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# All-cause and liver-related mortality risk factors in excessive drinkers: Analysis of data from the UK biobank

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## Abstract

**Background:** High alcohol intake is associated with increased mortality. We aimed to identify factors affecting mortality in people drinking extreme amounts of alcohol.

**Methods:** We obtained information from the UK Biobank on approximately 500,000 participants aged 40–70 years at baseline assessment in 2006–2010. Habitual alcohol intake, lifestyle and physiological data, laboratory test results, and hospital diagnoses and death certificate data (to June 2020) for 5136 men (2.20% of male participants) and 1504 women (0.60%) who reported consuming  $\geq 80$  or  $\geq 50$ g/day, respectively, were used in survival analysis.

**Results:** Mortality hazard ratios for these excessive drinkers, compared to all other participants, were 2.02 (95% CI 1.89–2.17) for all causes, 1.89 (1.69–2.12) for any cancer, 1.87 (1.61–2.17) for any circulatory disease, and 9.40 (7.00–12.64) for any liver disease. Liver disease diagnosis or abnormal liver function tests predicted not only deaths attributed to liver disease but also those from cancers or circulatory diseases. Mortality among excessive drinkers was also associated with quantitative alcohol intake; diagnosed alcohol dependence, harmful use, or withdrawal syndrome; and current smoking at assessment.

**Conclusions:** People with chronic excessive alcohol intake experience decreased average survival, but there is substantial variation in their mortality, with liver abnormality and alcohol dependence or other alcohol use disorders associated with a worse prognosis. Clinically, patients with these risk factors and high alcohol intake should be considered for early or intensive management. Research can usefully focus on the factors predisposing to dependence or liver abnormality.

## KEYWORDS

alcohol, alcohol dependence, all-cause mortality, excessive drinking, liver disease

\*GenomALC Consortium investigators are listed in Appendix.

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## INTRODUCTION

Many studies have compared all-cause mortality, mortality from predefined causes, or incidence of conditions of interest between groups of people classified by their self-reported alcohol intake (Corrao et al., 1998, 2004; Wood et al., 2018; Xi et al., 2017). Most have found associations between higher alcohol intake and poorer outcomes. Few studies have asked the complementary question—what happens to people who do consume hazardous amounts of alcohol? How much are their lives shortened, what are their causes of death, and what factors modify or predict mortality and morbidity in people with persistently high alcohol intake? There have been estimates of alcohol-associated disease burden based on the prevalence of high intake and the dose–response curve for mortality (Rehm et al., 2018), and studies based on follow-up of patients with alcohol dependence (Askgaard et al., 2017, 2020; Batty et al., 2009; Holst et al., 2017; Im et al., 2020), but information on long-term outcomes for excessive drinkers from the general population is scarce.

A direct approach to these questions requires prospective study of a substantial cohort of high-risk drinkers, representative of the general population and not biased toward patients seeking treatment. Our focus on the people at high risk requires an operational definition of “excessive” drinking. Reported consumption of 80g of alcohol per day for men, 50 grams per day or more for women, is frequently associated with adverse consequences (Corrao et al., 1997, 1998; Lelbach, 1976) (although lower limits are appropriate for public health messaging and for reduction of alcohol-associated risk across the population).

The UK Biobank is a prime source of relevant information for the general population of an economically developed country. That project recruited just over 500,000 UK-resident men and women, aged 40–70 years in 2006–2010, and the resulting resource (Sudlow et al., 2015) contains self-report information on alcohol use and on a wide range of personal, physiological, biochemical, and genetic characteristics. Subsequent information from death certificates and hospital records allows comparison of outcomes for excessive drinkers versus the rest of the participating population. Because the study sample is so large, it contains a substantial number of excessive drinkers even though they comprise only a small proportion of participants.

Our analysis of the UK Biobank data addresses questions related to risk in excessive drinkers. How do their all-cause mortality and the distribution of causes compare with those who do not meet excessive drinking criteria? In particular, how prominent is alcohol-associated liver disease (recognized as a major medical consequence of excessive drinking), or liver disease in general, among the causes of or contributors to death? What risk factors or predictors are associated with risk of death among excessive drinkers, and how large are their effects?

## SUBJECTS AND METHODS

Information used in this analysis was obtained from the UK Biobank (application number 18870). Recruitment and initial assessment of

just over 500,000 participants occurred between 2006 and 2010, targeted at the 40–69 years age group (actual range 37–73, median 58 years). Participants gave informed consent, and our application was approved by the UK Biobank through their procedures, consistent with the UK Biobank Ethics and Governance Framework (<https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics>, accessed 2022-06-21). A small number of participants who had withdrawn their consent after initial participation were excluded from the data analysis.

Information obtained at an assessment session included responses to computer-administered questionnaires, physiological measurements, and collection of blood samples for laboratory tests and genotyping. Questions about alcohol use included quantity and frequency of specified alcoholic beverages at the time of assessment, and a simple comparison with the amount 10 years previously. Participants' answers were used to calculate the number of standard drinks per week and hence the amount of alcohol in grams per day. Initial assessment included information about smoking, body mass index (BMI), blood pressure, and consumption of nonalcoholic beverages including tea and coffee. Details are available at <https://bioba.nk.ndph.ox.ac.uk/showcase/> (accessed 2022-06-21).

Excessive drinkers were defined, for this analysis, as participants with self-reported alcohol intake at the time of assessment greater than or equal to 80g/day for men, 50g/day for women and also (to ensure that they had long-term high exposure) similar or greater consumption 10 years previously.

Information on diagnoses from UK hospital encounters, and from death certificates, was coded using the International Classification of Diseases, 10th Edition (ICD-10). Death records were obtained in June 2020 and dates of death ranged from May 10, 2006 to April 26, 2020.

