had never drunk regularly in the past were more likely to remain non-drinkers, and only 10% of those who said in 1989 that they had never drunk regularly reported drinking in most weeks in the 1990-1 questionnaire, against 22% of the other respondents.

MORTALITY BY DRINKING HABIT AND CAUSE

In many of the analyses the deaths were grouped

into three main categories, depending on the nature of the evidence from previous studies. The first, accounting for 6% of all deaths, comprised the "alcohol augmented" causes and included injury or poisoning (ICD-9 codes 800-999) and those diseases that have long been known to be increased by regular alcohol consumption: cancers of the oral cavity (other than the salivary glands), pharynx (other than the nasopharynx), oesophagus, liver, and larynx (ICD-9 codes 141, 143-6, 148-9, 150, 155, and 161); alcoholic psychosis and dependence (ICD-9 codes 291 and 303); and cirrhosis of the liver (ICD-9 code 571). The second category, accounting for 33% of all deaths, comprised ischaemic heart disease (ICD-9 codes 410-414), and the final category comprised all other known causes of death.

For each of these three main categories and for all causes (including unknown), table III shows the relevance of the self reported consumption of alcohol in 1978 to the death rates over the next 13 years. In each case the analysis was subdivided according to whether or not some previous disease had been present in 1978, and, as in subsequent tables, the analyses in each line were separately standardised for age, smoking, and calendar year. Differences in these factors do not, therefore, bias comparisons within one line of men with different drinking habits, but they do bias comparisons between different populations of men. (In table III, for example, those who already had some previous disease in 1978 tended to be older than those who did not and hence had substantially higher death rates.) In each line of table III (and of all subsequent tables) tests of statistical significance are provided for the comparison of non-drinkers with those drinking 1-14 units of alcohol a week and for the trend in risk with the amounts drunk by regular drinkers.

In table III the alcohol augmented causes of death showed a significantly positive trend with the amount of alcohol consumed a week. Ischaemic heart disease did not but showed a somewhat greater mortality among those with no alcohol use than among those drinking 1-14 units of alcohol weekly, and the proportional difference appeared to be at least as great among those without previous disease as among those with it. Finally, there was an unexpectedly strong U shaped relation between alcohol use and mortality from the aggregate of all other diseases. In general, previous disease appeared to be of little relevance to the shapes of the relations with alcohol use. In the light of this finding further analyses combined the data from the two separate analyses for men with and without previous disease so as to reduce the effects of random variation.

Table IV shows a finer subdivision of alcohol use and a finer subdivision of the other causes of death. It also excludes the men with undefined alcohol use in 1978, reducing the total number of deaths from 3846 to 3328. When the other causes of death were divided into seven specific causes or groups of causes there was evidence among those who drank regularly of a progressive increase in risk with amount drunk for cerebrovascular disease, residual vascular disease, and respiratory disease but not for cancers of the lung, large bowel, or other sites or for all residual causes. Opposite results were, however, obtained when the risk of mortality was compared between non-drinkers and light drinkers (1-14 units a week). For no cause was there a significant increase in light drinkers, but for several there was a significant reduction.

The top three lines of table IV show rates for the three main categories of death, and these, together with the results for all causes, are displayed graphically in the figure. For all causes combined (panel a), there was a U shaped curve with a minimum mortality

TABLE III—*Annual mortality (per 1000 men) by alcohol consumption and history of previous disease reported in 1978 questionnaire. Values are death rates (SE) standardised for age, smoking habit, and year of death unless stated otherwise*

