blood pressure among adult twins, would be of interest.

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Influence of sex, age, body mass index, and smoking on alcohol intake and mortality

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Abstract

Objective—To examine the association between self reported alcohol intake and subsequent mortality from all causes and if the effect of alcohol intake on the risk of death is modified by sex, age, body mass index, and smoking.

Design—Prospective population study with baseline assessment of alcohol and tobacco consumption and body mass index, and 10-12 years' follow up of mortality.

Setting—Copenhagen city heart study, Denmark.

Subjects—7234 women and 6051 men aged 30-79 years.

Main outcome measure—Number and time of deaths from 1976 to 1988.

Results—A total of 2229 people died, 1398 being men. A U shaped curve described the relation between alcohol intake and mortality. The lowest risk was observed at one to six alcoholic beverages a week (relative risk set at 1). Abstainers had a relative risk of 1.37 (95% confidence interval 1.20 to 1.56) whereas those drinking more than 70 beverages a week had a relative risk of 2.29 (1.75 to 3.00). Among the drinkers, the risk was significantly increased only among those drinking more than 42 beverages a week. Sex, age, body mass index, and smoking did not significantly modify the risk function. The risk among heavy drinkers was slightly reduced when smoking was controlled for. The risk function was similar in the first and second period of six years of observation.

Conclusion—Alcohol intake showed a U shaped

relation to mortality with the nadir at one to six beverages a week. The risk function was not modified by sex, age, body mass index, or smoking and remained stable over 12 years.

Introduction

The impact of alcohol intake on mortality has been described in several large prospective studies from different countries.¹⁻¹¹ Apart from two studies,^{4,6} they all showed that the curve describing the risk of death in relation to alcohol intake is U shaped. This may have new public health implications. Before making recommendations about alcohol intake, the stability of the risk function across sex, age, and other common and established health hazards should be evaluated. Alcohol intake as well as its effect on mortality may be related to sex and age.¹² Among the relevant health hazards are extreme body weight and smoking. Both body weight and smoking are correlated to alcohol intake.^{3,12-14} Thinness, obesity, and smoking are associated with increased mortality.^{15,16}

We assessed the relation between alcohol intake and risk of dying and took into account sex, age, body mass index, and smoking habits and estimated the impact on the population mortality.

Subjects and methods

POPULATION

The study population comprised a random, age stratified sample of 19 698 people out of 87 172 aged 20

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or more, living in a defined area of Copenhagen in 1976. In the period 1976-8 the Copenhagen city heart study examined 14 223 subjects (response rate of 72.2%); 6456 were men and 7668 women. A detailed description of the study procedure has been published previously.¹⁷

EXAMINATION PROCEDURE

The participants filled in a self administered questionnaire concerning various health related issues, including drinking and smoking habits. Weight in light clothes and height without shoes were measured, and from these the body mass index was calculated as weight (kg) divided by the height (m) squared.

Alcohol intake—Participants were asked in multiple choice format to describe their intake of alcoholic drinks. These were classed as beverages: one beverage containing 9-13 g alcohol and being equivalent to one bottled beer, one glass of wine, or one measure of spirits. The choices were hardly ever/never, monthly, weekly, or daily. Abstinence because of treatment with drugs (disulfiram, etc) was noted, and the subject was excluded from the study. If a daily alcohol intake was reported the average number of beverages a week was reported. The supplementary, non-daily alcohol intake was estimated. (U Becker *et al*, personal communication) and added to the daily intake. The subjects were then classified according to the total weekly intake of alcohol: <1 beverage a week; one to six beverages a week; seven to 13 beverages a week; 14-27 beverages a week; 28-41 beverages a week; 42-69 beverages a week; or 70 or more beverages a week.

Smoking habits—The subjects reported if they had never smoked or were former or current smokers and whether they inhaled. Former smokers were divided into groups according to the number of years since they gave up and current smokers according to the amount of tobacco in grams. For the analysis seven groups were defined: those who never smoked; smokers who gave up more than five years before; smokers who gave up within the past five years; smokers of 1-19 g a day and smokers of more than 20 g a day.

FOLLOW UP

The vital status of the population sample was followed until 1 January 1988 by using the unique person identification number in the National Central Person Register. The observation time for each participant was the period from the initial examination (1976-8) until 1 January 1988 or until death (n=2229), disappearance, or emigration (39) during the observation period.

STATISTICAL ANALYSIS

The purpose of the analysis was to estimate relative risks of death, to elucidate potential interaction (modification), and to eliminate confounding.

