

# Effects of high alcohol intake, alcohol-related symptoms and smoking on mortality

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## ABSTRACT

**Background and Aims** Both high alcohol intake and alcohol dependence increase mortality, and both are associated with smoking. We aimed to compare the associations of quantity of alcohol, number of alcohol-related symptoms and smoking history with all-cause mortality, and to assess symptom count and smoking history as confounders or mediators of the effects of high alcohol intake. **Design** Survival was analysed by Cox regression with sex, body mass index, alcohol intake (overall and by beverage), maximum drinks on any day, alcohol symptom count and smoking status as potential predictors of age at death. **Setting** Australia. **Participants** Participants were apparently healthy volunteers consisting of 33 593 Australian adult twins and their relatives who completed questionnaires or interviews between 1979 and 2005. **Measurements** Data on alcohol use, smoking and occurrence of symptoms related to alcohol use disorders and death records from the Australian National Death Index. **Findings** A total of 3764 participants were matched with deaths occurring within Australia up to July 2014. Individually, alcohol intake [hazard ratio (HR) = 1.0082, 95% confidence interval (CI) = 1.0063–1.0102, per drink per week], beer intake (HR = 1.0159, 95% CI = 1.0123–1.0195, per drink per week), life-time maximum number of drinks in 1 day (HR = 1.0176, 95% CI = 1.0130–1.0221, per drink), symptom count (HR = 1.0867, 95% CI = 1.0633–1.1106, per symptom) and smoking status (HR = 2.82, 95% CI = 2.52–3.16 for smokers of 10+ cigarettes/day versus never-smokers) were each significant predictors of all-cause mortality. After adjustment for the independently significant predictors alcohol symptom count and smoking status, alcohol intake was no longer significant (adjusted HR = 1.0012 per drink per week, 95% CI = 0.9979–1.0145). **Conclusions** Number of symptoms related to high alcohol intake and tobacco smoking appear to account for the positive association between alcohol consumption and premature mortality.

**Keywords** Alcohol intake, alcohol symptoms, all-cause mortality, beer, smoking, wine.

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## INTRODUCTION

Many studies have explored the relationship between alcohol use and mortality. The usual focus has been on quantity of alcohol consumed, or whether alcoholic beverages vary in their potential for harm or benefit. Meta-analysis incorporating data from more than a million participants [1] showed that consumption of up to four drinks per day in men, or two per day in women, was associated with an approximately 15–20% reduction in mortality compared with those reporting no alcohol use, but greater amounts of alcohol were associated with higher mortality. The apparently beneficial effect of reported consumption of small amounts of alcohol may be due to confounding by

past excessive drinking among those abstaining at the time of ascertainment, or by other unmeasured characteristics of non-drinkers [2]. Most people in these population-based epidemiological studies report alcohol intake towards the left-hand (lower) end of the 'U-shaped' mortality curve, and many studies have used categorical questions about alcohol intake with a low cut-off for the highest category, so there is still uncertainty about the quantitative effects of high alcohol intake on all-cause or cause-specific mortality.

Arguments about confounding are also relevant to the increased mortality associated with high alcohol intake. Alcohol use disorders and associated symptoms are known to have effects on mortality. Initially, data from a US

population survey [3] suggested that the alcohol/mortality relationship was displaced upwards in those who had been alcohol dependent, with no significant effect on mortality among heavy or very heavy drinkers without dependence. Meta-analysis [4] showed that risk for all-cause mortality was three- to fivefold greater in those with alcohol use disorders compared to controls, although less in data from population surveys than in studies based on clinic recruitment. A similar meta-analysis on alcohol dependence [5] found a relative risk of 3.5 compared to controls. Subsequent publications have documented increased mortality in people with alcohol abuse or dependence [6], and a remarkable 25-year decrease in survival associated with hospital admission for alcohol use disorder in Scandinavia [7]. The strong association of alcohol use disorders with alcohol intake makes them potential confounders or mediators of the alcohol/mortality association. Another potential confounder is the association between excessive drinking and smoking, which is due at least partly to genetic overlap between liabilities to alcohol and nicotine addiction [8].

