

## Effects of alcohol consumption on mortality in patients with Type 2 diabetes mellitus

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### Abstract

*Aims/hypothesis.* Moderate alcohol intake has been associated with increased life expectancy due to reduced mortality from cardiovascular disease. We prospectively examined the effects of alcohol consumption on mortality in Type 2 diabetic patients in Switzerland.

*Methods.* A total of 287 patients with Type 2 diabetes mellitus (125 women, 162 men), recruited in Switzerland for the WHO Multinational Study of Vascular Disease in Diabetes, were included in this study. After a follow-up period of  $12.6 \pm 0.6$  years (means  $\pm$  SD), mortality from CHD and from all causes was assessed.

*Results.* During the follow-up, 70 deaths occurred (21 from CHD, 49 from other causes). Compared with non-drinkers, alcohol consumers who drank alcohol 1 to 15 g, 16 to 30 g and 30 g or more per day had the

following risk rates of death from CHD: 0.87 (95% CI: 0.25 to 2.51, NS), 0.00 (95% CI: 0.00 to 0.92,  $p$  less than 0.05) and 0.37 (95% CI: 0.01 to 2.42, NS), respectively. The corresponding risk rates of death from all causes were 1.27 (95% CI: 0.68 to 2.28, NS), 0.36 (95% CI: 0.09 to 0.99,  $p$  less than 0.05) and 1.66 (95% CI: 0.76 to 3.33, NS).

*Conclusions/interpretation.* In Swiss Type 2 diabetic patients moderate alcohol consumption of 16 to 30 g per day was associated with reduced mortality from CHD and from all causes. Alcohol intake above 30 g per day was associated with a tendency towards increased all-cause mortality. [Diabetologia (2003) 46:1581–1585]

**Keywords** Type 2 diabetes mellitus, alcohol consumption, mortality, cardiovascular disease.

Light to moderate alcohol consumption lowers the risk of CHD and has been associated with increased life expectancy due to reduced cardiovascular mortality [1, 2, 3, 4, 5]. The benefit of light to moderate alcohol intake could be highest in people at increased risk of CHD [4, 6]. Most published data demonstrating a cardio-protective effect of alcohol consumption were obtained in mixed populations, including primarily non-diabetic

subjects, and the proportion of diabetic patients included in these studies was not known. Recently the protective effect of light to moderate alcohol consumption on the risk of cardiovascular morbidity and mortality in patients with diabetes has been investigated [7, 8, 9, 10]. These studies confirmed the reduced mortality from CHD in female [8], male [9, 10] and mixed populations [7] of diabetic patients who drink alcohol, and are consistent with previous results in people without diabetes. All of these investigations were carried out in North America where drinking patterns [11] and type of alcoholic beverage are possibly different from those in other areas. Due to differences in the prevalence of cardiovascular risk factors and differences in ethnicity, a direct translation of results to other populations should be treated with caution.

The aim of our study was to find out whether results obtained in North American populations [7, 8, 9, 10]

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*Abbreviations:* HR, Hazard ratio; ICD-9, International Classification of Disease 9; RR, risk rate.

can be repeated in a well-defined, central European population representative for a whole country. We prospectively examined the relationship between self-reported alcohol consumption and death rates from CHD and from all causes in Type 2 diabetic patients who were members of the Swiss cohort of the WHO Multinational Study of Vascular Disease in Diabetes [12].

## Subjects and methods

**Study population.** The Swiss cohort [12] of the WHO Multinational Study of Vascular Disease in Diabetes [13, 14] included 533 patients selected randomly, according to the central protocol, from the diabetic patients of 231 local practitioners from all over the country [12]. The sample was representative of a large area including almost the entire country. Patients were stratified according to sex, age and duration of diabetes as follows: sex: 255 women, 278 men; age: 35 to 41 years (34.0% women, 32.4% men), 42 to 48 years (34.8% women, 35.3% men), 49 to 55 years (31.3% women, 32.4% men); duration: 1 to 6 years (34.0% women, 34.5% men), 7 to 13 years (30.1% women, 32.0% men), over 13 years (35.9% women, 33.5% men).

