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Alcohol consumption and mortality in individuals with diabetes mellitus

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Abstract

Studies have suggested that moderate alcohol consumption is associated with a reduced risk of CVD and premature mortality in individuals with diabetes mellitus. However, history of alcohol consumption has hardly been taken into account. We investigated the association between current alcohol consumption and mortality in men and women with diabetes mellitus accounting for past alcohol consumption. Within the European Prospective Investigation into Cancer and Nutrition (EPIC), a cohort was defined of 4797 participants with a confirmed diagnosis of diabetes mellitus. Men and women were assigned to categories of baseline and past alcohol consumption. Hazard

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; HR, Hazard ratio.

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ratios (HR) and 95 % CI for total mortality were estimated with multivariable Cox regression models, using light alcohol consumption (>0–6 g/d) as the reference category. Compared with light alcohol consumption, no relationship was observed between consumption of 6 g/d or more and total mortality. HR for >6–12 g/d was 0·89 (95 % CI 0·61, 1·30) in men and 0·86 (95 % CI 0·46, 1·60) in women. Adjustment for past alcohol consumption did not change the estimates substantially. In individuals who at baseline reported abstaining from alcohol, mortality rates were increased relative to light consumers: HR was 1·52 (95 % CI 0·99, 2·35) in men and 1·81 (95 % CI 1·04, 3·17) in women. The present study in diabetic individuals showed no association between current alcohol consumption >6 g/d and mortality risk compared with light consumption. The increased mortality risk among non-consumers appeared to be affected by their past alcohol consumption rather than their current abstinence.

Key words: Diabetes mellitus: Alcohol consumption: History of alcohol consumption: Mortality

In 2010, the International Diabetes Federation estimated the global prevalence of diabetes mellitus at 6·6 % in adults (age range 20–79 years)[1]. Diabetes is now one of the most common non-communicable diseases in the world and a major cause of premature illness and death in most countries[1]. To prevent diabetic complications and premature mortality, patients are recommended to adopt a healthy lifestyle as part of their self-management strategy[2].

Within the general population, moderate alcohol consumption has been associated with a lower incidence of cardiovascular mortality[3] as well as overall mortality[4] compared with non-consumers. Indeed, if people choose to drink alcohol, a moderate consumption – limited to one glass per d for women and two glasses per d for men – has been recommended for the general public by expert groups such as the World Cancer Research Fund[5]. This upper limit is also recommended to individuals with diabetes mellitus[2]. Moderate alcohol consumption has been suggested to reduce the risk of CHD morbidity and mortality in individuals with diabetes mellitus, relative to abstinence from alcohol[6,7]. However, a well-known difficulty in such comparisons is the use of non-consumers as the reference group. Indeed, it might include both lifelong abstainers but also former drinkers. This group has been shown to be very heterogeneous and, as a consequence, appears to be less healthy than moderate consumers[8,9]. Thus, non-consumers may not be an ideal reference group in epidemiological investigations of alcohol and health outcomes.

As for individuals who have experienced CVD, individuals with diabetes may have modified their drinking habits after diagnosis[10]. However, alcohol consumption in the past has hardly been investigated in relation to mortality in individuals with diabetes[7,11]. It has been reported in the general population that the relationship between alcohol consumption and mortality was attenuated when taking alcohol consumption in the past into account[12,13]. We investigated the association between alcohol consumption and mortality in individuals with diabetes using light alcohol consumption as a reference group and taking history of alcohol consumption into account.

Subjects and methods

Design and subjects

Within the European Prospective Investigation into Cancer and Nutrition (EPIC)[14], a subcohort was defined of participants with a confirmed diagnosis of diabetes mellitus at baseline (1992–8), as has been described earlier[15,16]. Data were available from eleven out of twenty-three study centres in five out of ten European countries (Denmark, Germany, Italy, The Netherlands and Spain). Self-reports of diabetes at baseline were confirmed by a second source of information, i.e. contact to a medical specialist or practitioner, self-reported use of medication for diabetes treatment, repeated self-report of diagnosis during follow-up or by further inquiry of the participant, or record linkage to a diabetes registry. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by ethical review boards of the single centres and the International Agency for Research on Cancer in Lyon, France. All subjects provided written informed consent.