IBM SPSS Statistics, version 22, was used for data management and statistical tests. The main results are based on survival analysis using either Kaplan–Meier or Cox regression methods. Because participants entered the study at differing ages and times, and exposure to alcohol-associated risk was over a substantial time, age at death was used as the survival variable. Except where comparisons were made between results for men and women, sex was included as a stratum in survival analyses. Analysis based on all-cause mortality was supplemented with more detailed analysis by cause of death, using only the underlying (primary) cause of death (UK Biobank field 40001). Subgroups were created for deaths from all cancers (ICD-10 C00 to C99), all circulatory diseases (ICD-10 I00 to I99), and all other causes except liver disease. Because of its strong association with alcohol use, we included a separate analysis for deaths from any liver disease (ICD-10 K70 to K76, covering both alcohol-associated liver disease and other liver diseases). Age at death was calculated from the year of birth (exact dates of birth are not available) and the date of death, and participants who had not died were censored at an age calculated from the difference between year of birth and 2020.

Frequency distributions for laboratory test results were plotted and examined visually; if appropriate, the results were  $\log_{10}$ -transformed to obtain more symmetrical distributions. Data (for

excessive drinkers only) were regressed on age at blood collection, separately for men and women, and the standardized residuals were saved for use as predictors in the survival analysis. The amount of alcohol reported by the excessive drinkers was also log-transformed. Binary variables such as the presence or absence of a diagnosis were coded as 0 (absent) or 1 (present).

## RESULTS

### Comparisons between excessive drinking and other participants

Among the UK Biobank participants, 5136 men (2.20% of male participants) reported drinking at or above 80g of alcohol/day with similar or greater consumption 10 years previously, and 1504 women (0.60% of female participants) reported drinking 50g/day or more at the time of assessment with similar or greater consumption 10 years earlier. These participants are referred to as the “excessive drinkers.” Descriptive information for excessive drinkers, and for all other participants, is shown in Table S1.

Eight hundred and eleven (12.2%) of the 6640 excessive drinkers and 29,448 (5.9%) of the other participants were recorded as having died from any cause by June 2020. Survival analysis showed a sex-adjusted hazard ratio (HR) of 2.02 (95% CI 1.89–2.17,  $p = 2.54 \times 10^{-86}$ ) for all-cause mortality among excessive drinkers, similar for men (1.99, 1.85–2.15) and women (2.09, 1.73–2.52). Estimated mean survival was 79.2 years for excessive drinkers and 83.1 years for all others in men, 80.4 and 82.5 years, respectively, in women (Figure 1). Results of survival analysis using only those who reported alcohol intake of 5–15g/day as the comparison group,

rather than all participants who did not meet the criteria for excessive drinking, gave slightly higher HRs (Table S2).

The proportions of total deaths and estimated HRs by major ICD-10 cause-of-death groups, comparing excessive drinkers against all other participants, are shown in Figure 2 and Table S3. Information on how these HR estimates change when other risk factors were added, firstly smoking status and then body mass index (BMI), waist/hip ratio (WHR), years of education, self-reported diabetes at the time of assessment, and systolic and diastolic blood pressures (SBP, DBP) are shown in Table 1.

Deaths attributed to diseases of the digestive system were more common among the excessive drinkers (9.5% of deaths) compared to other participants (3.4%), with the excess mostly due to liver diseases. Other causes of death were similar between the two groups (Figure 2, panel A). The highest proportion of deaths in both groups was from cancers and circulatory diseases. The HRs for most cause-of-death groups were in the range 1.5–2.5, consistent with our all-cause mortality estimate of 2.0. However, liver disease (HR 9.34, 95% CI 6.95–12.56) and mental and behavioral disorders (3.68, 2.44–5.56) had significantly higher HRs (Figure 2, panel B; Table S3).

### Risk factors for overall mortality in the excessive-drinking group

All-cause mortality was associated with diagnosed alcohol-associated liver disease (ICD-10 K70.0 to K70.9) and with alcohol dependence (ICD-10 F10.2, mental and behavioral disorders due to use of alcohol; dependence syndrome) (Table 2). For participants who did not have a diagnosis of dependence, other diagnoses within the ICD-10 F10 grouping of “mental and behavioral

