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Alcohol and mortality

Results from the EPOZ follow-up study

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Abstract. To investigate the association of alcohol intake with mortality from all causes, cardiovascular disease (CVD), cancer and other causes (e.g., accidents, violence, suicide), we performed an analysis of data obtained in a prospective follow-up study conducted in the Netherlands since 1977. Causes of death were defined for a cohort of 1,620 persons (760 men and 860 women) examined in 1977. During the 10-year follow-up period, 123 (7.6%) of the participants died. Frequency of alcohol consumption was obtained separately for wine, beer and liquor by means of a questionnaire. Although no significant association could be established between alcohol consumption and all-cause mortality, all-cause mortality tended to be lower in alcohol consumers compared to abstainers. The age- and sex-adjusted risk estimates of death from CVD were 0.29 (0.11–0.74), 0.46 (0.21–0.96) and 0.32 (0.13–0.77) for subjects with occasional, frequent and daily alcohol use, respectively, compared with those who did not drink at baseline. The mortality risks of never-drinkers and ex-drinkers were similar. A J- or U-shaped relation between alcohol consumption and CVD mortality could not be confirmed in our data but the available information on the amount of alcohol consumed was limited. No significant influence on the risk estimates of death from cancer or other causes was found. However, mortality tended to be higher for those who consumed more alcohol. The protective effect of alcohol intake on CVD mortality found in our data persisted after excluding subjects with cardiovascular or other major diseases at baseline from the analysis.

Key words: Alcohol, Cancer, Cardiovascular disease, Mortality

Introduction

As early as the 1920's it was suggested that frequent alcohol use may lower the risk of mortality [1]. However, recent studies have yielded unequivocal results. Some observed an inverse association between consumption of alcohol and cardiac mortality, the potentially beneficial effect of alcohol being reported as essentially due to consumption of wine [2, 3]. Others found no such effect [4], or suggested a U- or J-shaped curve resulting from a significantly increased mortality risk in the non-drinkers and the heavier drinkers [5–11]. It has been argued by several authors that the finding of a protective effect of alcohol use is biased due to pre-existing disease, which causes individuals with a high risk of mortality to stop alcohol drinking or to decrease the amount of alcohol consumed [12].

We studied the relationship between alcohol consumption and risk of death in a 10-year prospective follow-up study in the Netherlands. The aim was to study the risk of all-cause mortality and mortality from cardiovascular disease (CVD), cancer, and other causes (notably accidents, violence) associated with total alcohol consumption and the use of wine, beer and liquor.

Materials and methods

Study population and measurements. From 1975 to 1978 a population survey was undertaken in the Dutch town of Zoetermeer to assess the prevalence and determinants of several chronic diseases [13]. Zoetermeer is a suburb of the metropolitan area of The Hague, with a population of 60,000 at the time of the survey. All inhabitants of two rural and two urban districts of Zoetermeer, who were aged five years or more were invited for a medical examination. Of the 13,462 eligible subjects, only those above twenty years of age were included in the present analysis. The response in this age group was 75.6% (n = 6,547).

At baseline, measurements of blood pressure,

pulse rate, body mass index and total serum cholesterol were performed. A self-administered questionnaire was completed by each respondent for assessment of risk indicator status and was cross-checked by a research assistant or physician. Details of this initial study were published previously [13]. Alcohol consumption measurements were included in the study in 1977 and, therefore, are available for only one fourth (1,620 subjects) of the total cohort. Wine, beer and liquor were referred to in the questionnaire as separate items. Information on the frequency of alcohol consumption was obtained in closed-ended questions for each beverage separately. Alcohol intake was evaluated in the analysis by describing five categories as follows: 1) non-drinkers: those who did not drink wine, beer or liquor; 2) occasional drinkers: those who drank wine, beer or liquor less than one time a week (e.g., only at parties); 3) frequent drinkers: those who drank wine, beer or liquor one time a week or more; 4) daily drinkers: those who drank wine, beer or liquor every day; 5) ex-drinkers who used to drink wine, beer or liquor but were no longer drinking at the time of the baseline measurement. Similarly, five categories were defined for each of the three beverages (wine, beer, liquor).