Of 5457 initial self-reports, 4407 diabetes diagnoses were confirmed. A further 670 prevalent diabetes cases without self-reported diabetes at baseline were identified as a result of verification efforts in other projects within the EPIC. Thus, the overall cohort comprised 5077 individuals with confirmed diabetes at study entry. After exclusion of participants without follow-up data on vital status (n 23), participants in the highest or lowest 1 % of the ratio of energy intake:estimated energy requirement (n 133), deceased participants with missing date of death (n 1), and participants with missing information on the following: baseline questionnaire data (n 1), information on age at diabetes diagnosis (n 86), and information on present alcohol consumption (n 13) and lifetime alcohol consumption (n 35), the analytical sample included 4797 participants.

Exposure assessment

Information on alcohol consumption at recruitment was obtained from a FFQ applied during the baseline examination. The FFQ enquired about consumption of alcoholic beverages (cider, beer, wine and spirits) during the previous 12 months[14]. At recruitment, an 8 % sample (n 36 994) of EPIC study participants in each centre was randomly selected for a 24 h dietary recall interview that generated detailed information on all foods and beverages consumed during the day before the interview[17]. This detailed information was used to estimate the average alcohol content (g/d) contained in 'standard' glasses in the EPIC countries, as they provide information on the type of glasses, glass volume and levels of filling. These average alcohol content values were

estimated at the country level, separately for men and women, and by weighting for weekday *v.* weekend day, and seasonality. In addition, the 24 h dietary recall data were used to compute country-specific average consumption of alcohol per 100 g of beverage. This was done to transform average volumes (ml) of alcohol into average consumption (g), according to the particular alcohol subtypes consumed in the different countries.

Weekly consumption of wine, beer/cider, fortified wine and liquor (spirits) was assessed retrospectively at the ages of 20, 30, 40 and 50 years in a lifestyle factor questionnaire[18,19]. To estimate alcohol consumption at different ages and at recruitment, an algorithm was used that combined the information available on the length of time alcohol was consumed and the amount of alcohol consumed at these different ages for a given period. Rather than estimating the average lifetime consumption as a simple mean of alcohol intake at ages 20, 30, 40 years, etc., which would not capture information on different time lengths between ages where information is available, we calculated time lengths of alcohol consumption, and these were used in the analyses. The average alcohol content per glass was set at 12 g and cut-points were used of >0–6 g/d (0–0·5 glass, light consumption), >6–12 g/d (0·5–1 glass), >12–24 g/d (1–2 glasses), and in women > 24 g/d (2 or more glasses) and in men >24–60 g/d (2–5 glasses) and >60 g/d (5 or more glasses). Prior alcohol consumption was defined as none, always moderate and sometimes heavy (consumption of 2·5 times the upper recommended limit at certain ages, i.e. >30 g/d in women and >60 g/d in men). In the EPIC, the amount of alcoholic beverages consumed in history by comparable age cohorts at certain ages was validated by comparison of self-reported data with the respective per capita measures from 1950 to 1995. Ethanol intake estimates were on average about 72% compared with the per capita consumption data; only small differences in reproducibility between the various techniques existed and ranking individuals according to intake was acceptable[20].

Assessment of other covariates

Data on other sociodemographic and lifestyle factors, including smoking status, educational attainment, physical activity and medical history, were collected using a questionnaire or personal interview at baseline. Weight, height and waist circumference were measured at the baseline examination, and subsequently BMI as an index of general adiposity and the waist:height ratio as an index of abdominal adiposity were calculated[16]. Duration since diabetes diagnosis was calculated by subtracting the self-reported year of diagnosis or the exact date of diagnosis (only if the diagnosis was medically verified) from the age at baseline examination. Information on insulin therapy was either self-reported or obtained during medical verification.