Diabetes mellitus was diagnosed on a clinical basis. According to the central protocol [12, 13], a diabetic patient was defined as someone diagnosed at least 1 year earlier and receiving specific treatment for diabetes from a physician. All patients needing insulin treatment within 1 year of diagnosis were defined as having Type 1 diabetes [13]. The remaining patients were classified as Type 2 diabetic patients. Based on these definitions, 308 patients were identified as having Type 2 diabetes. For 287 patients with Type 2 diabetes (93.2%) data on self-reported alcohol consumption were available. Only these patients were included in our analysis. Thirteen patients left Switzerland and were lost for the final follow-up, but on all of them intermediary data were available and the day they left the country was provided by Federal authorities and their physicians. At baseline a standardised clinical examination was done, including a detailed questionnaire with information on diabetes diagnosis, duration and treatment, as well as on symptoms of vascular disease. In addition, height, weight and blood pressure were recorded. Urine was tested for proteinuria using the sulphosalicylic acid method. Venous blood was drawn to measure cholesterol and creatinine. A resting 12-lead electrocardiogram was recorded. These baseline investigations were done be-

tween February 1974 and May 1977. Analyses were carried out in accordance with the Declaration of Helsinki and the Swiss laws regarding data safety. Data used were made fully anonymous before the analyses and only aggregate are reported.

**Alcohol consumption.** At baseline, the self-reported consumption of alcoholic beverages was assessed and daily alcohol intake was calculated on the basis of weekly consumption of beer, wine and spirits. Depending on daily alcohol intake, four groups of patients were formed: group 1 with 0 g per day (non-drinkers); group 2 with 1 to 15 g per day; group 3 with 16 to 30 g per day; and group 4 with more than 30 g per day.

**Follow-up and outcome definition.** Life or death status was ascertained as per January 1st, 1988 after  $12.6 \pm 0.6$  years (means  $\pm$  SD, 5543 person-years). During the follow-up 70 deaths were identified. In deceased patients the underlying cause of death was established from a copy of the death certificate, hospital records, post-mortem reports (where available) and from additional information given by the deceased persons' physicians. The underlying cause of death was coded according to the International Classification of Disease 9 (ICD-9) [15]. CHD included ICD codes 410 to 414.

**Statistical analysis.** Data analysis was done using Excel (Microsoft Corporation, Redmond, Wash., USA), Statview (SAS Institute, Cary, N.C., USA) and PEPI 4.0 (Computer Programs for Epidemiologists, Brixton Books, Llanidloes, UK). Data are given as means  $\pm$  SD, as risk rates (RR) with a 95% CI or as incidence rates (rate per 1000 patient-years). Statistical assessment of differences between two or more groups was done using the two-tailed Student's *t* test or ANOVA as appropriate. Proportions and incidence rates were compared using Fisher's exact test. Survival analysis was done using Kaplan-Meier statistics and the Cox proportional hazards model. The Cox proportional hazards model was used to estimate the relative risk (and the 95% CI) associated with alcohol consumption and adjust it for other risk factors. Patients who left Switzerland were censored on the day they left the country. A *p* value of less than 0.05 was considered statistically significant.