We have conducted multiple questionnaire- and interview-based studies on Australian adult twin and family cohorts during the past 35 years, aimed at defining causes of variation in alcohol intake and dependence. These included questions about alcohol intake, symptoms or events associated with alcohol abuse or dependence and smoking. We have now compiled data throughout our studies to give estimates of alcohol intake and symptoms, and matched these against records of date and cause of death. This allows examination of relationships between amount of alcohol, alcohol-related symptom count and smoking history with the specific aims of:

1. assessing and comparing effects of self-reported alcohol intake, overall and by beverage; number of self-reported alcohol-related symptoms; maximum alcohol consumption on any day; and a score based on smoking history, on all-cause mortality;
2. determining whether adjustment for symptom count and smoking score decreases or eliminates the association between reported amount of alcohol and mortality; and
3. comparing the dichotomous DSM-III-R or DSM-IV alcohol dependence diagnosis and the ordinal symptom count as predictors of mortality in a subset of participants for whom DSM-defined alcohol dependence could be diagnosed or excluded.

## METHODS

### Design

Data on potential alcohol-related predictors of mortality were gathered from questionnaire- or interview-based

studies conducted between 1979 and 2005 on Australian adult twins and their relatives. Postulated predictors were included in Cox survival analysis (both singly and together), with age at death or censoring as outcome.

### Studies and participants

Alcohol-related information was extracted from records of 10 studies (summarized in Table 1) conducted between 1979 and 2005 on Australian adult twins and their relatives. Twin participants were approached initially through the Australian Twin Registry. There were two cohorts, comprising twins born before 1964 and therefore over the legal drinking age of 18 at the time of the first survey (cohort 1) and twins born between 1964 and 1971 who became eligible (over 18) for the later studies (cohort 2). Other studies included adult relatives (parents, children, siblings and spouses) of the cohorts 1 and 2 twins.

Initially, 33 594 people were identified as having participated in any study which gathered quantitative information on alcohol intake. One of these participants lacked critical information on date of birth, so 33 593 people were submitted for matching (as described below). After return of the results it was realized that one person had been submitted without surname information and would not have been matched, so the total of searched participants was 33 592.

Of the participants submitted for matching against death data, 32 231 had provided information about their alcohol intake on one or more occasions; 19 976 (62%) had data from only one occasion, 5569 from two, 3865 from three and 2821 from four or more occasions.

The previous studies had been approved by appropriate Ethics Committees and participants gave informed consent to the data collection and storage. This specific project was approved by both the QIMR Berghofer Medical Research Institute Human Research Ethics Committee and the Australian Institute of Health and Welfare (AIHW) Ethics Committee.

### Predictor variables

Information on alcohol intake (total and by beverage) at the time of each study, alcohol-related symptoms, life-time maximum number of drinks in a single day and smoking status were obtained from self-report, and body mass index (BMI) was calculated from height and weight. Estimates of alcohol intake were based on three types of information: for the past week, for a typical week and for usual frequency and quantity in the past 12 months. Symptom count was the number of symptoms (of 15) endorsed as ever occurring. Smoking was assessed as never/former/current, with division of current smokers into  $< 10$  or  $\geq 10$  cigarettes per day. Information on life-time alcohol dependence, by DSM-

**Table 1** Sources of data on alcohol use and alcohol-related symptoms. Cohort 1 comprised twins born before 1964 and cohort 2 twins were born between 1964 and 1971. A total of 36 581 people were recruited for any of the studies which gathered information on alcohol, and 33 392 were marked as completing a study. Of these, 32 231 provided information from which amount of alcohol, averaged over studies and over assessment methods, could be estimated. The total numbers in this table reflect the fact that many people participated in more than one of the studies.

Study (reference)	Years	n with alcohol data (male, female)	Age range	Alcohol data					Symptom count
				Past week	Typical week	Q × F	Max drinks		
Alcohol Challenge Twin Study (ACTS) [10]	1979–81	411 (199, 212)	18–34	Yes		Yes			
'Canberra' questionnaire [11]	1980–82	7342 (2738, 4604)	18–88	Yes		Yes			
ACTS follow-up [12]	1990–92	338 (159, 179)	28–45	Yes	Yes	Yes	Yes	Yes	Yes
Cohort 1 twins and relatives [13,14]	1988–89	14 517 (6172, 8345)	19–76	Yes	Yes	Yes	Yes	Yes	Yes
Cohort 2 twins and relatives [13,14]	1989–92	7610 (3373, 4237)	19–42	Yes	Yes	Yes	Yes	Yes	Yes
SSAGA study, cohort 1 twins [15]	1992–93	5909 (2059, 3850)	26–90	Yes		Yes	Yes	Yes	Yes
Older Australians study [16]	1993–95	2533 (800, 1733)	50–94	Yes		Yes	Yes	Yes	Yes
'Twin 89' Study, cohort 2 [13,14]	1996–2000	4664 (2103, 2561)	24–36	Yes		Yes	Yes	Yes	Yes
Alcohol and nicotine studies [17]	2001–05	9857 (4439, 5418)	18–93	Yes		Yes	Yes	Yes	Yes