Outcome ascertainment

Causes and dates of deaths were ascertained using record linkages with local, regional or central cancer registries, boards of health, or death indices (Denmark, Italy, The Netherlands, Spain). Germany identified deceased participants with follow-up mailings and subsequent inquiries to municipality registries, regional health departments, physicians and hospitals. Mortality data were coded according to the Tenth Revision of the International Classification of Diseases, Injuries and Causes of Death (ICD-10). For the cause-specific analyses, deaths from circulatory diseases (ICD-10 I00-I99), cancer (ICD-10 C00-D48) and all other known causes were grouped.

Statistical analyses

All statistical analyses were performed with SAS 9.2 (SAS Institute). Sex-specific categories of baseline alcohol consumption were defined as outlined previously. Hazard ratios (HR) and 95% CI for total and cause-specific mortality were calculated separately for men and women using Cox proportional hazard regression models, where light alcohol consumption (>0–6 g/d) was used as the reference category. In addition, HR were calculated using non-consumers as a reference category, with and without inclusion of participants categorised as former consumers. Centre and age at recruitment in 1-year categories were entered as stratum variables. Age was used as the primary time variable, with entry time defined as the subject's age in years at recruitment and exit time defined as the subject's age in years at death or censoring (lost to follow-up or the end of the follow-up period, whichever occurred first).

HR were adjusted for diabetes duration (years), insulin use (yes or no), co-morbidities (cancer, heart disease or stroke), smoking status (never, former (quit ≤ 10, 11–20 or >20 years ago) or current (smoking duration ≤10, 11–20, 21–30, 31–40 or >41 years, <15, 15–24 or >25 cigarettes smoked daily)), educational attainment (no, primary school, technical or professional school, secondary school, university or above), and employment status (yes, no or missing). A second model was additionally adjusted for three categories of alcohol consumption in the past: lifetime non-consumer (yes or no); always moderate (yes or no); sometimes heavy consumption in the past (yes or no). The influence of physical activity and dietary intake (fruit, vegetable, meat and fibre intake) on the model was investigated, but inclusion of these variables did not substantially change the effect estimates and were left out. A P value for non-linearity of the associations was calculated with a Wald χ^2 test using the categories and adjustment models as outlined above using restricted cubic spline regression. A P value for trend was calculated using the median alcohol consumption within categories as the continuous variable. In addition, HR for an increment of 12 g/d (one glass) for consumers at baseline only was estimated. Finally, risk for specific causes of death was derived from competing risk models in which separate regression coefficients for different causes of death were compared using the Wald χ^2 test and 95% CI were derived from robust estimates of the covariance matrix[21,22].

Table 1. Characteristics of 2652 men and 2145 women with diabetes mellitus according to categories of baseline alcohol consumption (g/d) (Mean values and standard deviations; numbers and percentages; medians and interquartile ranges (IQR))