From the municipal register of Zoetermeer, the vital status of the cohort could be determined [14]. Until May 1, 1987, the censor date, 490 members of the total cohort (7.5%) were lost to follow-up due to migration; because the dates of migration were unknown they were excluded from the analysis. During the ten-year follow-up 576 participants from the total cohort of 6,057 died (9.5%), 306 men (10.8%) and 270 women (8.4%). Causes of death were defined according to the International Classification of Diseases, ninth revision (ICD 9). Information on the cause of death was not available for 9 subjects (1.6%). Within the subpopulation for which alcohol intake was available, 43 cases (7.5%) died from cardiovascular disease (ICD 9, 390–459); 57 cases (9.9%) died from cancer (ICD 9, 140–239); 23 cases (4.0%) were coded to have died from accidents, violence, suicide and other traumatic causes (ICD 9, 800–999). Statistical analyses were based on those 123 cases of death.

Data analysis. In a preliminary analysis we studied the association of alcohol consumption with potential predictors of mortality. Multiple linear regression analysis was used to compare continuous variables. For categorical variables a logistic regression model was used. Those variables which showed a significant association with both the frequency of alcohol consumption and with mortality in our subpopulation were included as covariates in the Cox's proportional hazards model to assess the relationship between these possible confounding variables and survival. Regression coefficients were estimated by maximum likelihood procedures where the likelihood function was based on a conditional probability of failure [15]. Thus, the hazard rate for a certain category of alcohol consumption was adjusted for potential confounders by including these variables into the multivariate model. Relative risks were estimated as hazard ratios and are presented here with 95% confidence intervals.

Results

Baseline distributions of risk factors for mortality for the categories of alcohol consumption are presented in Table 1. At baseline, 26 (3.4%) of the men were non-drinkers and 25 (3.3%) were ex-drinkers. The proportion of occasional, frequent and daily drinkers were 134 (17.6%), 293 (38.5%), and 282 (37.1%), respectively. In women, 111 (12.9%) reported non-drinking and 47 (5.5%) ex-drinking; occasional, frequent and daily drinkers were 252 (29.3%), 300 (34.9%), and 150 (17.4%), respectively. The association of risk factors for mortality to alcohol intake was tested for men and women separately, while adjusting for differences in age. In men, alcohol intake was associated with cigarette smoking and the use of antihypertension drugs. In women, alcohol was associated with body mass index, systolic and diastolic blood pressure, pulse rate, cigarette smoking and the use of antihypertension drugs. In male ex-drinkers, a higher percentage had a history of stroke and of myocardial infarction compared to non-drinkers. Female ex-drinkers had a higher serum cholesterol, a higher percentage of cigarette smoking and history of chest pain and a lower systolic and diastolic blood pressure compared to non-drinkers.

Table 2 shows the association between alcohol consumption and all-cause mortality. Although mortality risk tended to be lower in those who used alcohol, in none of the analyses was a significant association found between alcohol use and all-cause mortality. Alcohol was significantly associated with a reduced cardiovascular mortality in the overall analysis (Table 3). A significant decrease in risk for CVD was observed for occasional and daily alcohol use, with the lowest mortality in the occasional drinkers for both men and women. There was no evidence of a dose-effect relationship. When adjusting for potential confounders, the association remained significant for occasional alcohol intake and relative risk estimates did not change materially. When stratifying by sex, occasional alcohol intake was significantly associated with a reduced risk of CVD in women only.

No association between alcohol intake and death from cancer and other causes was found (Tables 4 and 5). However, alcohol tended to increase the risk for cancer and death from other causes (predominantly accidents, violence and suicides). Particularly in women, risks of other causes of death increased

Table 1. Baseline characteristics, by alcohol consumption categories, EPOZ 1975–1978

Risk indicator	Non-drinkers	Ex-drinkers	Occasional drinkers	Frequent drinkers	Daily drinkers
Men					
Number of subjects	26	25	134	293	282
Body mass index (kg/m^2)	24.3	24.5	24.2	24.4	24.6
Systolic blood pressure (mmHg)	132.8	132.2	133.1	131.2	133.2
Diastolic blood pressure (mmHg)	79.9	80.1	80.6	80.6	80.9
Serum cholesterol (mmol l^{-1})	5.9	5.7	5.8	5.7	6.0
Pulse rate (beats/minute)	75.5	78.3	76.7	75.4	76.7
Cigarette smoking (%)	33.3	40.0	37.7	49.5	62.7[a]
Antihypertension drugs (%)	23.1	8.0	5.2[a]	6.5[a]	5.0[a]
Stroke (%)	0.0	4.0[a]	0.7	0.3	0.0
Myocardial infarction (%)	7.7	12.0[a]	0.7	2.4	3.2
Chest pain (%)	3.8	0.0	0.7	0.7	0.7
Heart failure (%)	8.0	16.7	0.8	2.1	2.5
Women					
Number of subjects	111	47	252	300	150
Body mass index (kg/m^2)	24.7	24.2	24.3	24.1	23.5[a]
Systolic blood pressure (mmHg)	131.4	125.8[a]	128.3	128.9	127.3[a]
Diastolic blood pressure (mmHg)	81.3	75.7[a]	78.0[a]	79.8	78.6[a]
Serum cholesterol (mmol l^{-1})	5.8	6.1[a]	5.8	5.8	5.8
Pulse rate (beats/minute)	79.6	79.0	79.5	77.5[a]	78.2
Cigarette smoking (%)	16.2	46.8[a]	35.2[a]	43.2[a]	54.4[a]
Antihypertension drugs (%)	24.3	31.9	15.9	11.7[a]	10.7[a]
Stroke (%)	1.8	2.1	0.0	0.0	0.7
Myocardial infarction (%)	2.7	6.4	0.4	0.0	0.7
Chest pain (%)	0.0	2.1[a]	0.0	0.0	0.7
Heart failure (%)	0.9	0.0	1.2	0.7	1.3