SSAGA = Semi-Structured Assessment for the Genetics of Alcoholism.

IIIR or DSM-IV criteria, was available for a subset of 11 009 participants. Further details are given in the Supporting information.

### Summary variables across studies

Because not all subjects participated in all studies, we averaged the estimates of alcohol intake and other potential predictor variables throughout all available times of study. For alcohol intake, we averaged past-week, typical week and quantity–frequency reports separately throughout occasions to obtain a summary variable for each. We also averaged all available alcohol intake reports to obtain an overall estimate. To obtain estimates for the major categories of alcoholic beverages, we averaged reports of beer, wine and spirits consumption (as number of drinks of each) throughout all available occasions. For the maximum number of drinks ever taken within a 24-hour period, we took the maximum number reported in any study, and for the symptom count and smoking score we used the average. Correlations between the summary variables are given in Supporting information, Table S2.

### National Death Index Search

Names and dates of birth for study participants were submitted to the Australian National Death Index [NDI; see <http://www.aihw.gov.au/national-death-index/> Accessed: 2017–07-24 (Archived by WebCite® at <http://www.webcitation.org/6sCx4Ft8B>)] for matching against their records. Where necessary, more than one surname per participant was submitted.

These NDI records do not contain information about deaths before 1980, but our studies began in 1979, so this is not a limitation. Deaths occurring outside Australia will not be matched, and in some cases acceptable matches may not be achieved for people who have died. Identifying information was matched against deaths occurring in Australian States and Territories up to the end of July 2014. Matching occurred using an algorithm based on date of birth, and family and personal names weighted for frequency of names within the index (i.e. a match for an uncommon name was given greater weight than a match for a common name). On receipt of the search results, they were ranked according to matching score and rechecked by a person experienced with NDI data.

### Statistical methods

Survival analysis was based on potential predictors from the questionnaire and interview studies, averaged throughout studies as described above, and the date of death or censoring (recoded to age at death or at 31 July 2014). Initially we used IBM SPSS, release 22 (IBM Corp., Armonk, NY, USA) for estimation of means

and correlations and for survival analysis. However, because our studies emphasized twins and their families, there is a genetic overlap between many of the subjects. This means that, to the extent that family members are similar to each other for genetic reasons (which will vary according to the heritability of the phenotypes), the number of independent observations is less than the number of participants and the standard errors for calculated statistics will be underestimated. [However, the point estimates themselves, including means, correlation coefficients and hazard ratios (HR), are not changed; only the SE and therefore the confidence intervals (CI) and *P*-values are affected.] To overcome this problem, we repeated the Cox regression analysis in Stata (StataCorp LLC, College Station, TX, USA) with the 'clustered robust standard error' option, grouping subjects by family to generate robust standard errors for the regression coefficients and for estimation of confidence intervals for hazard ratios. The assumption of proportional hazards was also tested using Stata, with the robust standard error option.

## RESULTS

### Number and causes of deaths

Of the 33 593 people whose names were submitted for matching to the NDI (18 853 women and 14 740 men), matches to death certificate data were found for 3764 (1915 women and 1849 men), or just greater than 11%.

For those known to have died, median ages at death were 76.0 years for women and 73.5 years for men. Median follow-up time, from the first study for each person to death or to July 2014, was 25.5 years. Of 3375 deaths for which causes had been coded (89.7% of all deaths), 580 women and 625 men (34.1, 37.3%) died of cancers; 584 women and 549 men (34.4, 32.8%) died of cardiovascular diseases; and 536 women and 501 men (31.5, 29.9%) died of other causes. In this paper, we focus on all-cause mortality.