	Men												
	0		>0–6		>6–12		>12–24		>24–60		>60		*P* for trend
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Number of subjects	197	7	576	22	377	14	504	19	684	26	314	12	
Age (years)													0·01
Mean	56·3		57·7		57·3		57·4		56·5		56·5		
SD	6·1		5·8		6·0		5·5		5·9		6·1		
Waist:height ratio													0·01
Mean	0·58		0·58		0·58		0·57		0·58		0·60		
SD	0·07		0·07		0·06		0·06		0·07		0·06		
BMI (kg/m^2)													0·02
Mean	28·1		28·6		28·6		28·3		28·4		29·6		
SD	4·6		4·4		4·1		4·1		4·3		4·0		
Diabetes duration (years)													0·09
Median	4·1		4·6		4·6		4·2		4·1		3·8		
IQR	1·8–8·2		2·1–9·9		2·0–9·5		1·9–9·4		1·9–9·1		1·9–8·4		
Insulin therapy	42	21	100	17	68	12	109	22	134	20	46	15	0·60
Past alcohol consumption													
None	21	11	18	3	1	0	1	0	0	0	0	0	<0·0001
Always moderate	104	53	489	85	340	90	413	82	483	71	108	34	<0·0001
Sometimes heavy	72	37	69	12	36	10	90	18	201	29	206	66	<0·0001
Smoking status													
Never	40	20	152	26	107	28	135	27	144	21	56	18	0·01
Former	80	41	260	45	173	46	224	44	322	47	128	41	0·86
Current	77	39	161	28	96	25	145	29	216	32	129	41	0·04
Education level													
None	14	7	15	3	9	2	15	3	36	5	28	9	0·004
Primary school	94	48	215	37	126	33	177	35	242	35	121	39	0·13
Technical/professional school	40	20	164	28	101	27	126	25	163	24	81	26	0·59
Secondary school	18	9	56	10	30	8	45	9	64	9	19	6	0·29
Longer (including college degree)	30	15	124	22	111	29	139	28	177	26	62	20	0·15
Currently employed	71	36	271	47	209	55	267	53	363	53	139	44	0·04
Co-morbidities													
Heart disease*	14	7	62	11	36	10	44	9	41	6	20	6	0·12
Stroke*	10	5	32	6	13	3	16	3	19	3	13	4	0·10
Cancer*	5	3	15	3	14	7	12	2	16	2	4	1	0·70
	Women												
	0		>0–6		>6–12		>12–24		>24				
Number of subjects	459	21	1039	48	279	13	203	9	165	8			
Age (years)													0·01
Mean	58·4		57·8		56·5		57·1		57·6				
SD	6·2		6·5		7·1		6·2		6·1				
Waist:height ratio													<0·0001
Mean	0·60		0·58		0·56		0·55		0·54				
SD	0·08		0·08		0·08		0·08		0·08				
BMI (kg/m^2)													<0·0001
Mean	30·3		30·1		28·8		27·9		27·4				
SD	5·4		5·7		5·4		5·1		5·1				
Diabetes duration (years)													0·24
Median	5·2		4·4		4·5		4·5		4·6				
IQR	1·9–10·3		1·8–9·4		2·1–9·1		1·9–8·0		1·6–6·9				
Insulin therapy	98	21	228	22	62	22	46	23	41	25			0·38
Past alcohol consumption													
None	266	58	107	10	5	2	3	1	2	1			<0·0001
Always moderate	181	39	913	88	269	96	184	91	108	65			<0·0001
Sometimes heavy	12	3	19	2	5	2	16	8	55	33			<0·0001
Smoking status													
Never	299	65	615	59	157	56	102	50	72	44			<0·0001
Former	89	19	262	25	75	27	52	26	44	27			<0·04
Current	69	15	161	16	47	17	47	23	49	30			<0·0001
Educational level													
None	47	10	30	3	6	2	11	5	6	4			0·002
Primary school	255	56	482	46	122	44	68	34	53	32			<0·0001
Technical/professional school	82	18	315	30	101	36	70	34	51	31			<0·0001
Secondary school	47	10	130	13	25	9	24	12	27	16			0·20
Longer (including college degree)	22	5	80	8	25	9	30	15	27	16			<0·0001
Currently employed	74	16	371	36	120	43	89	44	78	47			<0·0001
Co-morbidities													
Heart disease*	25	5	37	4	4	1	6	3	10	6			0·97
Stroke*	14	3	38	4	8	3	5	2	7	4			0·35
Cancer*	15	3	58	6	10	4	8	4	6	4			0·61

* Denominator decreased due to missing values.