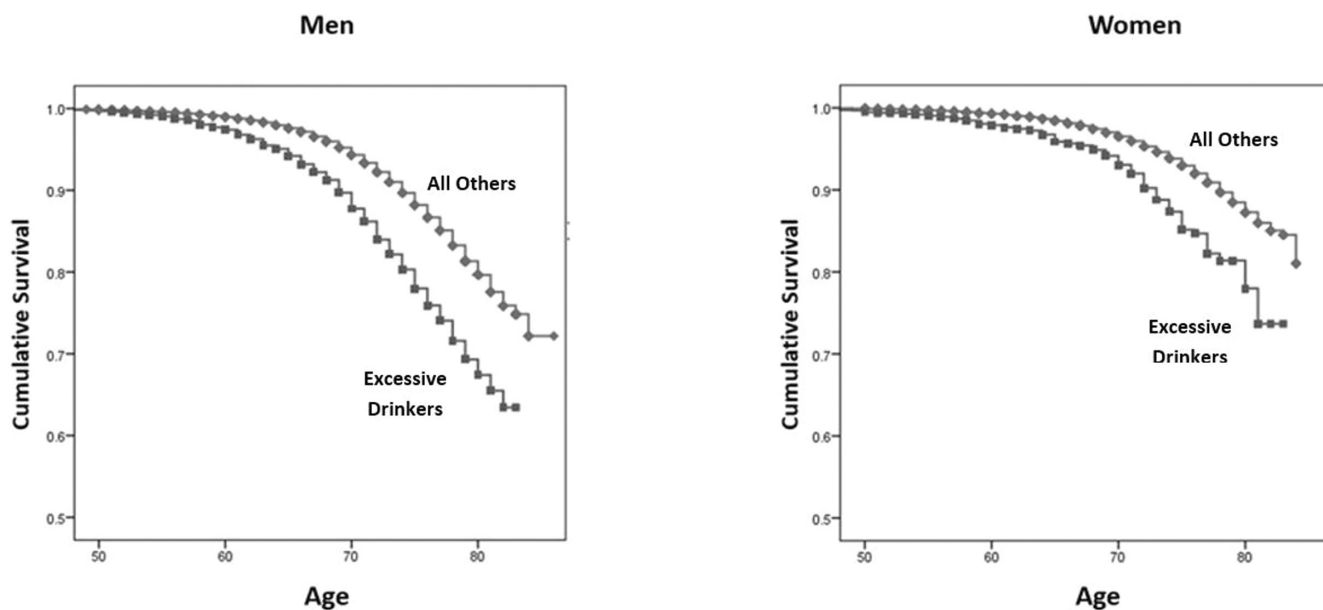
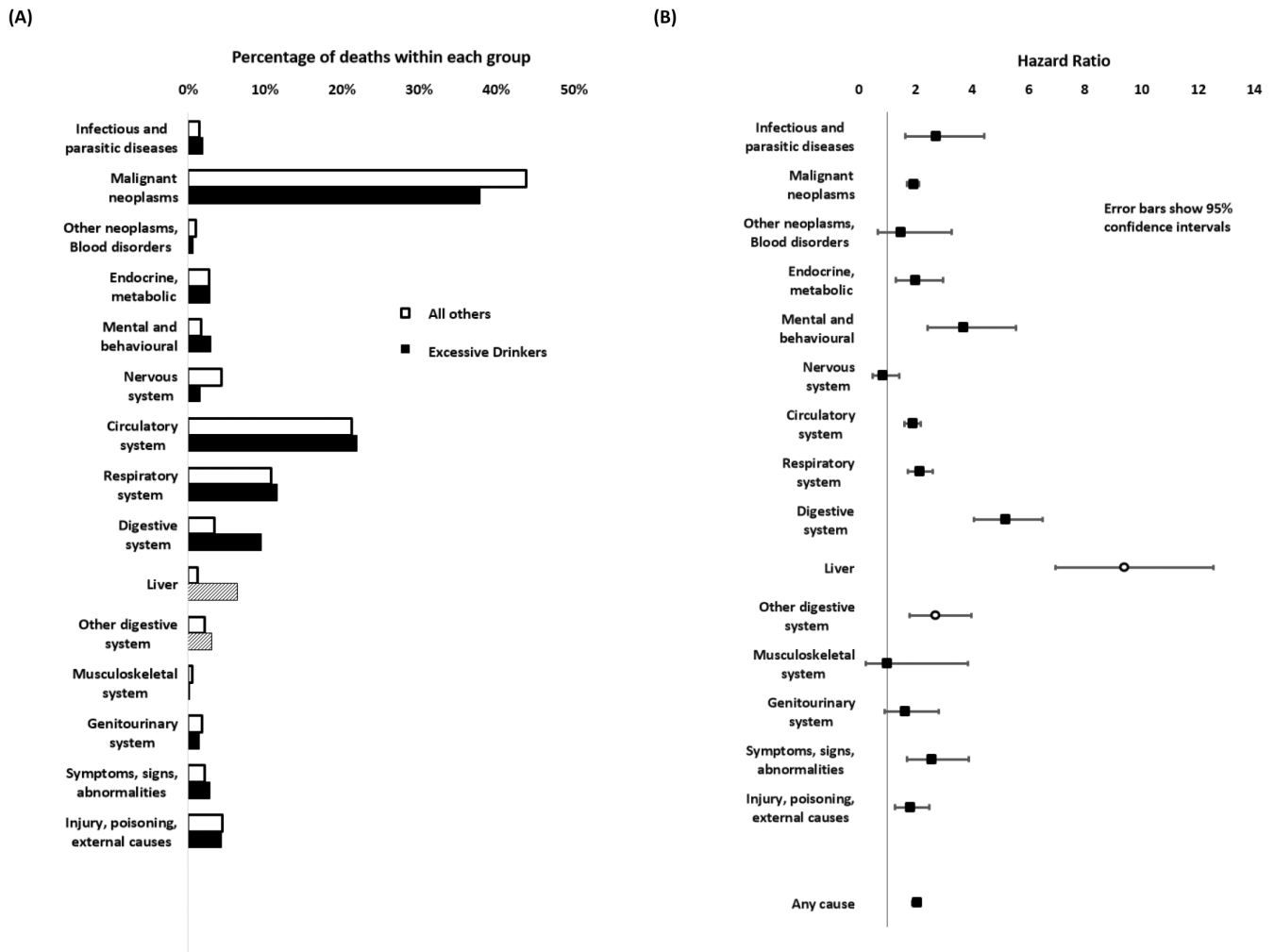


FIGURE 1 Kaplan–Meier survival analysis showing effects of excessive drinking on all-cause mortality. The lines contrast survival for the excessive drinkers and for all others. For men, the difference in mean estimated age at death was 3.9 years (79.2 vs. 83.1,  $p = 8.42 \times 10^{-75}$ ) and for women 2.1 years (80.4 vs. 82.5,  $p = 2.94 \times 10^{-15}$ ).



**FIGURE 2** Comparison of causes of death by major ICD-10 category in excessive drinkers and all other UK biobank participants (panel A), and hazard ratios for excessive drinkers compared to others by cause-of-death category (panel B). The vertical line in panel B indicates a hazard ratio of 1.0. Results for deaths attributed to digestive system diseases (ICD-10 K00 to K93) are further divided into those from liver disease (K70 to K76) and from other digestive disease (shown by lighter shading and error bars).

disorders due to use of alcohol," principally harmful use (F10.1) and withdrawal state (F10.3 or F10.4) were associated with increased mortality but to a lesser extent than for dependence (see Table 3). Other factors related to alcohol use including reported amount of alcohol (even though results in Table 2 are for people meeting the excessive drinking criteria) and smoking had highly significant detrimental associations with survival. For smoking, the major difference was between current and never/former smokers (at the time of assessment).