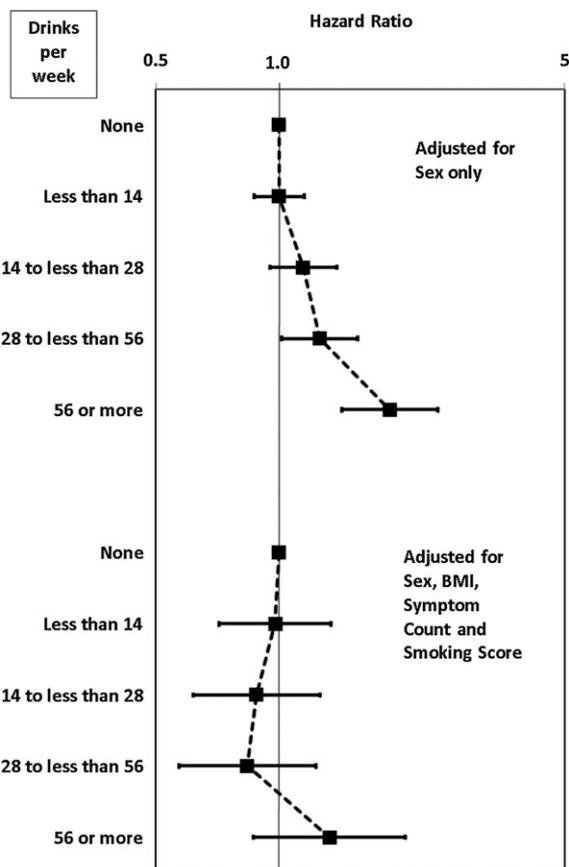
### Associations between alcohol and mortality (aim 1)

Initial results (Table 2) are from analyses in which each potential predictor's effect on mortality was considered separately. Tests of the proportional-hazards assumption showed statistically significant deviation for all the predictors in Table 2 except BMI and wine intake, but graphical assessment with Kaplan–Meier plots (shown for alcohol, symptom count and smoking group in Supporting information, Fig. S2) and residuals plots (not shown) suggested only minor deviations from constant relative hazard across time.

Reported alcohol intake was associated strongly and positively with mortality. This was true for average intake estimated from all sources of data, and also for the averages derived from past-week or usual quantity and frequency methods. Results were consistent across men and women (Supporting information, Table S3). Alcohol intake

**Table 2** Effects of alcohol- and smoking-related characteristics on survival. Cox proportional hazards analysis, with adjustment for within-family similarity. The decreased number of subjects and deaths in the multivariate analysis is due to missing data for some predictor variables. Hazard ratios (HR) are for men compared to women; per body mass index (BMI) unit; per drink per week; per drink; or per symptom, as appropriate. Hazard ratio for smoking score is per unit on the scale never = 0, ex = 1, current < 10 cigarettes/day = 2, current 10+ cigarettes/day = 3; comparison of groups 0 (never-smoker) and 3 (current 10+) showed HR 2.82, 95% CI 2.52–3.16.

	<i>n total</i>	<i>n deaths</i>	<i>B</i>	<i>Robust SE</i>	<i>P</i>	<i>HR</i>	<i>95% confidence interval</i>
<i>Univariate</i>							
Sex	33 296	3793	0.3606	0.0326	$1.68 \times 10^{-28}$	1.4342	1.3454–1.5288
BMI	30 747	3567	0.0128	0.0047	0.0068	1.0129	1.0036–1.0223
Alcohol	32 142	3575	0.0082	0.0010	$1.55 \times 10^{-15}$	1.0082	1.0063–1.0102
Beer	24 811	2739	0.0158	0.0018	$1.38 \times 10^{-17}$	1.0159	1.0123–1.0195
Wine	25 027	2692	−0.0037	0.0040	0.364	0.9963	0.9885–1.0041
Spirits	23 955	2605	0.0133	0.0050	0.0083	1.0134	1.0035–1.0234
Max drinks ever	26 400	2306	0.0174	0.0023	$1.70 \times 10^{-14}$	1.0176	1.0130–1.0221
Symptom count	26 351	2329	0.0831	0.0111	$7.82 \times 10^{-14}$	1.0867	1.0633–1.1106
Smoking score	31 687	3535	0.3333	0.0185	$9.12 \times 10^{-73}$	1.3956	1.3459–1.4471
<i>Multivariate</i>							
Sex	21 874	1743	0.1167	0.0544	0.032	1.1238	1.0101–1.2502
BMI	21 874	1743	0.0172	0.0073	0.018	1.0173	1.0029–1.0320
Alcohol	21 874	1743	0.0012	0.0017	0.496	1.0012	0.9979–1.0045
Max drinks ever	21 874	1743	0.0032	0.0034	0.356	1.0032	0.9965–1.0099
Symptom count	21 874	1743	0.059	0.0143	$3.60 \times 10^{-5}$	1.0608	1.0315–1.0909
Smoking score	21 874	1743	0.2992	0.0271	$2.19 \times 10^{-28}$	1.3488	1.2790–1.4224