Table 2. Overall mortality across categories of baseline alcohol consumption (g/d) for 2652 men and 2145 women with diabetes mellitus (Hazard ratios (HR) and 95 % confidence intervals)

	Men												
	0		>0–6		>6–12		>12–24		>24–60		>60		
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	*P* for trend
Median	0		2·3		8·9		17·6		39·6		81·2		
Light consumers as the reference group													
Cases/person-years	36/1727		85/4899		44/3237		62/4462		86/6188		60/2860		
Model 1*	1·62	1·05, 2·49	1		0·89	0·61, 1·30	0·85	0·60, 1·20	0·94	0·68, 1·30	1·24	0·86, 1·79	0·45
Model 2†	1·52	0·99, 2·35	1		0·92	0·63, 1·36	0·86	0·60, 1·22	0·91	0·66, 1·27	1·11	0·75, 1·63	0·99
Non-consumers as the reference group													
Model 1*	1		0·62	0·40, 0·95	0·55	0·34, 0·88	0·52	0·34, 0·82	0·58	0·38, 0·89	0·77	0·48, 1·22	0·45
Model 2†	1		0·66	0·43, 1·01	0·61	0·37, 0·99	0·56	0·36, 0·93	0·60	0·39, 0·93	0·73	0·45, 1·17	0·99
Lifetime non-consumers as the reference group, excluding former consumers (*n* 1874)													
Cases/person-years	4/184		85/4899		44/3237		62/4462		86/6188		60/2860		
Model 1*	1		0·41	0·13, 1·30	0·34	0·11, 1·10	0·36	0·11, 1·16	0·37	0·12, 1·22	0·68	0·21, 2·26	0·08
Model 2†	1		0·43	0·10, 1·87	0·37	0·08, 1·66	0·38	0·09, 1·73	0·40	0·09, 1·81	0·73	0·16, 3·37	0·06
	Women												
	0		>0–6		>6–12		>12–24		>24				
Median	0		1·3		8·3		16·4		37·3				
Light consumers as the reference group													
Cases/person-years	37/4237		73/9167		13/2523		20/1877		17/1507				
Model 1*	1·86	1·12, 3·08	1		0·86	0·46, 1·60	1·72	0·96, 3·07	1·77	0·95, 3·29			0·16
Model 2†	1·81	1·04, 3·17	1		0·85	0·45, 1·61	1·70	0·95, 3·05	1·66	0·85, 3·24			0·24
Non-consumers as the reference group													
Model 1*	1		0·54	0·33, 0·89	0·46	0·23, 0·94	0·93	0·48, 1·79	0·95	0·47, 1·79			0·16
Model 2†	1		0·55	0·32, 0·96	0·47	0·22, 1·02	0·94	0·46, 1·92	0·91	0·42, 2·00			0·24
Lifetime non-consumers as the reference group, excluding former consumers (*n* 1952)													
Cases/person-years	16/2528		73/9167		13/2523		20/1877		17/1507				
Model 1*	1		0·69	0·34, 1·41	0·55	0·23, 1·32	1·10	0·48, 2·51	1·20	0·49, 2·94			0·09
Model 2†	1		1·06	0·41, 2·73	0·89	0·28, 2·77	1·72	0·57, 5·16	1·71	0·52, 5·64			0·14

* Age- and centre-stratified and adjusted for diabetes duration, insulin therapy, co-morbidities (heart disease, stroke, cancer), smoking status, duration and intensity, educational attainment, and employment.
† Model 1 additionally adjusted for alcohol consumption in the past.

Results

At baseline, median alcohol consumption was 16·0 g/d in men and 1·8 g/d in women. During a median follow-up of 9·2 years, 373 men and 160 women died. Of those 533 deaths, 127 were due to CVD, 109 due to cancer, 132 due to other known causes and in 165 cases, information on the cause of death was not yet verified or the cause was unknown.

Men who reported a high alcohol consumption had a higher waist:height ratio and the lowest level of education, whereas women with a high alcohol consumption were more likely to have a lower waist:height ratio, have acquired a higher level of education and be currently employed (Table 1). In terms of past alcohol consumption, the group of male light consumers appeared to be more homogeneous compared with non-consumers. A vast majority of light consumers reported to have always consumed alcohol moderately in the past. The same pattern was observed among the mortality cases.