Because the substance use measures are strongly associated, an analysis including alcohol consumption, alcohol dependence, and smoking was conducted, with results shown in the second part of Table 2. Each remained significant, but diagnosis of alcohol dependence showed the most significant association. The effect size for amount of alcohol appears large in relation to the other factors included but, because this measure was log-transformed, the HR of 4.27 in the multivariate analysis applies to a 10-fold increase in alcohol intake. An alternative analysis, comparing excessive drinkers

with alcohol intake above versus below the sex-specific medians for this group, showed HR = 1.17 (1.02–1.35) in a multivariate analysis with alcohol dependence and smoking status.

Results for many laboratory test results had substantial associations with overall survival (Table S4), particularly but not only the liver function tests. For renal tests, there was an inverse relationship between urea and creatinine and mortality while there was a positive relationship between cystatin C and mortality. Among the other biochemical tests, apolipoprotein B and LDL cholesterol were both inversely associated with mortality, as were IGF-1 and calcium. The association with calcium, which is partly bound to albumin in serum, became nonsignificant when albumin was also included in the survival analysis. Higher results for C-reactive protein, sex hormone-binding globulin, and testosterone (in men) were associated with greater all-cause mortality. Significant associations with all-cause mortality were also found for white cell count; red cell count, mean cell volume, and red cell distribution width; platelet count; reticulocyte maturity and size; and spherical cell volume.

**TABLE 1** Comparison of hazard ratios between excessive drinkers and all other participants, showing results adjusted for sex only, then with addition of information on smoking status, then with addition of information on other recognized risk factors (as listed in the footnote).

	Sex only			Add smoking			Add others <sup>a</sup>		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
All-cause	2.02	1.89–2.17	1.70 × 10 <sup>-86</sup>	1.66	1.54–1.78	7.77 × 10 <sup>-45</sup>	1.70	1.56–1.84	9.86 × 10 <sup>-37</sup>
Infectious and parasitic diseases	2.69	1.63–4.44	1.15 × 10 <sup>-4</sup>	2.26	1.36–3.74	0.0016	2.29	1.24–4.22	0.0081
Malignant neoplasms	1.89	1.69–2.12	4.07 × 10 <sup>-28</sup>	1.58	1.41–1.78	2.97 × 10 <sup>-15</sup>	1.65	1.45–1.88	8.52 × 10 <sup>-14</sup>
Other neoplasms, blood disorders	1.45	0.65–3.27	0.365	1.37	0.61–3.09	0.450	1.65	0.67–4.06	0.273
Endocrine, nutritional, metabolic	1.96	1.29–2.97	0.0015	1.68	1.11–2.56	0.015	1.75	1.06–2.89	0.029
Mental and behavioral	3.68	2.44–5.56	6.05 × 10 <sup>-10</sup>	3.21	2.12–4.87	3.88 × 10 <sup>-8</sup>	2.86	1.74–4.70	3.25 × 10 <sup>-5</sup>
Nervous system	0.82	0.47–1.42	0.481	0.81	0.47–1.40	0.447	0.73	0.36–1.47	0.374
Circulatory system	1.87	1.61–2.17	3.59 × 10 <sup>-16</sup>	1.49	1.28–1.73	2.82 × 10 <sup>-7</sup>	1.50	1.26–1.78	5.45 × 10 <sup>-6</sup>
Respiratory system	2.12	1.72–2.60	9.83 × 10 <sup>-13</sup>	1.55	1.26–1.91	2.97 × 10 <sup>-5</sup>	1.53	1.21–1.95	4.46 × 10 <sup>-4</sup>
Digestive system	5.15	4.07–6.51	7.48 × 10 <sup>-43</sup>	3.98	3.14–5.05	3.01 × 10 <sup>-30</sup>	3.74	2.81–4.97	1.03 × 10 <sup>-19</sup>
Liver	9.34	6.95–12.56	1.17 × 10 <sup>-49</sup>	7.25	5.36–9.80	8.87 × 10 <sup>-38</sup>	6.67	4.63–9.62	2.72 × 10 <sup>-24</sup>
Other	2.67	1.79–3.99	1.67 × 10 <sup>-6</sup>	2.06	1.38–3.09	4.46 × 10 <sup>-4</sup>	2.01	1.24–3.24	0.0043
Musculoskeletal system	0.95	0.24–3.84	0.943	0.82	0.20–3.34	0.785	1.24	0.30–5.09	0.762
Genitourinary system	1.59	0.89–2.82	0.114	1.34	0.76–2.39	0.313	1.61	0.90–2.88	0.107
Symptoms, signs, abnormalities	2.56	1.68–3.88	1.09 × 10 <sup>-5</sup>	2.06	1.35–3.14	7.73 × 10 <sup>-4</sup>	2.57	1.61–4.10	7.99 × 10 <sup>-5</sup>
Injury, poisoning, external causes	1.77	1.26–2.48	8.89 × 10 <sup>-4</sup>	1.46	1.04–2.05	0.029	1.42	0.95–2.12	0.089

<sup>a</sup>Additional risk factors are BMI, WHR, age completed full-time education, self-reported diabetes, systolic and diastolic blood pressures.

### Risk factors for liver disease mortality

Because of the important association between alcohol and liver disease, we considered deaths ascribed to any liver disease (including but not limited to alcohol-associated liver disease) as a separate category. Fifty-two of 6640 (0.78%) excessive drinkers and 355 of 496,036 (0.07%) other participants died of liver diseases between the time of recruitment and June 2020.