The data were analysed by means of multiple Poisson regression models.¹⁸ The mortality was assumed to be constant within each 10 year age interval. The model was also fitted under the less restrictive assumption of constant mortality within the 5 year age intervals, and no significant differences were found in the estimates of the relative risks. A person observed in more than one age group contributed with corresponding observation time in both groups.

The first series of models included age and sex and one of the risk factors. A second series of models included sex, age, alcohol intake, and either body mass index or smoking and interaction between them. A final model included all five factors. Further details of the model analysis are given in the appendix.

In one analysis observation stopped after six years (1982). Data were also analysed for the following six years by using baseline as if all covariates were

collected in 1982, except age, to which six years was added. The risk functions derived from these two periods were compared.

The aetiological number—that is, the number of deaths that could possibly be attributed to excess drinking (more than one to six beverages a week)—was estimated as the aetiological fraction, as described by Miettinen,¹⁹ multiplied by the total number of deaths in the alcohol intake group. An analogous measure—the preventive number¹⁹—was estimated for the group who did not drink alcohol as the number of deaths that could possibly have been prevented by drinking one to six beverages a week.

Results

Owing to very low mortality in the age group 20-29 years and very high mortality in the group 80 years or more the analysis was restricted to the ages 30-79 years. Within this age range the baseline information was complete for 13 285 participants, who were followed up for a total of 131 256 person years.

During the follow up period 831 women and 1398 men died (table I). The distribution of subjects by alcohol intake was different in the two sexes. Ten per cent of the men but only 0.6% of the women drank more than 41 beverages a week, whereas 10.3% of the men and 34.2% of the women were abstainers.

TABLE I—Distribution of alcohol intake and numbers (percentages) of deaths by sex and alcohol intake

Alcohol intake (beverages a week)*	Men		Women	
	No of subjects	No (%) of deaths	No of subjects	No (%) of deaths
<1	625	195 (31.2)	2472	394 (15.9)
1-6	1183	252 (21.3)	3079	283 (9.2)
7-13	1825	383 (21.0)	1019	96 (9.4)
14-27	1234	285 (23.1)	543	46 (8.5)
28-41	585	118 (20.2)	72	6 (8.3)
42-69	388	99 (25.5)	29	5 (17.2)
>69	211	66 (31.3)	20	1 (5.0)
Total	6051	1398 (23.1)	7234	831 (11.5)

*One beverage contains 9-13 g alcohol.

ALCOHOL INTAKE AND MORTALITY

The risk function of alcohol and mortality was U shaped (fig 1). There was no interaction between either sex or age and the alcohol-mortality risk function. As the lowest risk was observed at one to six beverages a week, the relative risk at this level of alcohol intake was set at 1. The teetotallers had a significantly increased relative risk (1.37; 95% confidence interval 1.20 to 1.56). With increasing alcohol intake the relative risk increased steadily but did not increase significantly until an intake of 42-69 beverages a week, and at this level the relative risk was 1.44 (1.14 to 1.82). Subjects who drank 70 or more beverages a week had a relative risk of 2.29 (1.75 to 3.00).

ALCOHOL INTAKE AND BODY MASS INDEX

When body mass index was introduced as a possible interaction variable in the model of sex, age, and alcohol intake no change was seen in the risk function of alcohol-mortality. Thus, body mass index neither interacted with nor confounded the effect of alcohol intake on mortality.

ALCOHOL INTAKE AND SMOKING

There was no interaction between alcohol intake and smoking on the risk of dying. On the other hand, smoking was a weak confounder of the relation between alcohol intake and mortality as the curves describing the risk functions were slightly lower at high alcohol intake when smoking was considered (fig 2).

FIG 1—Relative risk of mortality in relation to alcohol intake. Risk set at 1.00 at lowest mortality at one to six beverages a week. Vertical lines are 95% confidence intervals

FIG 2—Relative risk of mortality in relation to alcohol intake. Curves describing estimates of different models and without covariates included (see text for further explanation)

Inhalation was included as a separate, significant risk factor but did not interact with or confound the alcohol-mortality relation.

ALCOHOL INTAKE, SEX, AGE, BODY MASS INDEX, AND SMOKING

When we included all five variables in the model the estimates were similar to the four factor model that included sex, age, alcohol, and smoking (fig 2).

Figure 3 shows the combined effects of the different health hazards. The risk ranged from 1 for light drinkers (one to six beverages a week) who did not smoke and were lean (body mass index between 20-25) to more than 9 for heavy drinkers (more than 70 beverages per week) who smoked a lot (more than 20 g of tobacco a day) and were obese (body mass index more than 32.5).