In men, alcohol consumption of 6 g/d or more was not associated with mortality compared with light consumption (Table 2). Adjustment for alcohol consumption in the past only marginally changed the estimates. Non-consumers at baseline seemed to be at a higher mortality risk than men consuming up to 6 g/d (HR 1·62, 95 % CI 1·05, 2·49). Further adjustment for alcohol consumption in the past attenuated this relationship. Compared with non-consumers at baseline, risk of death in light alcohol consumers was lower: multivariable HR was 0·62 (95 % CI 0·40, 0·95). Additional adjustment for past alcohol consumption slightly affected the associations. Further exclusion of former consumers from the comparison group, i.e. using lifetime non-consumers as the reference, lowered the risk estimates in men, but results were not significant anymore. HR were more imprecise since there were only a few case numbers among the lifetime non-consumers.

Among women, likewise, no association between an alcohol consumption of 6 g/d or more and mortality was observed compared with light consumption and with or without adjustment for past alcohol consumption. Women who did not consume alcohol at baseline had a higher mortality risk, with a HR of 1·86 (95 % CI 1·12, 3·08). The HR changed only marginally when adjusted for past alcohol consumption. As in men, female light consumers had a lower mortality risk of 0·54 (95 % CI 0·33, 0·89) compared with non-consumers at baseline. Further exclusion of former consumers led to higher, non-significant but more imprecise risk estimates due to low case numbers.

Among current consumers only (men: *n* 2455 and women: *n* 1686), an increment of 12 g/d was not associated with mortality: HR was 1·02 (95 % CI 0·96, 1·14) in men (*P* for trend=0·24) and 1·09 (95 % CI 0·93, 1·27) in women (*P* for trend=0·15). From the restricted cubic spline regression, the associations among consumers and non-consumers also did not appear to be non-linear: *P* values for non-linearity were *P*=0·85 in men and *P*=0·27 in women.

Cause-specific analyses, although hampered by small numbers, showed no lower or higher risk for cardiovascular or cancer mortality (Table 3). Higher risks were observed for mortality due to other known causes, for men who were non-consumers at baseline and women whose consumption was above the recommended upper limit. Most frequent causes of death included in this category were diabetes mellitus, diseases of the digestive system (mainly the liver) and respiratory diseases. The competing risk model showed that for women who consumed more than 6 g/d, the risk of dying from other causes or CVD was significantly higher than cancer mortality risk.

Table 4 displays mortality risk in non-consumers at baseline in subcategories of lifetime non-consumers, always moderate consumers and sometimes heavy consumers. In men, higher risk of death was only observed in those who were categorised as individuals who sometimes drank heavily in the past (HR 3·65, 95 % CI 1·62, 8·24). Due to small numbers, only two categories could be built for women; the higher mortality risk was seen in those categorised as former drinkers (HR 2·56, 95 % CI 1·32, 4·93).

Discussion

The present prospective multi-centric study of participants with diabetes mellitus showed no association between current alcohol consumption over 6 g/d and mortality risk compared with light consumption, also when past alcohol consumption was accounted for. Men and women who abstained from alcohol at baseline had a higher mortality risk compared with light consumers. The present study suggests that this higher risk was influenced by their past alcohol consumption rather than their current abstinence.

Several studies have investigated the association between alcohol and mortality in individuals with diabetes. A meta-analysis pooled six prospective studies and showed that mortality risk was decreased for a consumption of >0 and <6 g/d compared with non-consumers (relative risk 0·64, 95 % CI 0·49, 0·82). Furthermore, risks of fatal and total CHD were decreased with an alcohol consumption of >0 and <6, 6–18, and ≥18 g/d compared with non-consumers[7]. Moreover, among 404 diabetic and glucose-intolerant Japanese men, non-daily consumers had a decreased mortality compared with never consumers. No association was observed for former or daily consumers[6]. Considering the different reference category, these results seem to be in line with the present findings.