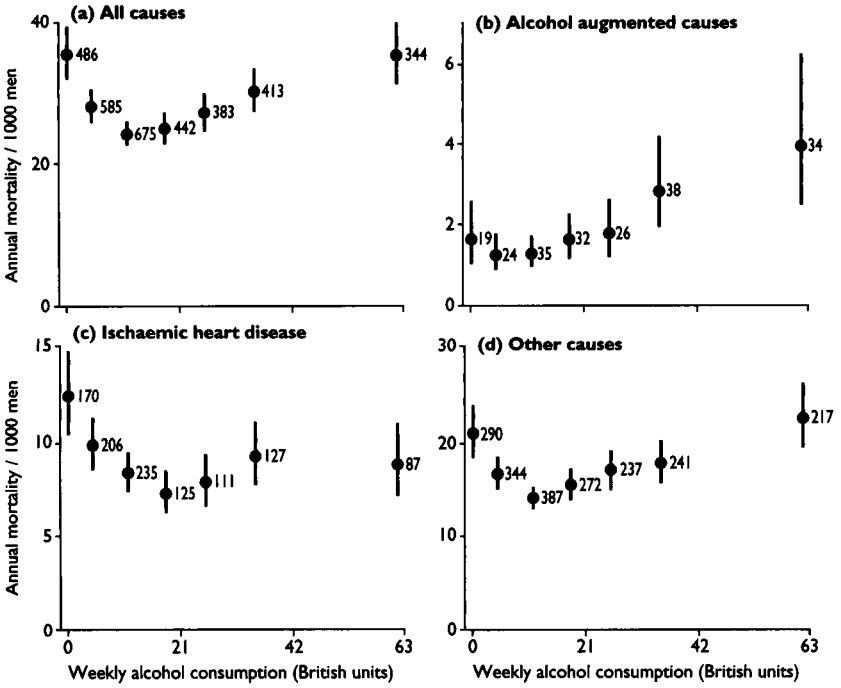
Cause of death and disease status in 1978	Total No of deaths	Units of alcohol consumed a week					χ^2_1 Test of alcohol effect	
		None	Undefined	1-14 (mean 8·3)	15-28 (mean 21·2)	≥29 (mean 46·0)	None *v* 1-4 units a week	Trend of 1-14 *v* 15-28 *v* ≥29 units a week
Alcohol augmented causes†:								
No previous disease	109	1·7 (0·6)	1·0 (0·3)	1·1 (0·2)	1·3 (0·3)	2·1 (0·5)	1·7	5·5*
Previous disease	126	1·7 (0·5)	2·7 (0·7)	1·6 (0·3)	2·1 (0·4)	4·9 (1·0)	0	16·2***
Ischaemic heart disease:								
No previous disease	378	7·6 (1·3)	5·5 (0·8)	4·5 (0·4)	3·9 (0·4)	4·0 (0·5)	5·7*	0·8
Previous disease	858	20·0 (2·1)	16·5 (1·6)	15·8 (0·9)	12·8 (0·9)	16·6 (1·4)	2·5	0·1
Other known causes:								
No previous disease	933	13·3 (1·5)	12·3 (1·1)	9·7 (0·5)	11·0 (0·8)	14·4 (1·2)	6·6**	15·3***
Previous disease	1364	29·6 (2·5)	25·8 (2·1)	23·0 (1·1)	23·3 (1·4)	28·1 (1·9)	4·4*	5·1*
All causes (including unknown):								
No previous disease	1450	22·7 (2·0)	18·9 (1·4)	15·6 (0·7)	16·6 (0·9)	20·8 (1·4)	13·7***	12·2***
Previous disease	2396	52·0 (3·3)	45·7 (2·7)	41·3 (1·4)	39·2 (1·7)	49·8 (2·5)	6·6**	6·2*

Values of χ^2 more extreme than 3·84, 6·64, and 10·83 correspond to P values of * < 0·05, ** < 0·01, and *** < 0·001 respectively.
†Injury, poisoning, liver disease, upper aerodigestive cancer, alcoholic psychosis.

TABLE IV—*Annual mortality (per 1000 men) by alcohol consumption reported in 1978 questionnaire (excluding those with undefined consumption). Values are death rates (SE) standardised for age, smoking, year of death, and history of previous disease unless stated otherwise*