Variation in liver disease mortality among excessive drinkers was associated with multiple risk factors (Table 4, Table S5). Smoking and alcohol-associated conditions including current smoking (at the time of assessment), amount of alcohol, and diagnosis of alcohol dependence were each associated with liver deaths; however, when these factors were considered together (Table 4, lower part), alcohol dependence was the most significant. Other alcohol use disorders, including harmful use (F10.1) without diagnosed dependence, were also associated with increased risk for liver disease mortality (Table 3).

Many of the laboratory test results from the baseline assessment showed significant associations with risk of death from liver disease (Table S5). The liver function tests gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alkaline phosphatase, and direct bilirubin each showed doubling or more of risk for each 1-Standard Deviation increase in the age- and sex-adjusted standardized residuals for the excessive drinkers group. For renal tests, creatinine, urea, and uric acid were inversely associated with risk, but cystatin C was not. There were also strong positive associations (higher values = higher risk) between deaths from liver

disease and sex hormone-binding globulin (SHBG) and testosterone (in men only), and negative associations (higher values = lower risk) for insulin-like growth factor-1 (IGF-1) and vitamin D. Associations with hematology tests were mostly related to erythrocyte size or shape, or to platelet count.

### Risk factors for cancer and circulatory disease mortality

Further analysis of risk factors, with separation of causes of death into cancers, circulatory diseases, and other causes, is shown in Tables S6 and S7. Cancer deaths in excessive drinkers were affected by smoking and alcohol dependence but not reported amount of alcohol. Circulatory system deaths were also affected by these factors and by diagnosed alcohol-associated liver disease. Mortality from the remaining causes of death except liver disease was associated with smoking, reported amount of alcohol consumed, alcohol dependence, and diagnosed alcohol-associated liver disease. Laboratory test associations for deaths attributed to cancers, circulatory diseases, and other causes are summarized in Table S7. For cancers, higher values for the liver function tests alkaline phosphatase and GGT, and for C-reactive protein, were associated with greater mortality. Higher values for urea and vitamin D were associated with lower cancer mortality. Among the hematology results, measures related to erythrocyte and reticulocyte size (MCV, RDW, reticulocyte, and spherical cell volumes) were significantly related to risk of death from any cancer.

TABLE 2 Risk factors affecting sex-adjusted all-cause mortality in excessive drinkers.

	Beta	SE	p-value	HR	95% CI
<i>Univariate associations</i>					
Body mass index (kg/m <sup>2</sup> )	-0.031	0.009	2.44 × 10 <sup>-4</sup>	0.969	0.953-0.986
Waist/Hip Ratio (%)	0.016	0.006	0.0031	1.017	1.006-1.028
Diabetes (self-report at baseline)	0.242	0.121	0.046	1.273	1.004-1.614
Mean Diastolic Blood Pressure	-0.007	0.004	0.060	0.993	0.986-1.000
Mean Systolic Blood Pressure	-0.005	0.002	0.013	0.995	0.991-0.999
Tea (cups per day)	-0.015	0.013	0.232	0.985	0.961-1.010
Coffee (cups per day)	0.011	0.017	0.539	1.011	0.977-1.045
Alcohol intake (log <sub>10</sub> grams per day)	2.373	0.319	9.72 × 10 <sup>-14</sup>	10.73	5.74-20.03
Smoking status (Ex vs. Never)	0.147	0.106	0.166	1.158	0.941-1.425
Smoking status (Current vs. Never)	1.062	0.105	5.47 × 10 <sup>-24</sup>	2.892	2.353-3.553
Alcohol dependence (1 = present)	1.565	0.087	9.33 × 10 <sup>-72</sup>	4.784	4.031-5.678
Any alcoholic liver disease, K70.0-K70.9 (1 = present)	1.969	0.099	9.41 × 10 <sup>-89</sup>	7.166	5.907-8.694
<i>Multivariate analysis</i>					
Alcohol intake (log <sub>10</sub> grams per day)	1.452	0.324	7.25 × 10 <sup>-6</sup>	4.274	2.266-8.061
Alcohol dependence (1 = present)	1.337	0.091	2.77 × 10 <sup>-49</sup>	3.807	3.188-4.547
Smoking status (Ex vs. Never)	0.179	0.106	0.091	1.196	0.972-1.472
Smoking status (Current vs. Never)	0.951	0.106	2.29 × 10 <sup>-19</sup>	2.588	2.104-3.183

Note: Results in the upper section (univariate associations) are not adjusted for the effects of the other factors listed, while the results in the lower section (multivariate analysis) estimate the independent effects of intake, dependence, and smoking (adjusted for each other).

For deaths due to circulatory diseases, many of the liver function tests showed positive (higher result = higher risk) associations. These included the liver enzymes alkaline phosphatase, AST (but not ALT) and GGT, direct (conjugated) bilirubin and globulins. Albumin showed a negative association. In addition, the renal tests urea and cystatin C showed significant associations, though in opposite directions, and higher values for both apolipoprotein B and LDL cholesterol were associated with lower risk. The hematology tests associated with cardiovascular deaths were similar to those identified for cancer deaths, size of erythrocytes, and related cells in the blood.

For deaths from all other causes except liver disease, the liver function and renal tests were significantly associated with risk, and in addition, there were associations with IGF-1, C-reactive protein, apolipoprotein B and both LDL and HDL cholesterol, calcium, vitamin D, SHBG, and testosterone (in men). The hematology tests showing significant association with other-cause deaths included the erythrocyte size-related ones mentioned previously, and also the red and white cell (total, monocyte, and neutrophil) counts.