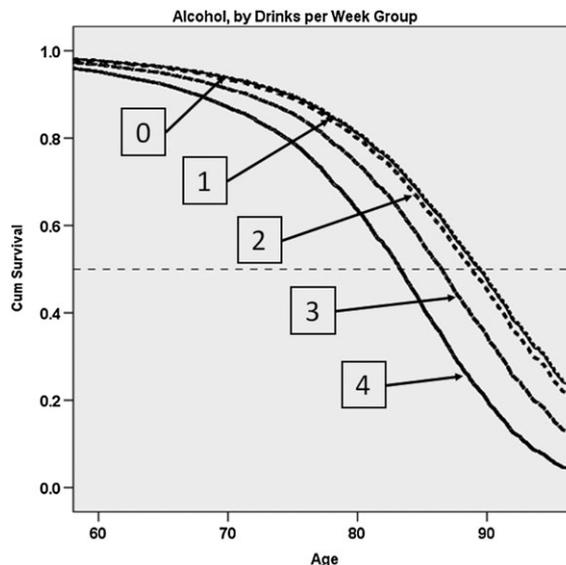


**Figure 1** Hazard ratios for all-cause mortality by alcohol intake, grouped as shown. Estimates and 95% confidence intervals, adjusted either for sex only or for sex, body mass index (BMI), symptom count and smoking score

estimated from responses to questions about number of drinks in a typical week also showed a significant association overall and in men; the association was not significant in women, but the 95% CI for men and women overlapped.

Results from calculation of alcohol intake as beer, wine or spirits, and estimation of the effects of each beverage type on all-cause mortality, are also shown in Table 2. Increasing beer intake had a substantial association with increased mortality, overall and in both men and women. Conversely, wine showed no association with mortality, and amount of alcohol as spirits did not show a significant association in women.

In order to assess the dose–response relationship between alcohol intake and mortality, we divided study participants into five groups according to their alcohol use (average number of drinks per week, derived from all studies and all three types of intake measure). The groups ranged from none to 56 or more drinks per week (eight drinks or 80 g of alcohol per day); the estimated hazard ratios and survival curves by group are shown in Figs 1 and 2. The highest category of alcohol intake, more than 56 drinks per week or 80 g of alcohol per day, was associated with a significantly increased hazard



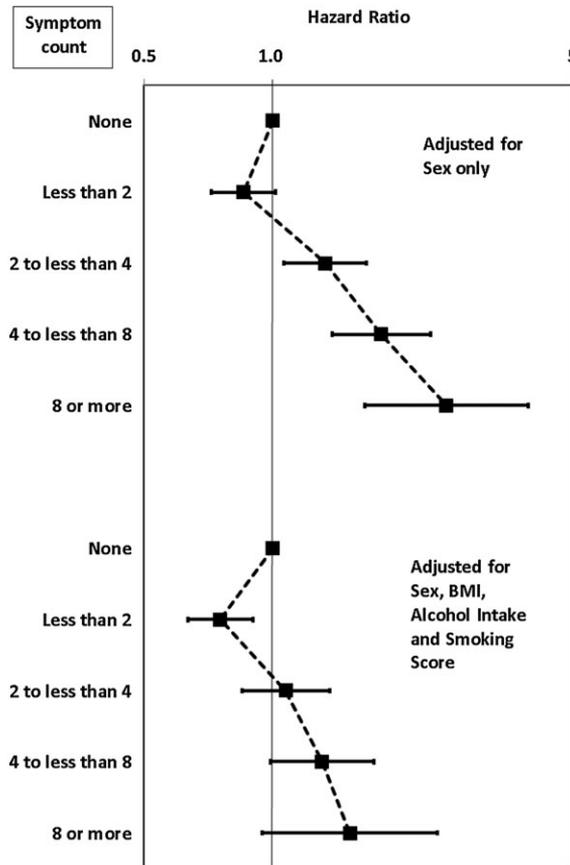
**Figure 2** Survival curves for any cause of death, by five alcohol intake groups. 0 = No alcohol use reported, 1 = any to < 14 drinks per week, 2 = 14 to < 28 drinks per week, 3 = 28 to < 56 drinks per week, 4 = 56 or more drinks per week. Survival curves are estimated from Cox regression on combined data from men and women, adjusted for sex. The interrupted horizontal line indicates median survival