Cause of death	Total No of deaths	Units of alcohol consumed a week							χ^2_1 Test of alcohol effect	
		None	1-7 (mean 4·6)	8-14 (mean 11·3)	15-21 (mean 18·0)	22-28 (mean 25·5)	29-42 (mean 35·0)	≥43 (mean 61·3)	None *v* 1-14 units a week	Trend of 1-14 *v* 15-28 *v* ≥29 units a week
Alcohol augmented causes†	208	1·6 (0·4)	1·3 (0·2)	1·3 (0·2)	1·6 (0·3)	1·8 (0·4)	2·9 (0·6)	4·0 (0·9)	0·7	20·9***
Ischaemic heart disease	1061	12·3 (1·2)	10·0 (0·8)	8·5 (0·6)	7·1 (0·6)	7·8 (0·7)	9·2 (0·9)	8·9 (1·0)	6·8**	0·5
Other known causes:	1988	19·8 (1·4)	16·4 (0·9)	14·0 (0·7)	15·4 (0·9)	16·9 (1·2)	17·9 (1·2)	23·3 (1·9)	10·4**	17·9***
Cerebrovascular disease	380	3·6 (0·5)	3·0 (0·4)	2·6 (0·3)	3·0 (0·4)	3·0 (0·5)	3·3 (0·5)	6·0 (1·1)	1·9	8·3**
Residual vascular disease	242	2·8 (0·5)	1·9 (0·3)	1·6 (0·2)	1·6 (0·3)	1·8 (0·4)	2·6 (0·5)	3·5 (0·8)	3·7	5·8*
Respiratory disease	234	2·0 (0·4)	1·5 (0·3)	1·7 (0·2)	1·3 (0·2)	3·0 (0·6)	2·5 (0·5)	3·5 (0·8)	0·6	9·9**
Lung cancer	163	1·1 (0·3)	1·8 (0·4)	1·5 (0·3)	1·0 (0·2)	1·0 (0·2)	1·4 (0·3)	2·3 (0·6)	0·9	0
Cancer of large bowel	127	0·9 (0·3)	1·3 (0·3)	0·7 (0·1)	1·7 (0·4)	1·5 (0·4)	0·7 (0·2)	1·8 (0·6)	0	0·5
Other cancers	508	5·7 (0·8)	4·2 (0·5)	3·6 (0·3)	4·5 (0·5)	4·2 (0·6)	4·9 (0·7)	3·7 (0·6)	5·5*	0·9
Residual known causes	334	3·9 (0·7)	2·9 (0·4)	2·4 (0·3)	2·6 (0·4)	2·7 (0·5)	3·0 (0·5)	3·2 (0·7)	2·9	0·9
All causes (including unknown)	3328	34·4 (1·8)	28·1 (1·2)	24·5 (0·9)	24·7 (1·1)	26·9 (1·4)	30·4 (1·6)	36·2 (2·3)	17·9***	16·7***

Values of χ^2 more extreme than 3·84, 6·64, and 10·83 correspond to P values of * < 0·05, ** < 0·01, and *** < 0·001 respectively.
†Injury, poisoning, liver disease, upper aerodigestive cancer, alcoholic psychosis.



Annual mortality (per 1000 men) from (a) all causes (including unknown), (b) alcohol augmented causes (cancers of the liver, larynx, oesophagus, mouth, etc; cirrhosis; alcoholism; or external causes), (c) ischaemic heart disease, and (d) other known causes by alcohol consumption reported in 1978. Points and bars are floating absolute risk and 95% confidence interval standardised for exact age, smoking habit, and history of previous disease[4] and values are numbers of deaths

around 8-14 units of alcohol a week. The mortality appeared somewhat greater (P=0·08) at 22-28 units a week, and there was a highly significant increase above the minimum for men drinking more than 28 units a week. For the alcohol augmented causes (panel b), the numbers of deaths were far smaller, but among those who drank alcohol regularly there was a progressive increase in risk from the lowest levels (1-7 and 8-14 units a week). For ischaemic heart disease (panel c) there was no significant trend in either direction among those using alcohol regularly, but there was some suggestion of a U shaped curve with the lowest mortality at 15-21 units a week. For all other known causes combined (panel d) those drinking 8-14 units a week had the lowest hazards, with a progressive increase in risk at progressively higher weekly consumption.

These differences in mortality, both between regular drinkers drinking different amounts and between non-drinkers and light drinkers, were not limited to one age group or to any part of the period of follow up. Table V shows that the differences occurred both in those aged under 75 and in older men but were greater in the younger age group. Table VI shows that the differences were present both in the first five years of observation and in the last eight years and appeared, if anything, slightly more extreme in the later period.