Regardless of pre-existing diabetes, moderate alcohol consumption has been linked to a lower risk of atherosclerotic diseases and overall mortality compared with non-consumers, which could be explained by beneficial changes in lipid metabolism, endothelial function, inflammation, haemostatic balance, insulin sensitivity and blood pressure[23]. These favourable effects are particularly relevant in individuals with diabetes, in whom coronary risk factors are highly prevalent[11,24]. In the general population, the relationship between alcohol and mortality has been consistently described as a J- or U-curve. This was confirmed in a meta-analysis of thirty-four prospective studies, where consumption of up to four drinks per d in men and up to two drinks per d in

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Table 3. Cause-specific mortality in men and women with diabetes mellitus
(Hazard ratios (HR) and 95 % confidence intervals)

	Men					
	0 g/d		>0–6 g/d		>6 g/d	
	HR	95 % CI	HR	95 % CI	HR	95 % CI
CVD mortality						
Cases/person-years		7/1727		22/4899		64/16 747
Model 1*	1·55	0·59, 4·07	1		1·36	0·78, 2·37
Model 2†	1·51	0·57, 3·95	1		1·38	0·78, 2·43
Cancer mortality						
Cases/person-years		6/1727		18/4899		45/16 747
Model 1*	1·28	0·46, 3·59	1		0·84	0·46, 1·56
Model 2†	0·97	0·32, 2·98	1		0·88	0·47, 1·65
Other known causes						
Cases/person-years		14/1727		21/4899		59/16 747
Model 1*	2·82	1·31, 6·08	1		0·86	0·50, 1·48
Model 2†	2·66	1·22, 5·81	1		0·75	0·43, 1·30
	Women					
	0 g/d		>0–6 g/d		>6 g/d	
CVD mortality						
Cases/person-years		10/4237		14/9167		10/5907
Model 1*	2·78	0·87, 8·81	1		2·36‡	0·84, 6·58
Model 2†	3·79	0·99, 14·53	1		2·47§	0·87, 6·99
Cancer mortality						
Cases/person-years		12/4237		22/9167		6/5907
Model 1*	1·89	0·76, 4·62	1		0·50	0·18, 1·38
Model 2†	1·50	0·55, 4·07	1		0·54	0·19, 1·54
Other known causes						
Cases/person-years		14/4237		11/9167		13/5907
Model 1*	4·79	1·35, 16·92	1		2·93‖	1·05, 8·17
Model 2†	6·14	1·51, 24·89	1		2·79¶	0·98, 7·96

* Age- and centre-stratified and adjusted for diabetes duration, insulin therapy, co-morbidities (heart disease, stroke, cancer), smoking status, duration and intensity, educational attainment, and employment.
† Model 1 additionally adjusted for alcohol consumption in the past.
‡ Values were significantly different for risk estimate derived from competing risk model *v.* cancer mortality ($P=0·04$).
§ Values were significantly different for risk estimate derived from competing risk model *v.* cancer mortality ($P=0·05$).
‖ Values were significantly different for risk estimate derived from competing risk model *v.* cancer mortality ($P=0·02$).
¶ Values were significantly different for risk estimate derived from competing risk model *v.* cancer mortality ($P=0·03$).

women was inversely associated with total mortality compared with non-consumers[4].

We did not observe an association between a current alcohol consumption of more than 6 g/d and mortality risk compared with light consumers. However, the meta-analysis of Koppes *et al.*[7] has shown that consumption of 0–6 g/d may already give protection compared with abstinence. These findings demonstrate that a consumption above 6 g/d is not associated with mortality compared with a condition that is already considered beneficial. Thus, this does not mean that alcohol consumption is not associated with mortality in diabetic individuals, but that the difference between the protection associated with light consumption and a higher consumption is not significantly different.