## Results

**Patient characteristics (Table 1).** Baseline characteristics of patients who died, patients who survived and

**Table 1.** Baseline characteristics of patients studied

Variable	All patients (n=287)	Patients who survived (n=217)	Patients who died (n=70)	<i>p</i> values for survivors vs non-survivors
Age (years)	46.2 $\pm$ 5.9	45.5 $\pm$ 6.0	48.4 $\pm$ 5.2	<i>p</i> <0.001
Sex (male/female)	162/125	116/101	46/24	<i>p</i> =0.096
Duration of diabetes (years)	9.2 $\pm$ 6.1	8.8 $\pm$ 5.9	10.4 $\pm$ 6.4	<i>p</i> =0.053
BMI (kg/m <sup>2</sup> )	27.6 $\pm$ 5.2	27.4 $\pm$ 5.3	28.0 $\pm$ 4.7	<i>p</i> =0.462
Systolic BP (mmHg)	141 $\pm$ 21	138 $\pm$ 19	149 $\pm$ 24	<i>p</i> <0.001
Diastolic BP (mmHg)	91 $\pm$ 12	91 $\pm$ 12	93 $\pm$ 12	<i>p</i> =0.076
Cholesterol (mmol/l)	6.5 $\pm$ 1.4	6.6 $\pm$ 1.4	6.8 $\pm$ 1.4	<i>p</i> =0.094
Triglycerides (mmol/l)	2.4 $\pm$ 2.7	2.1 $\pm$ 1.9	3.3 $\pm$ 4.3	<i>p</i> =0.001
Creatinine ( $\mu$ mol/l)	119 $\pm$ 36	107 $\pm$ 23	122 $\pm$ 60	<i>p</i> =0.003
Glucose (mmol/l)	10.1 $\pm$ 4.1	9.8 $\pm$ 4.1	10.8 $\pm$ 3.9	<i>p</i> =0.079
Nicotine (cigarettes/day)	4 $\pm$ 8	4 $\pm$ 8	5 $\pm$ 9	<i>p</i> =0.192
Alcohol (g per day)	12 $\pm$ 28	11 $\pm$ 22	16 $\pm$ 41	<i>p</i> =0.228

Data are proportions or means  $\pm$  SD

**Table 2.** Absolute and relative risk of death (unadjusted) from CHD and all causes for given alcohol intakes

	Total number of patients (n)	Deaths (n)	Death rate (per 1000 person-years)	Risk rate (RR)	(95% CI)	p value <sup>a</sup>
Death from CHD:						
Daily alcohol intake 0 g/d <sup>b</sup>	153	15	8.8	1		
Daily alcohol intake 1-15 g/d	61	5	7.7	0.87	(0.25–2.52)	1.000
Daily alcohol intake 16–30 g/d	42	0	0	0.00	(0.00–0.92)	0.037
Daily alcohol intake >30 g/d	31	1	3.3	0.37	(0.01–2.42)	0.555
Death from all causes:						
Daily alcohol intake 0 g/d	153	37	21.8	1		
Daily alcohol intake 1-15 g/d	61	18	27.6	1.27	(0.68–2.28)	0.491
Daily alcohol intake 16–30 g/d	42	4	7.7	0.36	(0.09–0.99)	0.047
Daily alcohol intake >30 g/d	31	11	36.2	1.66	(0.77–3.33)	0.204

<sup>a</sup> Fisher's exact test (PEPI 4.0)

<sup>b</sup> g/d: gram per day

**Table 3.** Results of the Cox proportional hazards regression model<sup>a</sup> for patients with an alcohol intake of 0 to 30 g per day

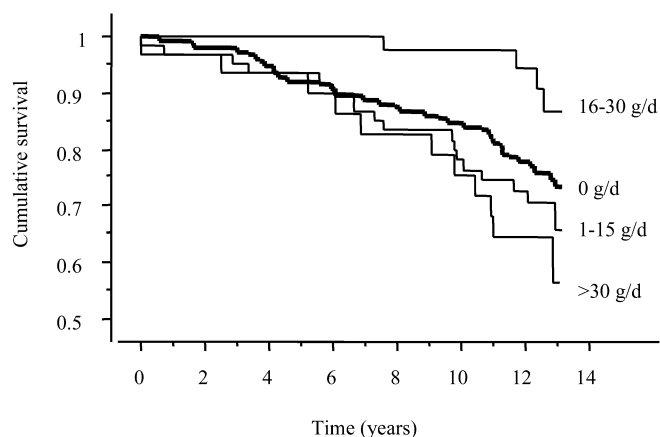
Death from all causes (patients drinking 0 to 30 g of alcohol per day)			
	HR <sup>b</sup>	(95% CI)	p value
All patients (256)	0.97	(0.94–1.01)	0.176
Women (123)	0.98	(0.91–1.06)	0.598
Men (133)	0.95	(0.91–0.99)	0.023