Discussion

These observations on mortality in relation to self reported drinking habits a few years previously have to be interpreted with the knowledge that drinking habits might change over time and are difficult to assess reliably by questionnaire. So far as changes since 1978 were concerned, the information obtained was reasonably encouraging. Most of the surviving members of the cohort continued to drink much the same amount, so that the observed mortality could be related to the amount drunk in 1978 with some confidence. Changing habits and inaccuracies in the estimation of the amounts drunk will, however, have blurred the differences between groups. Even random errors would mean that the true differences in risk associated with the regular consumption of different amounts may well be greater than those observed,[6] and any systematic changes or errors could systematically change the shape of the dose-response relations.

MORTALITY IN REGULAR DRINKERS

The observation that the mortality from several of the causes studied increased with the amount drunk accords with much clinical and epidemiological evidence, notably that for the causes that we have categorised as alcohol augmented. The similar relations with cerebrovascular disease and other diseases of the circulatory system (other than ischaemic heart disease) accord with previous observations on haemorrhagic stroke and hypertension[7-9] and on cardiomyopathy or alcoholic heart muscle disease.[10] Alcohol can also affect the development of pneumonia,[11] which was given as the underlying cause of 43% of the respiratory system deaths and is likely to have been the terminal illness in many of the additional 42% that were attributed to chronic bronchitis or other such diagnoses. The present results strengthen the conclusion that high levels of consumption of alcohol increase the risk of these diseases.

NON-DRINKERS AND LIGHT DRINKERS

For most of the causes of death studied, the mortality was higher in non-drinkers than in light drinkers irrespective of whether individual subjects had reported previous ill health (table III). These differences cannot easily be attributed to bias or to chance, although they might by chance have appeared to be greater than they really were. Possible explanations are the inclusion among the non-drinkers of some heavy drinkers who did not wish to admit to their habit or who had given up alcohol, particularly if they had

TABLE V—*Annual mortality (per 1000 men) by alcohol consumption reported in 1978 questionnaire and age group. Values are death rates (SE) standardised for age, smoking, year of death, and previous history of disease unless stated otherwise*

Cause of death	Total No of deaths	Units of alcohol consumed a week						χ^2_1 Test of alcohol effect	
		None	1-7 (mean 4·6)	8-14 (mean 11·3)	15-21 (mean 18·0)	22-28 (mean 25·5)	29-42 (mean 35·0)	≥43 (mean 61·3)	None v 1-14 units a week	Trend of 1-14 v 15-28 v ≥29 units a week
Alcohol augmented causes:										
Age <75 years	140	1·8 (0·6)	1·0 (0·2)	1·0 (0·2)	1·3 (0·3)	1·7 (0·4)	2·1 (0·5)	3·9 (1·1)	2·8	17·8***
Age ≥75 years	68	1·8 (0·7)	2·8 (0·9)	2·5 (0·7)	2·8 (0·9)	2·1 (0·8)	7·3 (2·8)	5·0 (2·1)	0·4	3·6
Ischaemic heart disease:										
Age <75 years	567	8·6 (1·2)	6·6 (0·7)	5·8 (0·5)	4·6 (0·5)	5·0 (0·6)	6·5 (0·8)	6·2 (0·9)	4·5*	0·1
Age ≥75 years	494	28·0 (3·5)	23·6 (2·6)	20·0 (1·9)	17·6 (2·2)	19·6 (2·7)	20·4 (2·9)	20·2 (3·5)	2·5	0·5
Other known causes:										
Age <75 years	935	13·4 (1·5)	9·1 (0·7)	8·9 (0·6)	8·2 (0·7)	9·6 (0·9)	9·6 (0·9)	14·7 (1·6)	5·0*	5·8*
Age ≥75 years	1053	49·2 (4·2)	46·7 (3·6)	35·3 (2·3)	46·1 (4·1)	47·3 (4·6)	52·9 (5·2)	58·4 (7·0)	5·2*	12·8***
All causes (including unknown):										
Age <75 years	1684	24·0 (2·0)	17·0 (1·0)	16·2 (0·8)	14·7 (0·9)	16·6 (1·2)	18·4 (1·3)	24·3 (2·0)	10·1**	8·3**
Age ≥75 years	1644	80·5 (5·6)	73·9 (4·5)	59·0 (3·1)	66·7 (4·6)	69·9 (5·4)	80·2 (6·3)	84·5 (8·0)	7·9**	8·4**

Values of χ^2 more extreme than 3·84, 6·64, and 10·83 correspond to P values of * <0·05, ** <0·01, and *** <0·001 respectively.
†Injury, poisoning, liver disease, upper aerodigestive cancer, alcoholic psychosis.