[a] Different from non-drinkers category at 5 per cent level.

with increasing alcohol intake, although none of the risk estimates reached conventional levels of statistical significance.

When analyzing wine, beer and liquor intake separately we found no differences between the mortality risk associated with the three types of beverages (data not shown). In an analysis in which ex-drinkers were analyzed separately, risks for those who quit alcohol use were similar to those who had never used alcohol. The relative risks and 95% confidence intervals for all-cause, CVD, cancer mortality and mortality from other causes for those who stopped compared to those who never used alcohol were 1.06 (0.48–2.32), 0.84 (0.28–2.46), 1.13 (0.27–4.72) and 1.82 (0.25–12.92), respectively.

Finally, we studied whether the inverse association between alcohol and mortality could be attributed to pre-existing morbidity, by analyzing only subjects free from cardiovascular and other major morbidity at baseline (n = 927). This analysis also showed a decrease in risk for CVD death for those who consumed alcohol, the relative risk estimates being 0.11 (0.01–0.76), 0.12 (0.02–0.70) and 0.08 (0.01–0.55) for occasional, frequent and daily drinkers, respectively. In addition, we excluded deaths in the first three years of follow-up as they may be ascribed to undiagnosed morbidity at baseline and may have led to decreased alcohol consumption. In this analysis the inverse association of alcohol to CVD mortality also remained statistically significant, the relative risk estimates for occasional and daily drinkers being 0.31 (0.10–0.89) and 0.34 (0.12–0.90), respectively.

Discussion

In this prospective follow-up study, a strong statistically significant inverse association was observed between baseline measurements of alcohol use and the subsequent risk of cardiovascular death. The association was independent of putative confounders such as body mass index, serum cholesterol, blood pressure, cigarette smoking, pulse rate, antihypertension drug use and persisted after exclusion of subjects with a history of stroke, myocardial infarction, chest pain, heart failure and diabetes at baseline. No significant association was found between alcohol intake and all-cause mortality. However, overall mortality tended to be consistently lower in men and women who consumed alcohol, while risks for cancer mortality and death from other causes tended to be

Table 2. Relative risks (RR) and 95% confidence intervals (95% CI) for all-cause mortality, by baseline alcohol consumption categories, EPOZ 1977–1987

Alcohol consumption category	Number of subjects	Number of deaths	Age-sex-adjusted RR (95% CI)	Fully adjusted[a] RR (95% CI)
All subjects				
Non-drinkers & ex-drinkers	209	27	1.00 (reference)	1.00 (reference)
Occasional drinkers	386	23	0.61 (0.35–1.05)	0.65 (0.36–1.17)
Frequent drinkers	593	42	0.84 (0.51–1.37)	0.93 (0.54–1.57)
Daily drinkers	432	31	0.78 (0.45–1.32)	0.81 (0.44–1.45)
Men				
Non-drinkers & ex-drinkers	51	9	1.00 (reference)	1.00 (reference)
Occasional drinkers	134	8	0.52 (0.20–1.33)	0.49 (0.18–1.33)
Frequent drinkers	293	28	0.88 (0.41–1.85)	0.84 (0.38–1.83)
Daily drinkers	282	23	0.75 (0.34–1.61)	0.59 (0.26–1.31)
Women				
Non-drinkers & ex-drinkers	158	18	1.00 (reference)	1.00 (reference)
Occasional drinkers	252	15	0.67 (0.33–1.33)	0.86 (0.40–1.81)
Frequent drinkers	300	14	0.73 (0.36–1.47)	0.81 (0.37–1.73)
Daily drinkers	150	8	0.82 (0.36–1.86)	1.28 (0.51–3.15)

[a] Adjusted for age, body mass index, serum cholesterol, systolic blood pressure, diastolic blood pressure, pulse rate, cigarette smoking, history of antihypertension drug use.