ratio (HR = 1.87, 95% CI = 1.42–2.45) and with death approximately 8 years earlier compared to those reporting no alcohol.

#### Alcohol intake and potential confounders (aim 2)

The measures of alcohol intake showed significant correlations among themselves and with other alcohol-related measures (maximum number of drinks in a single day, symptom count) and smoking score (Supporting information, Table S2, Fig. S3). Similar relationships existed between symptom count and the other variables (Supporting information, Table S2, Fig. S4). Most associations were similar for men and women, but high total alcohol intake and high symptom count were associated more with high beer intake in men and with high wine intake in women.

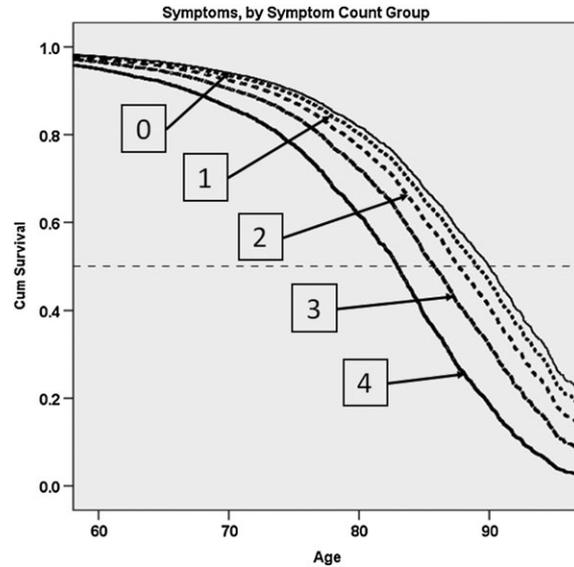
In order to separate the effects of alcohol quantity from the potential confounders, each of which were associated significantly with all-cause mortality (Table 2), we repeated Cox regression analysis on the 21 874 subjects (including 1743 deaths from any cause) who had data for overall alcohol intake, maximum number of drinks in a day, symptom count, smoking score and BMI. From this analysis (also in Table 2), we find that mortality is associated more strongly with alcohol symptom count than with the quantity of alcohol or with maximum number of drinks in a day; and smoking status is highly significant but does not eliminate the association with alcohol symptom count.



**Figure 3** Hazard ratios for all-cause mortality by symptom count, grouped as shown. Estimates and 95% confidence intervals, adjusted either for sex only or for sex, body mass index (BMI), alcohol intake and smoking score

In view of the significant effect of symptom count on all-cause mortality, we plotted hazard ratios (Fig. 3) and survival curves (Fig. 4) by symptom count group. There was little difference between the group reporting no symptoms and the group reporting fewer than two. As symptom count increased beyond two, risk increased, and for the most extreme group (reporting eight or more symptoms) there was an apparent loss of 7 years of life compared to those who reported they were symptom-free.

Because smoking score had a major effect on mortality, we repeated the survival analysis using only the data from self-declared never-smokers. Results (Supporting information, Table S4) were similar to those for the entire sample but numbers were decreased substantially, particularly at the upper end of the alcohol intake or symptom count distributions. This led to larger standard errors and less-significant associations, but the effect sizes (beta coefficients and hazard ratios) for alcohol intake and symptom count were slightly larger among the never-smokers than in the entire sample.