TABLE VI—*Annual mortality (per 1000 men) by alcohol consumption reported in 1978 questionnaire and period of follow up. Values are death rates (SE) standardised for age, smoking habit, and history of previous disease unless stated otherwise*

Cause of death	Total No of deaths	Units of alcohol consumed a week							χ^2_1 Test of alcohol effect	
		None	1-7 (mean 4·6)	8-14 (mean 11·3)	15-21 (mean 18·0)	22-28 (mean 25·5)	29-42 (mean 35·0)	≥43 (mean 61·3)	None v 1-14 units a week	Trend of 1-14 v 15-28 v ≥29 units a week
Alcohol augmented causes†:										
Years 1-5 of follow up	76	0·9 (0·4)	1·6 (0·5)	1·5 (0·4)	1·1 (0·3)	1·6 (0·5)	1·5 (0·5)	3·2 (1·2)	1·0	1·1
Years 6-13 of follow up	132	2·2 (0·7)	1·2 (0·3)	1·3 (0·2)	1·9 (0·4)	1·9 (0·5)	4·4 (1·2)	4·7 (1·4)	4·0*	24·6***
Ischaemic heart disease:										
Years 1-5 of follow up	387	9·5 (1·4)	7·5 (0·9)	8·0 (0·9)	6·8 (0·9)	6·6 (1·0)	7·7 (1·2)	7·3 (1·3)	1·6	0·3
Years 6-13 of follow up	674	14·6 (1·7)	11·9 (1·1)	9·0 (0·7)	7·4 (0·8)	8·6 (1·0)	10·3 (1·2)	10·2 (1·5)	5·3*	0·2
Other known causes:										
Years 1-5 of follow up	608	13·9 (1·7)	12·4 (1·2)	11·0 (1·0)	10·7 (1·2)	9·7 (1·2)	11·6 (1·4)	18·7 (2·8)	0·6	1·9
Years 6-13 of follow up	1380	24·3 (2·0)	19·4 (1·3)	16·3 (0·9)	18·9 (1·4)	22·6 (1·9)	22·7 (1·9)	26·9 (2·6)	11·7***	17·3***
All causes (including unknown):										
Years 1-5 of follow up	1084	24·2 (2·2)	21·9 (1·7)	20·6 (1·3)	18·8 (1·6)	18·1 (1·7)	21·0 (1·9)	28·8 (3·1)	1·0	1·1
Years 6-13 of follow up	2244	42·2 (2·8)	32·7 (1·7)	27·5 (1·2)	29·1 (1·6)	33·6 (2·1)	37·6 (2·5)	41·7 (3·2)	20·4***	18·2***

Values of χ^2 more extreme than 3·84, 6·64, and 10·83 correspond to P values of * < 0·05, ** < 0·01, and *** < 0·001 respectively.
†Injury, poisoning, liver disease, upper aerodigestive cancer, alcoholic psychosis.

given up because of incipient disease; confounding between drinking habits and behaviour that was conducive to good health or to disease; and an effect of small amounts of alcohol in protecting against the development or fatality of disease.

In case some doctors had preferred not to say what their real drinking habits were we had suggested that they might like to reply that they drank occasionally (less than weekly), thus, we hoped, avoiding the classification of some heavy drinkers with non-drinkers. The non-drinkers certainly included some former drinkers, but the evidence of our 1989 inquiry suggested that only about 5% had ever been heavy drinkers (more than 42 units a week) and that nearly all of the non-drinkers in 1978 had always abstained. Indeed, some in replying added personal notes indicating that they had tried alcoholic drinks on various occasions and had found that they did not like them. Moreover, we were able to remove from the non-drinkers 43 former drinkers who had spontaneously reported that they had previously been regular users of alcohol, but their mortality proved to be only 17% higher than that of the non-drinkers—a non-significant difference. It seems unlikely, therefore, that the inclusion of a few more former drinkers among non-drinkers could have increased the mortality by more than a few per cent, except, perhaps, in the category of alcohol augmented disease (in which there were in our non-drinkers five deaths from cancers of the upper aerodigestive tract, three from cancer of the liver, and two from cirrhosis of the liver).