Table 3. Relative risks (RR) and 95% confidence intervals (95% CI) for CVD mortality, by baseline alcohol consumption categories, EPOZ 1977–1987

Alcohol consumption category	Number of subjects	Number of deaths	Age-sex-adjusted RR (95% CI)	Fully adjusted[a] RR (95% CI)
All subjects				
Non-drinkers & ex-drinkers	209	15	1.00 (reference)	1.00 (reference)
Occasional drinkers	386	6	0.29 (0.11–1.74)	0.23 (0.07–0.73)
Frequent drinkers	593	14	0.46 (0.21–0.96)	0.61 (0.26–1.38)
Daily drinkers	432	8	0.32 (0.13–0.77)	0.37 (0.13–1.00)
Men				
Non-drinkers & ex-drinkers	51	5	1.00 (reference)	1.00 (reference)
Occasional drinkers	134	3	0.36 (0.08–1.50)	0.29 (0.05–1.62)
Frequent drinkers	293	12	0.68 (0.24–1.92)	0.77 (0.23–2.49)
Daily drinkers	282	7	0.42 (0.13–1.30)	0.38 (0.10–1.38)
Women				
Non-drinkers & ex-drinkers	158	10	1.00 (reference)	1.00 (reference)
Occasional drinkers	252	3	0.23 (0.06–0.83)	0.19 (0.03–1.04)
Frequent drinkers	300	2	0.24 (0.05–1.08)	0.26 (0.05–1.32)
Daily drinkers	150	1	0.24 (0.03–1.87)	0.43 (0.04–3.86)

[a] Adjusted for age, body mass index, serum cholesterol, systolic blood pressure, diastolic blood pressure, pulse rate, cigarette smoking, history of antihypertension drug use.

higher. There was no evidence that the association between alcohol and death was limited to a specific type of alcoholic beverage (i.e., wine, beer, liquor).

A limitation of our study is the lack of detailed information on the absolute quantity of alcohol consumed. A more general issue is that alcohol consumption was measured only once at baseline. Although it is difficult to predict the effect of the absence of quantity of alcohol intake and of random fluctuations in alcohol use on the risk estimates, this type of misclassification has most likely led to an underestimation of the true associations between alcohol and mortality. Alcohol consumption might have been affected by disease status. However, when we excluded patients with a history of cardiovascular disease from the cohort, only minor changes in the risk estimates occurred. Further, our 10-year follow-up period may have been too short to show an increased risk for diseases with long induction periods including CVD and cancer. Therefore, the

Table 4. Relative risks (RR) and 95% confidence intervals (95% CI) for cancer mortality, by baseline alcohol consumption categories, EPOZ 1977–1987

Alcohol consumption category	Number of subjects	Number of deaths	Age-sex-adjusted RR (95% CI)	Fully adjusted[a] RR (95% CI)
All subjects				
Non-drinkers & ex-drinkers	209	8	1.00 (reference)	1.00 (reference)
Occasional drinkers	386	14	1.25 (0.52–2.96)	1.42 (0.57–3.49)
Frequent drinkers	593	21	1.47 (0.64–3.34)	1.57 (0.64–3.79)
Daily drinkers	432	14	1.27 (0.51–3.12)	1.31 (0.50–3.42)
Men				
Non-drinkers & ex-drinkers	51	2	1.00 (reference)	1.00 (reference)
Occasional drinkers	134	4	1.21 (0.21–6.65)	1.14 (0.20–6.39)
Frequent drinkers	293	12	1.80 (0.40–7.98)	1.44 (0.31–6.64)
Daily drinkers	282	10	1.50 (0.33–6.78)	1.01 (0.21–4.65)
Women				
Non-drinkers & ex-drinkers	158	6	1.00 (reference)	1.00 (reference)
Occasional drinkers	252	10	1.30 (0.47–3.53)	1.72 (0.58–5.05)
Frequent drinkers	300	9	1.24 (0.43–3.50)	1.39 (0.44–4.33)
Daily drinkers	150	4	1.07 (0.29–3.82)	1.52 (0.39–5.87)

[a] Adjusted for age, body mass index, serum cholesterol, systolic blood pressure, diastolic blood pressure, pulse rate, cigarette smoking, history of antihypertension drug use.