## DISCUSSION

As expected, the high and persistent alcohol intake which defined the excessive drinker group was associated with increased mortality compared to other UK Biobank participants. Nevertheless, many of the people in this category do survive into old age, and apart from an excess of liver disease, the causes of death are

similar to those for other participants. Within the excessive-drinking group, risk factors with substantial effects on mortality have been identified; firstly alcohol dependence (and to a lesser extent harmful use without documented dependence) and secondly liver disease (either as a documented clinical diagnosis or inferred from abnormality in biochemical liver function tests). Smoking, which is common among the excessive drinkers, also affects mortality within this group.

## Mortality associated with excessive drinking

All-cause mortality risk was approximately doubled in UK Biobank participants who reported long-term very high alcohol intake, compared to all other participants. HRs were similar in the men and women despite the different cutoffs for excessive drinking, supporting the decision to use 80g/day for men and 50g/day for women.

Inspection of the proportions for underlying or primary causes of death, coded as ICD-10 diagnoses, showed that cancers and circulatory diseases were the most common categories in both the excessive drinkers and all other participants (see Figure 2, panel A). Survival analysis by reported cause of death (Figure 2, panel B) showed HRs significantly above 1 for most groups of causes and with (except for liver disease and mental conditions) confidence intervals which included the all-cause mortality HR estimate of 2.0. Although excessive drinkers have poorer survival (HR > 1), the distribution of causes of death other than liver disease is similar to that for the rest of the population.

**TABLE 3** Associations between alcohol use disorders (ICD-10 F10 diagnoses, “mental and behavioral disorders due to use of alcohol”), and risk of mortality from any cause and by major cause-of-death categories, in excessive drinkers without a diagnosis of F10.2, dependence.

	HR	95% CI	p-value
<i>Any cause</i>			
Dependence F10.2	4.78	4.03–5.68	$9.33 \times 10^{-72}$
Any F10 (but not dependence)	2.66	2.20–3.22	$9.39 \times 10^{-24}$
Intoxication F10.0 (but not dependence)	2.36	1.63–3.43	$6.17 \times 10^{-6}$
Harmful use F10.1 (but not dependence)	2.62	2.14–3.22	$2.25 \times 10^{-20}$
Withdrawal F10.3 or F10.4 (but not dependence)	5.11	3.11–8.40	$1.25 \times 10^{-10}$
Unspecified F10.9 (but not dependence)	19.86	7.40–53.3	$2.90 \times 10^{-9}$
<i>Any liver (not HCC)</i>			
Dependence F10.2	20.66	11.87–35.9	$8.41 \times 10^{-27}$
Any F10 (but not dependence)	9.24	4.14–20.7	$5.91 \times 10^{-8}$
Intoxication F10.0 (but not dependence)	0.05	0.00–1.47 $\times 10^4$	0.638
Harmful use F10.1 (but not dependence)	11.48	5.14–25.7	$2.72 \times 10^{-9}$
Withdrawal F10.3 or F10.4 (but not dependence)	16.17	3.79–69.0	$1.70 \times 10^{-4}$
Unspecified F10.9 (but not dependence)	0.05	0.00–4.16 $\times 10^{41}$	0.953
<i>Any cancer</i>			
Dependence F10.2	1.84	1.24–2.74	0.0026
Any F10 (but not dependence)	1.63	1.16–2.31	0.0052
Intoxication F10.0 (but not dependence)	1.51	0.75–3.05	0.251
Harmful use F10.1 (but not dependence)	1.73	1.20–2.50	0.0032
Withdrawal F10.3 or F10.4 (but not dependence)	3.08	1.15–8.26	0.026
Unspecified F10.9 (but not dependence)	0.05	0.00–1.25 $\times 10^{11}$	0.837
<i>Any CVD</i>			
Dependence F10.2	3.66	2.48–5.39	$6.60 \times 10^{-11}$
Any F10 (but not dependence)	2.52	1.70–3.76	$5.19 \times 10^{-6}$
Intoxication F10.0 (but not dependence)	1.69	0.69–4.13	0.249
Harmful use F10.1 (but not dependence)	2.78	1.84–4.21	$1.22 \times 10^{-6}$
Withdrawal F10.3 or F10.4 (but not dependence)	1.28	0.18–9.15	0.806
Unspecified F10.9 (but not dependence)	0.05	0.00–7.76 $\times 10^{16}$	0.888
<i>Other (not CA, CVD, LIVER)</i>			
Dependence F10.2	7.59	5.83–9.88	$2.28 \times 10^{-51}$
Any F10 (but not dependence)	3.86	2.82–5.29	$4.47 \times 10^{-17}$
Intoxication F10.0 (but not dependence)	4.55	2.72–7.60	$7.06 \times 10^{-9}$
Harmful use F10.1 (but not dependence)	3.11	2.19–4.41	$2.19 \times 10^{-10}$
Withdrawal F10.3 or F10.4 (but not dependence)	9.72	4.97–19.0	$3.03 \times 10^{-11}$
Unspecified F10.9 (but not dependence)	73.21	26.79–200	$5.69 \times 10^{-17}$

Note: The rows for dependence are included for comparison.

Abbreviations: CA, cancers; CI, confidence intervals; CVD, cardiovascular diseases; HCC, hepatocellular carcinoma; HR, hazard ratio.

Smoking, which is more common among the excessive drinkers than among the other participants, accounts for part of the mortality difference between these groups. Although mortality is higher in the excessive drinkers, not all of this increase is directly attributable to alcohol; part is due to other characteristics of the excessive drinker group. Most large-scale studies on alcohol-associated mortality have accounted for smoking in their data analysis, so comparisons between our HR estimates and previous

ones should take this into account (relevant information is shown in [Table 1](#)).

### Risk factors for mortality among excessive drinkers

Although survival curves appear to diverge by age 60 ([Figure 1](#)), around three-quarters of the male excessive drinkers are projected to



TABLE 4 Risk factors affecting sex-adjusted mortality from any liver disease (ICD-10 codes K70 to K77) in excessive drinkers.