FIG 3—Relative risks of mortality in relation to alcohol intake at specified levels of smoking and body mass index. Relative risk set at 1.00 for lean, non-smoker with alcohol intake of one to six beverages a week. Smoker—more than 20 g tobacco a day; obese—body mass index more than 32.5 kg/m²; lean—body mass index 20-25

OBSERVATION TIME

The analysis was repeated with the observation time divided into the first and the second periods of six years. There was a small but insignificantly increased risk of dying in the second six year period. The increase was the same in all alcohol intake groups.

AETIOLOGICAL AND PREVENTIVE FRACTIONS

Table II shows the effect on numbers of deaths of five other hypothetical distributions of alcohol consumption in the population. We assumed that the excess deaths are actually attributable to alcohol intake and that other covariates influencing mortality are equal in the different alcohol intake groups. If all had been abstainers the total number of deaths would have risen from the observed 2229 to 2676. The number of

deaths attributable to an alcohol intake of more than one to six beverages a week was found to be 117 of the total of 2229 deaths. The number of deaths attributable to abstaining rather than drinking one to six beverages a week was 159. If the entire population were drinking one to six beverages a week the number of deaths is seen to be reduced by 276 to 1953. The recommended level of alcohol intake would have only little effect on reducing mortality in the present population. Figure 4 shows that the distribution of estimated excess deaths was different between men and women. Thus 92.2% of the excess deaths among women related to alcohol were found in the group of teetotallers whereas only 32.9% of the excess deaths among men were found in that group.

FIG 4—Relative risk of mortality and excess number of deaths among men and women in relation to alcohol intake. Line shows relative risk of death from alcohol intake. Bars indicate number of deaths among men and women attributable respectively to drinking

Discussion

We found no significant modification by sex, age, body mass index, and smoking of the well known U shaped risk function for alcohol mortality. Smoking was found to be a weak confounder of the estimates of relative risk of death from alcohol intake, while body mass index did not confound the risk function.

EXPLANATION OF RISK FUNCTION

Many have questioned the validity of self reported alcohol intake, but until now one of the available methods to obtain the information (sales reports, collateral information, etc) has proved to be more valid.²⁰ We made no attempt to validate the subjects' reported histories. Trained staff went through the histories as reported in the questionnaire with the subject. Subjects had no reason to deny their alcohol intake, as may be the case, for example, in data collected for insurance purposes. Still, the alcohol intake may have been underreported. If the underreporting was equal at all levels the observed risk function would be moved to the left of the true risk function, which means that the present study would overestimate the risk of dying from given reported levels of alcohol intake in the groups with higher alcohol intake, while the nadir, also moving to the left, would be at a lower intake. If the underreporting was unequal and stated abstainers actually included

TABLE II—Distribution of deaths by sex and differences between deaths as observed in present study and under assumption of specified hypothetical alcohol intake

Distribution of alcohol intake	No of deaths			Difference*		
	Men	Women	Total	Men	Women	Total
As observed	1398	831	2229	0	0	0
All abstainers	11695	981	2676	-297	-150	-447
Excessive drinkers consuming one to six beverages a week	1290	822	2123	+108	+9	+117
Abstainers drinking one to six beverages a week	1451	937	2388	+53	+106	+159
All drinking one to six beverages a week	1237	716	1953	+161	+115	+276
As recommended†	1324	827	2151	+74	+4	+78

*Difference between number of deaths as observed and as estimated under hypothetical distribution of alcohol intake; + = prevented deaths; - = excess deaths.

†Recommendations: men <28 beverages a week, women <14 beverages a week. It is assumed that habits are reduced to 14-27 and seven to 13 beverages a week, respectively, for participants with alcohol intake exceeding the recommended limits.

drinkers or former drinkers, this would, as pointed out by Shaper,²¹ contribute to the explanation of the U shape. If this is the case, one would expect a higher proportion of people developing alcoholic cirrhosis among the so-called abstainers than among those drinking one to six beverages a week. In the present population there was no increased risk of alcoholic liver disease among women who did not drink and only a slightly increased risk for men (data submitted for publication). This suggests that underreporting was not common among teetotallers in the present population. A recent review by Marmot and Brunner agrees with this finding.²² The question has been examined further by Jackson *et al* who were able to separate former drinkers from abstainers and showed that with respect to coronary heart disease former drinkers are at a lower risk.²³ The distribution of women by different groups of alcohol intake (table I), with 34% non-drinkers and 43% light drinkers, indicates that the abstainers are not an atypical group.

Another explanation of the shape of the risk function would be higher prevalence of ill health among abstainers than among drinkers.²⁰ We repeated the survival analysis by using the first six and the second six years of observation time separately. We found that the relative risk of dying was 7% higher during the second six years of follow up and that this was the same in all alcohol intake groups. This strongly indicates that the higher mortality among abstainers was not due to a higher morbidity at baseline.