Table 5. Relative risks (RR) and 95% confidence intervals (95% CI) for other causes mortality, by baseline alcohol consumption categories, EPOZ 1977–1987

Alcohol consumption category	Number of subjects	Number of deaths	Age-sex-adjusted RR (95% CI)	Fully adjusted[a] RR (95% CI)
All subjects				
Non-drinkers & ex-drinkers	209	4	1.00 (reference)	1.00 (reference)
Occasional drinkers	386	3	0.52 (0.11–2.30)	0.76 (0.14–3.86)
Frequent drinkers	593	7	0.93 (0.26–3.26)	1.27 (0.29–5.52)
Daily drinkers	432	9	1.55 (0.45–5.32)	1.92 (0.45–8.18)
Men				
Non-drinkers & ex-drinkers	51	2	1.00 (reference)	1.00 (reference)
Occasional drinkers	134	1	0.26 (0.02–2.89)	0.34 (0.02–4.17)
Frequent drinkers	293	4	0.49 (0.08–2.69)	0.59 (0.08–3.87)
Daily drinkers	282	6	0.82 (0.16–4.09)	0.70 (0.11–4.24)
Women				
Non-drinkers & ex-drinkers	158	2	1.00 (reference)	1.00 (reference)
Occasional drinkers	252	2	0.81 (0.11–5.63)	2.20 (0.18–25.49)
Frequent drinkers	300	3	1.32 (0.21–8.01)	2.23 (0.19–25.34)
Daily drinkers	150	3	2.58 (0.42–15.65)	9.47 (0.84–105.52)

[a] Adjusted for age, body mass index, serum cholesterol, systolic blood pressure, diastolic blood pressure, pulse rate, cigarette smoking, history of antihypertension drug use.

possibility of a change in the direction of the association between alcohol consumption and all-cause mortality should be considered in further follow-up.

As to the issue of confounding of the relation between alcohol and mortality, a large number of prognostic characteristics deserve consideration. From a previous study of the entire cohort we knew that risk indicators independently related to all-cause mortality were age and diabetes mellitus in both sexes; pulse rate, smoking habits, antihypertension drug use and history of myocardial infarction most clearly in men; and body mass index and systolic blood pressure especially in women [14]. We adjusted for potential confounding factors by multivariate modelling and stratification by sex. HDL-cholesterol may be a potential confounder [16, 17]. In our data total serum cholesterol was unrelated to alcohol consumption and mortality, while measurements on HDL-cholesterol were not available at baseline. In a study of 212 men undergoing coronary

angiography, HDL-cholesterol levels were increased and total cholesterol levels were decreased with increasing alcohol consumption, suggesting that HDL-cholesterol may be an intermediate factor [18]. If this is true, a reasonable question is whether to adjust for the intermediate factor HDL-cholesterol in the analysis [19]. Some residual confounding in the risk estimates may still be present because of incomplete information on nutritional status, e.g., fish and garlic consumption [10, 20], and aspirin use [21, 22].

Our results support those of a number of other prospective studies suggesting a protective effect of alcohol on CVD mortality [23–27]. In some of these studies the pattern of the association between alcohol and CVD mortality appears to be curvilinear. There was no statistically significant evidence for a J- or U-shaped relationship in our data, but the fact that we do not know the exact grams of alcohol use per day does not allow us to make a firm statement on the shape of the curve. Frequent drinkers (alcohol once a week) may have consumed a large amount of alcohol at that time. Also, it may be argued that we have been looking almost exclusively at the left-hand side of a J- or U-shaped curve between alcohol and mortality [28]. Indeed, our findings on CVD mortality and alcohol consumption in women are compatible with a U-shaped relationship (see Table 3).

The mechanisms underlying a lower CVD risk associated with alcohol intake are hypothetical. It has been reported in earlier studies that a beneficial effect of alcohol on CVD is mediated through an increase of HDL-cholesterol levels, decrease of plasma fibrinogen concentration, increased fibrinolytic activity or decreased platelet aggregability [29]. Baseline data on these putative protective factors were not available in our study.

In conclusion, our results suggest that occasional to frequent alcohol use may be associated with decreased CVD risk, but has no statistically significant effect on overall mortality risk. Although alcohol may be associated with a significantly reduced risk of CVD mortality and, possibly, with a reduction in overall mortality (non-significant in the present study), our study shows a non-significant increased risk of cancer mortality and death from other causes as well. These possibly adverse effects associated with alcohol consumption have important implications from a clinical and public health point of view. We could not confirm earlier reports of a protective effect of alcohol intake on mortality being specific for one type of alcoholic beverage. Finally, there was no evidence for a difference in mortality between those who never used and those who quit using alcohol in our data.

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