	Beta	SE	p-value	HR	95% CI
<i>Univariate associations</i>					
Body mass index (kg/m <sup>2</sup> )	-0.030	0.033	0.363	0.970	0.909–1.036
Waist/Hip Ratio (%)	0.058	0.021	0.0065	1.059	1.016–1.104
Diabetes (self-report at baseline)	0.695	0.408	0.089	2.004	0.900–4.461
Mean Systolic Blood Pressure	-0.007	0.008	0.387	0.993	0.978–1.009
Mean Diastolic Blood Pressure	-0.008	0.014	0.589	0.992	0.966–1.020
Tea (cups per day)	-0.178	0.067	0.0074	0.837	0.734–0.953
Coffee (cups per day)	-0.148	0.083	0.073	0.862	0.733–1.014
Alcohol intake (log <sub>10</sub> grams per day)	5.063	0.979	2.34 × 10 <sup>-7</sup>	158.0	23.18–1077
Smoking status (Ex vs. Never)	-0.301	0.450	0.503	0.740	0.306–1.787
Smoking status (Current vs. Never)	1.312	0.397	9.51 × 10 <sup>-4</sup>	3.712	1.705–8.080
Alcohol dependence (1 = present)	3.028	0.283	8.41 × 10 <sup>-27</sup>	20.66	11.87–35.94
<i>Multivariate analysis</i>					
Alcohol intake (log <sub>10</sub> grams per day)	2.704	1.014	0.0077	14.94	2.047–108.9
Alcohol dependence (1 = present)	2.649	0.297	4.63 × 10 <sup>-19</sup>	14.14	7.903–23.31
Smoking status (Ex vs. Never)	-0.167	0.451	0.711	0.846	0.350–2.047
Smoking status (Current vs. Never)	0.989	401	0.014	2.687	1.225–5.896

Note: Results in the upper section (univariate associations) are not adjusted for the effects of the other factors listed, while the results in the lower section (multivariate analysis) estimate the independent effects of intake, dependence, and smoking (adjusted for each other).

live to age 78 and of the female excessive drinkers, to 81. There is substantial variation in mortality within the excessive drinking group, and we have identified multiple factors associated with differences in risk.

Conventional risk factors such as obesity and blood pressures were not good predictors of mortality in the excessive drinkers. This may be a matter of power (numbers and length of follow-up). Given the association between obesity and liver disease, including alcohol-associated liver disease, the negative association between BMI and mortality and the comparatively weak association between WHR and mortality are surprising. The lack of a significant protective effect of coffee intake on liver disease mortality is also unexpected but is probably due to lack of power.

As can be seen from Figures S1 and S2, the effects of alcohol dependence and alcohol-associated liver disease are greater than those of excessive drinking alone on survival. The importance of alcohol dependence rather than quantitative alcohol intake supports conclusions from previous studies (Dawson, 2000; Roerecke & Rehm, 2013; Whitfield et al., 2018), in which mortality associations with symptom count for alcohol dependence, or with alcohol dependence diagnosis, were more significant than those with the participants' reported alcohol intake. Alcohol dependence and high alcohol intake are strongly associated but have at least some differences in their causes, as shown by the genetic correlation between them being significantly less than 1 (Mallard et al., 2021; Whitfield et al., 2004). In this analysis of mortality affecting excessive drinkers, the presence of a recorded diagnosis of alcohol dependence had a substantial and detrimental association with survival which applied across the major groupings of causes of death (except for cancers, for which  $p = 0.055$ ).

Our results cannot answer the question of how alcohol dependence (as distinct from high alcohol intake) leads to or is associated with increased mortality. One obvious possibility is that those who are dependent consume more alcohol, but our multivariate analysis including both dependence and intake does not support this. Another hypothesis is that those with dependence are likely to have poorer social support than people who drink excessively without diagnosed dependence. Alcohol dependence is likely to co-exist with other substance use disorders or psychiatric conditions, and possibly with despair and feelings of being unable to control events, but the biological link between these and mortality is unclear.

Many biochemical and metabolic factors are known to be affected by alcohol intake (Whitfield et al., 2013), and several of these, particularly liver enzymes, are associated with mortality in the general population (Rahmani et al., 2019). Although it is reasonable to suppose that abnormal liver function tests in excessive drinkers without known liver disease are in fact an indication of liver damage and will be associated with a poorer prognosis, there is little published information to substantiate this. Here, we show that measures of liver damage (alkaline phosphatase, AST, GGT), and hepatic excretory and synthetic function (direct bilirubin, albumin) significantly predict deaths from any cause (Table S4), from cancers, cardiovascular disease (Table S7), and from liver disease (Table S5). Having results in the top quintile for alkaline phosphatase, AST or GGT is associated with a more than twofold risk for all-cause mortality compared to those in the lowest quintile for excessive drinkers (see Figure S3). However, mortality was not associated with ALT except for deaths ascribed to liver disease, and the AST/ALT ratio offered no predictive advantage over AST alone.

Direct bilirubin was associated with mortality, but total and indirect bilirubin were not. The probable explanation is that the “signal” (direct bilirubin being associated with mortality) is obscured by “noise” from variation in indirect bilirubin (which is not associated) when total bilirubin is tested as the predictor variable. Indirect or unconjugated bilirubin, mainly reflecting red cell turnover, makes up about four-fifths of the total bilirubin in both the overall UK Biobank population and in the excessive drinkers. Direct bilirubin reflects defective excretion after conjugation of bilirubin in the liver and is therefore a more sensitive index of minor or early alcohol-associated liver dysfunction.