**Figure 4** Survival curves for any cause of death, by five symptom count groups. 0 = No symptoms reported, 1 = any to < 2, 2 = 2 to < 4, 3 = 4 to < 8, 4 = 8 or more. Survival curves are estimated from Cox regression on combined data from men and women, adjusted for sex. The interrupted horizontal line indicates median survival

#### Alcohol dependence, symptom count and mortality (aim 3)

Analysis of effects of alcohol dependence was possible only in a subset of 11 009 subjects for whom diagnostic classification according to DSM-III-R or DSM-IV was available. Results for effects of alcohol dependence and symptom count on mortality in this subset, separately and in combination, are shown in Table 3.

On its own, alcohol dependence was associated with an approximate doubling of the sex-adjusted hazard ratio compared to never-dependent participants. Symptom count, as a continuous variable, had a slightly more significant effect. These two measures are related strongly to each other (Supporting information, Fig. S5). When both were included in the survival analysis, the effect size for each was decreased and only the symptom count remained statistically significant.

#### DISCUSSION

Compared to previous studies on alcohol and mortality, ours has the advantages of multi-occasion data on alcohol intake using several approaches to estimation of quantity of alcohol, and substantial information about life-time history of symptoms and events associated with alcohol use disorders. This has allowed us to compare effects of alcohol intake and life-time symptom experience.

From our analysis the symptom count was the most relevant measure of harmful drinking, and it was associated strongly with DSM-IV alcohol dependence status in the

**Table 3** Effects of alcohol dependence, alone or in combination with symptom count, on all-cause mortality. Cox proportional hazards analysis, with adjustment for within-family similarity. Sex-adjusted, and confined to subjects with known life-time alcohol dependence status. Hazard ratios (HR) are for alcohol dependent compared to non-dependent subjects, or per symptom, as appropriate.

	<i>n total</i>	<i>n deaths</i>	<i>B</i>	<i>Robust SE</i>	<i>P</i>	<i>HR</i>	<i>95% confidence interval</i>
Univariate, sex-adjusted							
Alcohol dependence	10 970	505	0.6821	0.14	$6.40 \times 10^{-7}$	1.978	1.512–2.587
Symptom count	10 235	472	0.1145	0.02	$2.40 \times 10^{-7}$	1.121	1.074–1.171
Multivariate							
Alcohol dependence	10 235	472	0.2818	0.18	0.118	1.326	0.931–1.887
Symptom count	10 235	472	0.0856	0.03	0.0039	1.089	1.028–1.155

subgroup for which this diagnosis could be made or excluded. It displaced maximum number of drinks in any day, another potential index of dependence, in the survival analysis which included both. Either alcohol-related symptom count is a more reliable index of true alcohol intake over the long term than reported number of drinks in the weeks or months before participation, or (more probably) the adverse effects of high alcohol intake on mortality are mediated through the events included in our symptom count data. In either case, studies on effects of alcohol on ill health or mortality would benefit from gathering information on history of symptoms and events associated with alcohol use disorders. If recruiting from clinical sources symptom information should be recorded, because symptom count will give increased power compared to the binary classification as ever or never alcohol-dependent.

As mentioned above, previous studies on associations between alcohol use disorders and mortality have reported HR of 2–5, depending on the definition of the predictor and on the source for recruitment [4]. Making some assumptions about the relationship between symptom count and dependence, we can compare our results with the previous reports. Based on the relationship shown in Supporting information, Fig. S5, we assume that the average non-dependent person has a symptom count of 1 and a dependent person has a symptom count of 11. Given the univariate hazard ratio, per symptom, of 1.085, then the hazard ratio for dependent compared to non-dependent people will be  $1.085^{10}$ , or approximately 2.25. This is at the lower end of previous estimates for the effect of alcohol dependence on mortality, but compatible with the estimates from other population-based studies.

There have been many studies comparing effects of beer and wine consumption on alcohol-related mortality. Most have emphasized low to moderate alcohol use, and the possibly protective effects of wine on cardiovascular disease. We found that higher beer consumption was associated with higher mortality, but higher wine consumption was not. This is similar to results from a Danish study [9], which showed that people in their highest intake category (> 35 drinks per week) had increased all-cause mortality if

the alcohol was from beer or spirits but not if it was taken as wine. The possibility that wine is less harmful than other alcoholic beverages has been discussed widely, and our results are consistent with this, but there are many potential confounders (such as social class, diet, consumption with meals, lower probability of use in binge-drinking) which cannot be separated out easily.