By means of registers the groups of non-responders were also followed.²⁴ This population was on average from a lower social class and older and had thus experienced a higher morbidity and mortality. We have no reason to believe though that the alcohol-mortality relation is different among responders and non-responders.

The variables of sex, age, smoking, and body mass index did not contribute to the explanation of the shape of the curve. Age was a confounder, but when stratifying on 10 year age groups and estimating the relative risks we found no interaction with alcohol intake on mortality. This was in contrast with the analysis from the Kaiser-Permanente experience, which found younger people to be at greater relative risk of dying from alcohol than older people.¹¹ The study reported this to be mainly because of deaths from violence and traffic accidents among young people, which is a less prominent problem in Denmark.

The possible relation between alcohol intake and body mass index¹³ and the effect of body mass index on mortality¹⁵ made it relevant to look for possible interaction between alcohol intake and body mass index. In the Kaiser-Permanente study,¹² body mass index was proposed as a confounder with respect to the effect of alcohol intake.² In our study, however, body mass index neither confounded nor modified the estimates of the alcohol-risk function.

In some studies, including ours, smoking has confounded the estimates of the effect of alcohol on mortality, while in others it has not.^{3,10} Like Kono *et al*²⁵ we found no interaction between smoking and alcohol intake in their effect on the risk of dying.

Many studies have described the distribution of causes of death according to alcohol intake. A consistent finding has been that death due to ischaemic heart disease is predominant among teetotallers whereas cancers and cirrhosis are the main causes of death among heavy drinkers.^{1,6,9-11} Previous studies suggest that the protective effect of a moderate intake of alcohol on cardiovascular disease may be due to the positive correlation between moderate intake and plasma concentrations of high density lipoprotein²⁶ and an inverse relation between intake and platelet aggregability.²⁷

Public health implications

- The association between alcohol intake and mortality is U shaped
- The study found that the nadir of the curve is at one to six drinks a week
- Total abstainers have a relative risk of mortality of 1.37, heavy drinkers a relative risk of 2.29
- Sex, age, body mass index, and smoking do not significantly modify the risk function
- Simple messages about benefits of total abstinence may not be appropriate

SHOULD WOMEN DRINK LESS THAN MEN?

Women seem to be more susceptible to alcohol intake than men with respect to development of liver disease.²⁸ This has been used as a basis for advising women to drink less than men. In the public health context it may be more appropriate to advise on the basis of general risk measures than on the basis of the small fraction of the population prone to develop cirrhosis. Our analysis revealed no interaction between sex and alcohol intake on the risk of dying from all causes. Thus, the relative risks of dying from alcohol intake were the same for men and women.

Our study indicates that mortality is unaffected by alcohol intake in a rather broad range from one to 41 beverages a week. Other investigators have chosen to report the relative risk as a function of few groups of alcohol intake.^{3,5,6,8,10} The estimates of relative risk from these studies describe a V shaped rather than a U shaped curve. The relative risk of death due to alcohol intake did not increase significantly until the intake reached 42-69 beverages a week, at which level the mortality equals that of teetotallers. When the risk function describes a steadily increasing curve the definition of a threshold of hazardous drinking is, of course, quite arbitrary.

To put the alcohol-mortality relation into a public health perspective we calculated the aetiological fraction of each alcohol intake group (fig 4). We found that among women who drink more than six beverages a week only nine deaths (0.1% of deaths among women) were related to alcohol intake. In contrast, the preventive fraction—the number of deaths related to abstaining among women—was 106. The aetiological and preventive fractions among men were more equally distributed. It should be kept in mind that the aetiological fraction comprises two components: the increased relative risk in one particular group of alcohol intake and the number of people in that group. Moreover, alcohol intake is probably greater among the non-participants, which would not affect the alcohol-mortality risk function but on the other hand may lead to underestimation of the aetiological fraction on a population level.

Furthermore, we have made five suppositions of different alcohol intake in the population, as shown in table II. It is important to note that these estimations are of hypothetical origin and rest on the assumption of equal distribution of covariates as age and observation time among alcohol intake groups.

CONCLUSION

Our study contributes to a more precise description of the U shaped relation between alcohol intake and the risk of death as four potential confounding and interacting variables were excluded. Furthermore, our findings suggest that simple messages about the benefits of total abstinence may not be appropriate.