Among the excessive drinkers in UK Biobank, liver function tests and presence of liver disease are associated with causes of death not obviously involving the liver, particularly cardiovascular disease. A study in Sweden showed that alcohol-associated liver disease was associated with significantly (>fourfold) increased all-cause mortality, with >40% of these deaths being liver-related (Hagstrom et al., 2021). The association between liver function tests and all-cause or cardiovascular mortality is well documented for the general population (Kunutsor et al., 2014, 2015; Rahmani et al., 2019), consistent with reports associating nonalcoholic liver disease or liver enzymes with cardiovascular disease risk (Francque et al., 2016; Pazoki et al., 2021).

Several measures related to erythrocyte size, including red cell count, mean cell volume, red cell distribution width, and reticulocyte and spherical cell size, were strongly associated with mortality (larger cells = higher risk) in the excessive drinkers. Examination of the correlation matrix, and factor analysis of these tests (results not shown), suggested that all except red cell distribution width were associated with each other and presumably with variation in erythrocyte maturation and/or red cell membrane characteristics. Erythrocyte size (MCV) has long been recognized as being increased by high alcohol intake, and a small prospective study in patients attending a hospital emergency department (Conigrave et al., 1993) showed increased rates of alcohol-associated illness including liver disease or gastrointestinal bleeding in men in the top quintile for MCV. Association between erythrocyte size and mortality including mortality from primary liver cancer has also been reported (Yoon et al., 2016) in the general population. Red cell distribution width has been shown to be associated with mortality, but most reports are on patients with renal disease (Roumeliotis et al., 2020) or on acute mortality after hospital admission (Su et al., 2014; Zurauskaite et al., 2018). It is currently unknown how variation in erythrocyte characteristics in excessive drinkers (or indeed in others) is associated with variation in mortality.

Other test results associated with all-cause mortality include markers of renal function. Both urea and creatinine showed inverse associations (higher result = lower risk) with mortality. It is possible that the association with urea is due to impairment of liver function, as urea is synthesized in the liver, but this does not apply to creatinine. It is possible that the associations for these two tests are due to them acting to some extent as markers of protein intake (urea) and muscle mass (creatinine). The associations for cystatin C,

another measure of glomerular filtration rate, are positive (higher result = higher risk). Cystatin C is derived from nucleated cells, is cleared from the blood by the kidneys, and is less subject to the non-renal sources of variation affecting urea or creatinine. Therefore, mortality in excessive drinkers may be associated with both decreased renal function and poor nutritional status.

Several other tests showed significant associations with mortality which were consistent with those reported for the general population. C-reactive protein reflects chronic inflammation and predicts all-cause and cardiovascular mortality (Emerging Risk Factors et al., 2010), and the similar association in excessive drinkers is to be expected. Lower vitamin D results were associated with higher mortality, again as expected from previous studies (Schottker et al., 2014). The associations for IGF-1, SHBG, and testosterone, although strong and consistent with at least some previous reports (Andreassen et al., 2009; Gyawali et al., 2019), do not have ready explanations.

Lipid risk factors such as apolipoproteins and lipoprotein cholesterol fractions had associations with mortality which were unlike those expected for the general population. Higher levels of apolipoprotein B and LDL cholesterol were associated with lower mortality from all causes, from cardiovascular diseases, and from liver diseases, and the association was in the same direction for cancers.

## Limitations

The nature of the data used for this analysis imposes some limitations. Only those who survived to age 40 were eligible for participation in the UK Biobank, so alcohol-associated mortality earlier in life could not be assessed. The conclusions may not be applicable to non-UK populations, although risk factor information can probably be generalized to other economically advanced societies. Only a small proportion of participants had died by the cutoff date used; this does not appear to lead to insufficient power because the starting number was large but the causes of death may change over time as the average age of the cohort increases. Some of those who did not meet both the current and 10 years previously criteria for excessive drinking would have been drinking at hazardous levels, or may have done so previously. This will tend to diminish rather than increase the mortality differences between the excessive drinkers and others and it will not have affected the identification of factors influencing risk within the excessive drinker group. The requirements that the excessive drinker group should have reported high intake at the time of assessment, and similar or greater intake 10 years previously, mean that many of them would have alcohol dependence if assessed by widely used psychiatric criteria. Our analysis used documented hospital diagnoses and it should be recognized that this is the basis of the identification of dependence or harmful use as a risk factor for mortality. Diagnoses may be incomplete, with disease being present but not recorded during life, and causes of death listed on death certificates can be inaccurate. In relation to the two risk factors of

diagnosed alcohol dependence and alcohol-associated liver disease, it is possible that these overlap because identification of alcohol dependence or other alcohol use disorders may have led to diagnosis of alcohol-associated liver disease or vice versa.

Overall, the strengths afforded by such a large unselected cohort outweigh the limitations and make it possible to address questions about the natural history of high alcohol intake in ways which have not previously been possible.

## Clinical and research implications

Clinically, identification and early intervention for excessive drinkers with alcohol dependence and/or alcohol-associated liver damage could divert at least some of them toward abstinence, and there is evidence (Subhani et al., 2021) that feedback about liver damage can motivate patients to reduce alcohol intake. For research directions, alcohol-associated liver disease risk in excessive drinkers is known to be affected by genetic variation (Schwantes-An et al., 2020), and larger studies should provide additional loci, define likely pathways, and lead to investigation of possible associations between polygenic risk scores for liver disease and mortality. Similarly, identification of causes of alcohol dependence, distinct from those affecting alcohol intake, would allow testing of these against the mortality data. The role of alcohol in changing erythrocyte and erythrocyte precursor size and membrane characteristics, and how these affect mortality, also deserves further investigation.

## AUTHOR CONTRIBUTIONS

JBW, DS, and TRM involved in conception and design of the work, and acquisition of data. JBW involved in analysis and interpretation of data. JBW, DS, and TRM involved in drafting the work or revising it critically for important intellectual content and final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## CONFLICT OF INTEREST

TRM has conducted clinical research with AbbVie, Genfit, Gilead, and Merck, but none of these are related to this manuscript.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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## APPENDIX

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