Some doctors might have specifically given up alcohol because of symptoms of incipient disease without declaring that they had developed a "life threatening or disabling disease or condition." No such explanation could, however, have accounted for the excess mortality for ischaemic heart disease in non-drinkers, as the participants in the study had been asked in detail whether they had ever suffered from any form of vascular disease or had been treated for diabetes. All who replied "yes, definitely" or "not sure" were classed as having had previous disease, and the negative trend in mortality from non-drinkers to light drinkers was, in proportionate terms, somewhat weaker in those who reported previous disease than in those who did not (table III). Neither could this explanation have accounted for much of the excess mortality from other conditions in non-drinkers because, had it done so, the excess would have been expected to disappear after a few years. This did not happen. On the contrary, the excess tended to become more extreme with the passage of time (that is, after the first five years' observations) rather than the reverse (table VI).

Confounding is difficult to exclude but is an unsatisfactory explanation unless a plausible factor can be suggested. Smoking could be one, but it was allowed for by standardisation. In so far as this was inadequate, the residual deficiency would be expected to reduce the risk in non-drinkers (who smoked relatively little) compared with light drinkers (who in the past had smoked more, table I). Dietary differences would also, if anything, be expected to reduce the risk in non-drinkers, as relatively more reported changing to a healthier diet (for example, by reducing saturated fats), and non-drinkers in other studies have been reported to have had a relatively healthy diet rather than the reverse.[12]

There remains the possibility that the consumption of small amounts of alcohol may protect against the development of certain diseases. In the case of ischaemic heart disease extensive reviews of the epidemiological and physiological evidence have supported the idea,[1 13] as have subsequent publications.[14-16] Case-control and cohort studies in which lifelong non-drinkers and former drinkers have been separated have eliminated the possibility that the relatively high mortality in non-drinkers could be explained by the inclusion among them of former heavy drinkers, and small amounts of ethanol have been shown to have some haematological effects that would be expected to reduce the risk of arterial thrombosis: notably an increased concentration of high density lipoproteins and of plasminogen activator inhibitor, a reduced tendency for platelets to aggregate, and a decreased concentration of fibrinogen.[17-20]

It therefore seems probable that some of the reduction in mortality in light drinkers compared with non-drinkers might have been an artefact due to the inclusion with non-drinkers of a few heavy drinkers who had stopped drinking before 1978 but that this artefact accounted for only a small part of the reduction. Part might have been due to chance, and part was probably due to the antithrombotic effect of alcohol on the risk of ischaemic heart disease. In addition low levels of alcohol consumption could have reduced the risk of cerebrovascular diseases and "residual" vascular diseases because the former include cerebral thrombosis and the latter include aortic aneurysm, arteriosclerosis, and myocardial degeneration, which may share some aetiological factors with ischaemic heart disease.[3]

EFFECT ON TOTAL MORTALITY

What impact the various protective and adverse effects of moderate alcohol consumption will have on total mortality is unclear. Ischaemic heart disease is such a major cause of death in late middle and early old age (31% of deaths in men aged 50-89 in England and Wales and 33% in our study population) that if mortality was really reduced by a third this would compensate for a substantial increase in risk from alcohol related causes. The evidence available before

1992 has been reviewed by Beaglehole and Jackson, who found that total mortality was consistently greater in middle aged men with heavy alcohol consumption than in those with light or moderate consumption but not consistently greater than in those who abstained.[21] They concluded, however, that it was premature to form conclusions about the overall impact of light and moderate drinking because there was too little evidence about the differential effects at different ages. For elderly men, they could cite only the results of one small study in Massachusetts, which showed a significant reduction in mortality with levels of consumption up to 34 g ethanol a day (corresponding to about 28 British units a week).[22] Before middle age, however, the situation might be very different as chronic diseases are of much less importance than accidents and violence as causes of death and, although the absolute mortality is low, there is little reason to expect any material protective effect of alcohol. Moreover, the relevance of alcohol use before middle age to mortality in middle or old age is not known.