<sup>a</sup> Multivariate model adjusted for age, duration of diabetes, BMI, cholesterol, systolic blood pressure and nicotine consumption

<sup>b</sup> HR: Hazard ratio

all patients combined are shown in Table 1. There were significant differences between patients who died, patients who survived with respect to age ( $p<0.001$ ), systolic blood pressure ( $p<0.001$ ), triglycerides ( $p=0.001$ ) and creatinine ( $p=0.003$ ).  $P$  values for sex distribution ( $p=0.096$ ), duration of diabetes ( $p=0.053$ ), diastolic blood pressure ( $p=0.076$ ) and cholesterol ( $p=0.094$ ) and fasting plasma glucose ( $p=0.079$ ) did not quite reach statistical significance.

**Alcohol consumption and mortality (Tables 2 and 3, Fig. 1).** The self-reported consumption of alcoholic beverages and the calculated average daily alcohol intake was documented in all patients. A total of 153 patients (54 men, 99 women) consumed no alcoholic beverages (group 1, non-drinkers); 61 patients (46 men, 15 women) consumed 1 to 15 g per day (group 2); 42 patients (33 men, 9 women) consumed 16 to 30 g per day (group 3); and 31 patients (29 men, 2 women) consumed more than 30 g per day (group 4). During a follow-up of  $12.6\pm 0.6$  years (5543 person-years) 70 patients (24.4%) died. In 21 patients death from CHD was documented. In 42 patients consuming 16 to 30 g alcohol per day no deaths from CHD were registered (for comparison with the non-drinker group a  $p$  value of 0.037 was considered to be significant). Alcohol consumption above 16 g per day (group 3 and 4 combined) resulted in a significant reduction in mor-



**Fig. 1.** Kaplan-Meier cumulative function of survival (total mortality) by different degrees of daily alcohol consumption. The thick line denotes patients with an alcohol intake of 0 g per day. Other alcohol-intake groups are as indicated (1 to 15 g, 16 to 30 g and more than 30 g per day). Grams per day are denoted in the figure by g/d.

tality from CHD (RR=0.14; 95% CI: 0.02 to 1.04;  $p=0.024$ ). Moderate alcohol consumption (16 to 30 g per day) also reduced deaths from all causes (RR=0.36; 95% CI: 0.09 to 0.99;  $p=0.047$ ). Low ( $p=0.491$ ) and high ( $p=0.204$ ) alcohol intake did not significantly impact on mortality in this population. Subanalyses using the Cox proportional hazard model and adjusted

for age, duration of diabetes, BMI, cholesterol level, systolic blood pressure and smoking (Tables 2 and 3) indicated a significant reduction ( $p=0.023$ ) in relative risk of all-cause mortality in men with light to moderate alcohol consumption (0 to 30 g per day). No such effect of alcohol consumption on mortality was shown in women ( $p=0.598$ ). Similar analyses on the risk of death from CHD are not included, as they would be based primarily on only five events in people with light or moderate alcohol consumption (1 to 30 g per day).