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Appendix

Statistical analysis

The ages were grouped into A intervals $(\theta_0, u_1) \dots (u_{A-1}, u_A)$ and the intensity μ of dying was assumed to be constant $u_a, a = 1 \dots A$, over each of these age intervals. Besides age (a) the risk factors considered were sex (s), body mass index (b), alcohol intake (c), and smoking habits (h), the latter three by the value at the time of the initial examination.

Firstly, the mortality of people in one risk group was analysed, by assuming that they have the same age dependent mortality. If t_{0i} is the age at the first examination, t_i the age at the end of the observation, and t_{ai} the time observed in age group a, $a = 1 \dots A$ we get

$$t_i = t_{0i} + t_{1i} + \dots + t_{Ai}$$

for each person. If we let $d_{ai} = 1$ indicate that the person dies during the observation period in age group a and let

$$d_i = d_{1i} + \dots + d_{Ai}$$

then the d_i s will indicate whether the person died during the observation period.

The intensity of dying can be written

$$\mu(t) = \sum_a \mu_a I(t \in (u_{a-1}, u_a))$$

where I is the indicator function. The probability of surviving age t_i , given age t_{0i} at the first examination, can be calculated as

$$S(t_i) = \prod_a \exp(-t_{ai} \mu_a), i = 1, \dots, n$$

and the density is equal to

$$f(t_i) = \mu(t_i) S(t_i)$$

Letting d be the number of people with $d_i = 1$, we get the likelihood function²⁹

$$\begin{aligned} L(\mu) &= \prod_{i=1}^d f(t_i) \prod_{i>d} S(t_i) \\ &= \prod_a \mu_a^{d_a} \exp(-t_a \mu_a), \text{ with} \\ d_a &= \sum_i d_{ai} \text{ and } t_a = \sum_i t_{ai} \end{aligned}$$

This likelihood function is proportional to

$$\prod_a (t_a \mu_a)^{d_a} \exp(-t_a \mu_a)$$

which is (proportional to) the likelihood function for the Poisson distribution. Thus, data can be analysed in a model where $(d_a)_{a=1 \dots A}$ is independently Poisson distributed with parameter $t_a \mu_a$. Here t_a can be interpreted as an offset variable and μ_a as the intensity.²²

When we include the risk factors of sex and alcohol intake this results in a model with intensity μ_{asc} depending on the alcohol intake group (c) and sex.

In this model it is possible to test the multiplicative (or log-linear) model with intensity

$$\mu_{asc} = \mu_{as} \theta_c, c = 1 \dots 7$$

which implies that an increased alcohol intake has the same effect on all sex and age groups. The product model has the advantage of being easily described and having easily interpreted results. The effect of a given alcohol intake can be described by the relative risk, defined as the ratio between sex and age specific intensities. Comparing a high alcohol intake ($c=7$) with a low one ($c=2$) results in the relative risk of

$$\mu_{as7}/\mu_{as2} = \theta_7/\theta_2$$

Choosing $\theta_2=1$ gives a baseline mortality μ_{as} corresponding to a low alcohol intake of one to six beverages a week and relative risk compared with the group equal to the θ s.

Other factors can be included in the model. A model allowing body mass index (b) to interact with alcohol intake has the intensity

$$\mu_{ascb} = \mu_{as} \theta_{cb}, c = 1 \dots 7, b = 1 \dots 5$$

In this model it is possible to test if the interaction is significant. The model without the interaction has the intensity

$$\mu_{ascb} = \mu_{as} \theta_c \psi_b, c = 1 \dots 7, b = 1 \dots 5$$

In this model the relative risks for body mass index were the same in all age, sex, and alcohol groups (a,s,c), and the relative risks for alcohol intake were the same in all age, sex, and body mass index groups (a,s,b).

Data were analysed by means of GENSTAT 5, a general statistical program.³⁰

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ONE HUNDRED YEARS AGO

VIVISECTION IN A NUTSHELL.

At Prince's Hall this week Mr. Arthur Arnold put the case against vivisection in a nutshell. "If cruelty were allowable," he said, "because good results were certain to follow from it, society might sanction vivisection as applied to malefactors and children." These nutshell pronouncements on public questions usually take everything for granted which needs to be proved, and this is no exception. Cruelty is the infliction of unnecessary pain. Mr. Arnold assumes that such is inflicted, and then condemns it. If the infliction of pain alone were the accepted criterion, then Mr. Arnold could never eat a mutton chop, and his conscience would forbid the matutinal rasher, nor could he ever again drive behind a horse or a gelding, nor consent to any of the customary farmyard operations (performed without anaesthetics), not to speak of the slaughterhouse, the rabbit warren, and the field sports to which game of all kinds fall victims. (BMJ 1894;ii:1264.)