Participants in our study mainly live to a fairly advanced age, and our design differs from other studies which have recruited a cohort with a narrow age range and followed them for a set period. Effects of alcohol on mortality in younger people, or on people recruited from hospitals or clinics because of clinically relevant alcohol use disorders, may show differences from our results. However, restricting our analysis to younger people (born in or after 1940) gives a median age at death (for those who died during the observation period) of 53 years (interquartile range = 44–62) and shows similar results to the entire cohort for all-cause mortality (see Supporting information, Table S5). In particular, the symptom count information is still a better predictor than reported alcohol intake.

Turning to the implications of our results, epidemiological results can help in formulating public health messages about alcohol use, and in generating hypotheses about biological mechanisms through which alcohol causes harm. The fact that mortality is associated more strongly with symptoms associated with alcohol use disorders than with the reported quantity of alcohol used need not lead to changes in advice about drinking, because the obvious route to reduction of life-time symptom counts is limitation of alcohol intake. Clinically, patients who present with alcohol-related disease (including dependence) will usually report multiple symptoms as well as high intake. However, in searching for explanations of the link between alcohol use and mortality, it will be important to consider the disruptions to lifestyle, diet or social support networks associated with high alcohol intake. These must have some biological connection to the mortality outcome, but there is a need to consider mechanisms beyond the biochemical or metabolic changes arising directly from exposure to ethanol or its metabolites.

## Declaration of interests

None.

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

**Table S1** Questions related to alcohol symptoms, used to compile the alcohol symptom count. See Table 1 for information on the constituent studies. Questions about symptoms or alcohol-related events were not included in the earlier 'Canberra' questionnaire or in the Alcohol Challenge Twin Study (ACTS).

**Table S2** Rank correlations between alcohol, smoking and body mass index (BMI) variables. Female correlations above the diagonal, male correlations below.

**Table S3** Effects on all-cause mortality by sex. Cox proportional hazards analysis, with adjustment within-family similarity.

**Table S4** Effects on all-cause mortality in never-smokers (smoking score = 0). Cox proportional hazards analysis, with adjustment within-family similarity. Hazard ratios

(HR) are per body mass index (BMI) unit, per drink per week, per drink and per symptom, as appropriate.

**Table S5** Effects on all-cause mortality in younger people, born in 1940 or later. Cox proportional hazards analysis, with adjustment within-family similarity. Hazard ratios (HR) are per body mass index (BMI) unit, per drink per week, per drink and per symptom, as appropriate. Hazard ratio for smoking score is per unit on the scale never = 0, ex = 1, current < 10/day = 2, current 10+/day = 3.

**Figure S1** Cumulative frequencies for number of drinks per week, assessed from questions on number of drinks in the past week, number of drinks in a typical week, and usual quantity  $\times$  frequency, for men and women.

**Figure S2** Kaplan–Meier plots. Observed survival for men and women by (a) alcohol intake group (0 = none, 1 = less than 14, 2 = 14 to less than 28, 3 = 28 to less than 56, 4 = 56 or more drinks per week), (b) symptom count group (0 = no symptoms reported, 1 = any to < 2, 2 = 2 to < 4, 3 = 4 to < 8, 4 = 8 or more) and (c) by smoking group (0 = never smokers, 1 = former smokers, 2 = current smokers < 10/day, 3 = current smoker  $\geq$  10/day).

**Figure S3** Relationships between total weekly number of drinks (grouped, on  $x$ -axis) and individual beverage types (drinks per week), maximum number of drinks in 1 day (life-time), symptom count (life-time) and smoking score (on the scale 0 = never smoker, 1 = ex-smoker, 2 = current smoker < 10/day, 3 = current smoker  $\geq$  10/day). Shown separately for men and women.

**Figure S4** Associations between symptom score (grouped, on  $x$ -axis) and alcohol intake (overall and by beverage, in drinks per week), maximum life-time daily drinks (number of drinks) and smoking score (on the scale 0 = never smoker, 1 = ex-smoker, 2 = current smoker < 10/day, 3 = current smoker  $\geq$  10/day). Shown separately for men and women.

**Figure S5** Relationship between calculated average symptom count, and alcohol dependence (AD) by DSM -IV criteria, in 5863 study participants for whom both were available.