## Discussion

Prospective epidemiological studies have shown that moderate alcohol consumption noticeably reduces the risk of cardiovascular morbidity and mortality [3, 4, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]. These studies primarily targeted healthy adults and showed that moderate alcohol consumption led to a 20 to 60% reduction of cardiovascular mortality. Recent data obtained in North American populations also suggest that moderate alcohol consumption has a beneficial effect on cardiovascular morbidity [27] and mortality [7, 8, 9, 10] in patients with Type 2 diabetes. However, the two recently published reports had a shorter follow-up than our study and included health professionals, who are in many respects specific study populations [8, 10]. One study had a comparable mixed population and similar follow-up to ours [7], but it investigated people with a mean age of 68 years, a large proportion (50%) of whom were being treated with insulin. In contrast, our study had younger patients (mean age 46 years), and fewer patients dependent on insulin. This could partly explain why CHD-related deaths occurred in only about 10% of our study population, compared to 20% in the study referred to [7]. Moreover, 53% of people in our study did not drink, whereas 10% were ranked as heavy drinkers (more than 30 g alcohol per day). In the US study [7] only 43% were non-drinkers and less than 4% were heavy drinkers. Despite these differences, the relative risk of death from CHD was reduced to a similar extent in diabetic patients in Europe and the United States [7] with moderate alcohol consumption, indicating that ethnicity, drinking pattern and type of alcoholic beverage have little effect on the protective effects of alcohol consumption. Similar findings on selected populations (US male physicians and US female nurses [8, 10]) and a recent study on drinking pattern and type of beverages [11] support this hypothesis.

When adjusted for other cardiovascular risk factors, the cardioprotective effect of moderate alcohol consumption remained in Type 2 diabetic men. In the Type 2 diabetic women of our cohort no significant cardioprotective effect could be shown. This contrasts to previous findings in a healthy population [4] and in diabetic women [8]. The most likely reason for this discrepancy is that the majority of women in our study

were non-drinkers (79.2%) or consumed a maximum of 15 g alcohol per day (12%). Only 8.8% of the diabetic women consumed 16 g or more alcohol per day. The limited number of patients included in the study and the moderate alcohol consumption by a small number of women did not allow us to detect an effect on mortality in women.

In contrast to previous reports, our study also investigated the relative risk of all-cause mortality in association with alcohol consumption, providing evidence that moderate alcohol consumption has a beneficial effect on CHD mortality, while also reducing all-cause mortality. Our data do not explain these findings. They do, however, indicate that moderate alcohol intake (16 to 30 g per day) was beneficial with regard to mortality from CHD and from all causes, whereas lower and higher alcohol consumption were associated with a tendency towards a higher mortality risk. This suggests that the relationship between alcohol consumption and mortality is depicted by a U-shaped curve, which is consistent with several epidemiological studies on the relationship between alcohol consumption and all-cause mortality [2, 5] or cardiovascular disease [28, 29]. The underlying mechanisms for this U-shaped curve are ill defined. However, most of the studies claim that the descending limb of the curve is attributable to reduced death from cardiovascular disease [28, 30]. High alcohol consumption facilitates the progression of neuropathy [31] and suppresses hepatic gluconeogenesis, thus increasing the risk of hypoglycaemia [32]. It is not clear whether these factors contribute to the greater mortality observed with high alcohol consumption or whether other confounding factors, e.g. life-style associated with high alcohol intake, contribute to the present and previous findings.

The power of our study lies in its well-defined cohort of European Type 2 diabetic patients (the Swiss cohort of a multinational WHO study), the long follow-up period and small dropout rate. We cannot exclude the possibility that our small sample size failed to allow detection of subtle differences in mortality rates, particularly in women. Moreover, it cannot be ruled out that the group with light to moderate alcohol intake contained especially healthy patients, with moderate alcohol consumption simply a marker of overall healthy behaviour, as suggested previously [10].

In summary, this study confirms that moderate alcohol consumption reduces CHD mortality as well as all-cause mortality in a relatively young, well-defined European diabetic cohort. Although the associations observed do not prove a causal relationship, our findings indicate that moderate intake of alcohol can be tolerated in the diet of patients with diabetes mellitus. However, in light of major clinical and public health problems associated with heavy drinking, recommendations on alcohol consumption must be made on an individual basis, after carefully assessing the risks and benefits of changes in drinking behaviour.

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