These results show that the choice of reference category can have a substantial influence on the interpretation of an observed association between alcohol consumption and mortality. We chose light alcohol consumers as a reference group, because it has been shown that non-consumers (including former drinkers) as well as lifetime abstainers do not constitute a useful reference category. First, lifetime abstinence of alcohol is not normative in many high-income countries. As a consequence, this group is relatively small and members of this group differ from consumers in many other health determinants[9]. Second, the inclusion of former drinkers in the reference group when investigating alcohol consumption has been under discussion for over two decades[10,13]. We observed that non-consumers had a higher mortality risk compared with light consumers at baseline when controlled for confounders including co-morbidities. In general, this can be explained by the following: (1) these individuals were lacking the favourable physiological effects of alcohol reported above or (2) these individuals quit due to health reasons. The second explanation supports the hypothesis that the group of non-consumers may include the so-called 'sick-quitters', which originates from findings of Shaper *et al.*[13]. This hypothesis reads: a separation of abstainers into lifelong abstainers and former consumers leads to less pronounced or to a complete disappearance of beneficial effects observed in moderate consumers relative to non-consumers. Individuals who quit consuming alcohol due to health reasons are more vulnerable to mortality and, thus, may be responsible for some or most of the higher risk of abstainers[13,25]. However, Costanzo *et al.*[10] concluded in a

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Table 4. Overall mortality in non-consumers at baseline compared with light consumers at baseline (Hazard ratios (HR) and 95 % confidence intervals)

	Men						
	0 g/d						
	Lifetime non-consumers		Always moderate		Sometimes heavy in the past		
	HR*	95 % CI	HR*	95 % CI	HR*	95 % CI	>0–6 g/d
n	21		104		72		576
Cases/person-years	4/184		15/890		17/654		85/4899
	1·47	0·34, 6·36	1·09	0·56, 2·16	3·65	1·62, 8·24	1
	Women						
	0 g/d				>0–6 g/d		
	Lifetime non-consumers		Former consumers				
n	266		193		1039		
Cases/person-years	16/2528		21/1708		73/9167		
	1·31	0·65, 2·67	2·56	1·32, 4·93	1		

* Age- and centre-stratified and adjusted for diabetes duration, insulin therapy, co-morbidities (heart disease, stroke, cancer), smoking status, duration and intensity, educational attainment, and employment.

review that the protective effect seen for moderate alcohol consumption does not appear to be substantially related to the fact that former consumers are included in the reference group. In their meta-analysis, Di Castelnuovo *et al.*[4] showed that the protective effect of alcohol among the general population was lower when former consumers were excluded, but still significant. On the other hand, Friesema *et al.*[12] found that lifetime alcohol consumption was not related to mortality or CVD incidence, whereas current consumption was associated with lower CVD and mortality risk compared with never drinkers. Since our population consisted of individuals with diabetes mellitus, their diagnosis or the existence of co-morbidities are plausible explanations for their decision to quit consuming alcohol. This would mean that their ill health rather than their alcohol consumption drove the association. If participants reduced their alcohol consumption after their diabetes diagnosis but before baseline assessment, this might have underestimated the association with mortality.

A limitation of the study was that the power was low. Therefore, it is possible that we failed to detect a true association between current alcohol consumption and mortality risk. In addition, information on current and past alcohol consumption was based on self-report, which might have introduced recall bias. Due to misreporting or the fact that the questions asked about alcohol consumption at defined ages only, misclassification into categories of lifelong abstainers, former and current consumers may have occurred. Moreover, no information was available about the onset and times and reasons for cessation of alcohol consumption. However, in a large cohort study, methods of assessing current and past alcohol consumption are restricted and a self-administered questionnaire has been judged to generate reliable and valid estimates[20,26].

In conclusion, these results are in support of the current advice that individuals with diabetes mellitus can consume alcohol within the recommended upper limits. The increased mortality risk among non-consumers appeared to be affected by their past alcohol consumption rather than their current abstinence. In addition, the present study supports the hypothesis that former consumers, abstinent at point of entry into the study, do not constitute a useful reference category. The choice of reference category and the inclusion of former consumers can substantially affect the interpretation of risk estimates.

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