When the effects of alcohol use in middle or old age are considered, the relation to mortality is not the only, or even in many cases the most important, issue because the social and antisocial effects of alcohol can be so large. Nevertheless, the relation to all cause mortality in middle age is still of substantial medical and public health interest, and the present evidence suggests that in this particular population the net effect of moderate alcohol use may be to reduce overall mortality, with the minimum total mortality in the two consumption groups with means of 11 and 18 units a week (spanning a range of about 1 to 3 units a day). In comparison with these groups doctors who reported drinking 29-42 units a week (average 35 units) had about 20% higher total mortality and those consuming more than 42 units a week (average 61 units) had about 40% higher mortality.

The existence of a U shaped relation between alcohol and total mortality means that, when the relevance of mortality to the upper limits that might be advised for usual alcohol consumption is considered, the appropriate comparison for people drinking somewhat more than the suggested limit is with those drinking somewhat less and not with abstainers. The "crossover level," above which the risk among drinkers starts to exceed that among abstainers, is not of any particular relevance to public health. What matters, at least in terms of mortality, is the level at which the risk starts to increase to an important extent with respect to dose. The findings in the present study must, however, be assessed in the light of all the evidence from all studies, especially since the numbers of deaths of non-drinkers and of those reporting consuming over 42 units a week, though larger than in many other studies, are both too small for statistical stability.

In most other studies a protective effect against ischaemic heart disease has also been found, although not always to quite as great an extent, and in two other large cohort studies (one British[16] and one American[23]) total mortality in previously healthy men began to increase from about the same level. In the American study mortality began to increase above two units a day, but units in the United States are 50% greater than in Britain and the two units in the American study[23] correspond to three in ours. It may be, therefore, that the turning point for males in middle or old age is around two to three units a day.

The upper limit for sensible drinking in the British Department of Health's current guidelines is 21 units a week for men,[24,25] and the present results provide no evidence for any upward revision (especially as the upper limit in such guidelines may in practice be followed only approximately, human nature being what it is). They do, however, indicate that such guidelines should not only stress the disadvantages in terms of total mortality of consistently exceeding the upper limit but also acknowledge the important health disadvantages, at least in middle or old age, of total abstinence.

Public health implications

- Small amounts of alcohol are associated with a lower risk of death from ischaemic heart disease, and from several other causes
- Above about 21 units (14 American units) of alcohol a week there was a progressive increase in many causes of death
- This 13 year study of 12 000 doctors showed that the lowest overall mortality occurred in men drinking about 8-14 glasses of beer, wine, etc, a week
- The men studied were aged between about 50 and 90 years, and the same conclusion might not apply to younger men or to women, in whom the mix of causes of death is different

All the organisations and most of the individuals whose support and assistance were acknowledged in the accompanying paper on mortality in relation to smoking also supported this work or helped in other ways. In addition, we are particularly grateful to the collaborating doctors who provided the extra personal information; D Lane for advice on respiratory diseases; E Greaves and V Evans for help in reviewing the 1978 questionnaires; and most of all I Sutherland, co-author of the smoking study, who helped greatly in this one by tracing doctors and maintaining records. Cathy Harwood prepared the manuscript.

Appendix: Floating absolute risks

Let there be (n+1) different alcohol categories from zero (the lowest) to n (the highest), and let R be the average death rate per 1000 person years when all of these are combined. Ignoring for the moment the lowest category, let d_i (i=1, ..., n) denote the difference between the observed and the expected number of deaths (O−E) in the i^{th} category of alcohol replies, and let c_{ij} (i=1, ..., n and j=1, ..., n) denote the inverse of the matrix of the variances and covariances of $d_1, \ldots, d_n$. For each particular value of i, define β_i to be the sum for all possible values of j (from j=1 to j=n) of the quantities $c_{ij} \times d_j$. This means that β_i is the "one step" estimate of the log of the ratio of the death rate in the i^{th} category of alcohol consumption to that in the lowest (the zero) category. It can be shown that the covariance of β_i with β_j, where i and j are different, is c_{ij}. For each particular value of i, let a_i denote the mean of the (n−1) of these covariances that involve β_i, and then $\bar{a}$ denotes the mean of $a_1, \ldots, a_n$. Now we extend the range of the subscripts to include zero (the lowest alcohol category), and define $\beta_0=0$. Define $s_0^2=\bar{a}$, and (for each particular positive value of i) define $s_i^2=\bar{a}+c_{ii}-2a_i$. Finally, we define β to be a weighted average of the quantities $\beta_0, \beta_1, \ldots, \beta_n$ with the weights inversely proportional to $s_0^2, s_1^2, \ldots, s_n^2$ respectively, and let $b_i=(\beta_i-\beta)$ ln R. Now, the log of the standardised death rate in the i^{th} group (i=0, 1, ..., n) is approximately b_i, with standard deviation s_i. The 95% confidence limits for b_i are $(b_i+1{\cdot}96\ s_i)$ and $(b_i-1{\cdot}96\ s_i)$, and exponentiation of these three quantities yields the previously described "floating absolute risks" and their confidence limits,[4] which are used throughout this paper.

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Is travel prophylaxis worth while? Economic appraisal of prophylactic measures against malaria, hepatitis A, and typhoid in travellers

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Abstract

***Objectives*—To estimate the costs and benefits of prophylaxis against travel acquired malaria, typhoid fever, and hepatitis A in United Kingdom residents during 1991.**

***Design*—Retrospective analysis of national epidemiological and economic data.**

***Main outcome measures*—Incidence of travel associated infections in susceptible United Kingdom residents per visit; costs of prophylaxis provision from historical data; benefits to the health sector, community, and individuals in terms of avoided morbidity and mortality based on hospital and community costs of disease.**

***Results*—The high incidence of imported malaria (0·70%) and the low costs of providing chemoprophylaxis resulted in a cost-benefit ratio of 0·19 for chloroquine and proguanil and 0·57 for a regimen containing mefloquine. Hepatitis A infection occurred in 0·05% of visits and the cost of prophylaxis invariably exceeded the benefits for immunoglobulin (cost-benefit ratio 5·8) and inactivated hepatitis A vaccine (cost-benefit ratio 15·8). Similarly, low incidence of typhoid (0·02%) and its high cost gave whole cell killed, polysaccharide Vi, and oral Ty 21a typhoid vaccines cost-benefit ratios of 18·1, 18·0, and 22·0 respectively.**

***Conclusions*—Fewer than one third of travellers receive vaccines but the total cost of providing typhoid and hepatitis A prophylaxis of £25·8m is significantly higher than the treatment costs to the NHS (£1·03m) of cases avoided by prophylaxis. Neither hepatitis A prophylaxis nor typhoid prophylaxis is cost effective, but costs of treating malaria greatly exceed costs of chemoprophylaxis, which is therefore highly cost effective.**

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Introduction

Of the 28 million British travellers in 1991, 12·6 million travelled to destinations outside North America and central Europe and 756 000[1] travelled to malarious regions. Because of a perceived risk of diseases in tropical destinations, many intending travellers seek information on recommended immunisations and malaria chemoprophylaxis. To meet the demand many groups provide information about chemoprophylaxis and eminent authorities advise a range of vaccines, presuming these measures to be cost effective. Public health policy has not challenged that belief. We used economic analysis to evaluate pretravel prophylaxis in travellers. We aimed at providing an estimate of costs and benefits of various prophylactic regimens against malaria, typhoid fever, and hepatitis A. We adopted the framework of cost-benefit analysis to determine whether the prophylaxis was worth while, and within this framework we examined cost effectiveness of alternative vaccines and prophylactic regimens that could be used as part of a preventive strategy.

Methods and sources of data

Health sector costs were derived from records of a sample of patients treated in a hospital for tropical diseases. Costs to the individual were based on estimated time off work, costed according to wages and adjusted for cost of employment, as reported by the Department of Employment for 1991. Prices used were unit costs recorded in the *British National Formulary* No 22 (1991) for existing vaccines and in the *British National Formulary* No 26 (1993) for new vaccines and drugs. Benefits were computed as avoided costs of illness.

INCIDENCE OF DISEASE IN TRAVELLERS

As country specific information on infectious disease was largely unknown, we estimated the incidences of hepatitis A, typhoid fever, and malaria in United Kingdom residents returned from disease endemic regions. The incidence of travel associated infections in journeys to endemic countries defined by the World Health Organisation[2] was expressed as a proportion