**SYNERGISTIC INTERACTION BETWEEN BODY MASS INDEX AND ALCOHOL AND THE RISK OF CHRONIC LIVER DISEASE**

**A PROSPECTIVE COHORT STUDY NESTED WITHIN THE UK COLLABORATIVE TRIAL OF OVARIAN CANCER SCREENING (UKCTOCS)**

**ABSTRACT**

**Objective** To investigate the relationship between alcohol consumption, body mass index (BMI) and chronic liver disease (CLD), and examine the interaction between alcohol and BMI on the incidence of CLD.

**Design** Prospective cohort study

**Setting** Women recruited to the UKCTOCS trial between 2001 and 2005

**Participants** ~~109,742~~ 109,481women recruited to UKCTOCS from England were followed up for an average of ~~9.2~~ 5.1 years. Participants were divided into 3 BMI groups (normal, overweight, obese) and 4 alcohol consumption groups (none, <1-15, 15-20 and ≥21 units/week), to generate 12 groups representing combinations of BMI and alcohol groups.

**Main outcome measures** Hazard ratios (HR) for first presentation of an event related to CLD (liver-related event, LRE) was identified from HES inpatient and outpatient episodes, cancer registrations and death certificates.

**Results** ~~615 (0.56%)~~ 354 (0.32%) participants experienced an LRE. Increasing BMI was associated with increased risk of LRE: the HRs adjusted for age and alcohol consumption compared to normal BMI were 1.46 (95% CI; 1.13-1.90) ~~1.46 (95% CI; 1.20-1.77)~~ and 2.27 (95% CI; 1.73-2.99) ~~2.40 (95% CI; 1.96-2.93)~~ in the overweight and obese groups, respectively. A J-shaped relationship was observed between alcohol consumption and LRE, with the lowest risk in moderate drinkers (<1-15 units/week). Consuming no alcohol was associated with increased risk of LRE (HR adjusted for age and BMI 1.43 (95% CI; 1.12-1.81) ~~1.54 (95% CI; 1.30-1.83)~~), as was drinking 16-20 and ≥21 units weekly (adjusted HRs 1.42 (95% CI; 0.81-2.49) and 2.59 (95% CI; 1.45-4.65) ~~1.32 (95% CI; 0.85-2.05) and 2.01 (95% CI; 1.22-3.32)~~ respectively). Presence of two risk factors resulted in a higher risk than presence of a single risk factor.

After adjustment for factors associated with the metabolic syndrome, the HR of an LRE in obese women consuming ≥21 units/week was 5.25 (95% CI; 1.65-16.71) ~~5.3 (95% CI; 2.16-12.99)~~ compared to 1.86 (95% CI; 1.30-2.66) ~~2.17 (95% CI; 1.67-2.83)~~ in the obese only group and 2.29 (95% CI; 0.84-6.28) ~~1.73 (95% CI; 0.71-4.23)~~ in those with normal BMI consuming ≥21 units/week. This suggests a supra-additive effect of alcohol and obesity, supported by a synergy index of 2.1 (0.5-8.3). Adjustment for features of the metabolic syndrome resulted in a reduction in HR associated with the combination of elevated BMI and alcohol consumption suggesting that these factors contribute to the risks associated with BMI but do not fully account for the elevated risk.

**Conclusion** Greater than normal BMI and alcohol consumption are independent risk factors for CLD, with evidence of a supra-additive interaction between the two when present at high levels.

**Key words: chronic liver disease, body mass index, alcohol, UKCTOCS**

**INTRODUCTION**

Chronic liver disease is the 5th commonest cause of death in the UK, and the only major cause of mortality and morbidity that is increasing. Above normal body mass index (BMI) and alcohol consumption are major causes of liver disease, although the influence of BMI on the risk of liver disease in women is not conclusive. [1](#_ENREF_1), [2](#_ENREF_2) Further, the interaction between alcohol and BMI and risk of liver disease is not well understood. The rising levels of liver disease, and the high prevalence of excess alcohol consumption coupled with the epidemic of obesity in the Western world demonstrate the need to further understand the roles of alcohol and BMI and their interaction in chronic liver disease.

In a large cohort of women we investigated the incidence of chronic liver disease and its relationship to alcohol and BMI, and examined the interaction between these two risk factors.

**METHODS**

**Study population.** Between April 2001 and October 2005, 202,638 post-menopausal women aged between 50 and 74 were recruited through 13 regional trial centres in England, Wales and Northern Ireland into the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[3](#_ENREF_3) Participants completed questionnaires at recruitment (including self-reported height and weight) and at postal follow-up 3.5 years post randomisation (questions included weekly alcohol consumption, smoking status and presence of certain medical conditions). Socioeconomic status was estimated for each participant in England using the Index of Multiple Deprivation (IMD).[4](#_ENREF_4)

**Exposures**. The exposures of interest were BMI and weekly alcohol consumption. Participants self-reported height and weight on the recruitment questionnaire, and BMI was calculated (BMI (kgm-2) = weight (kg) / (height (m))2). As there are no existing population estimates for the range of BMI a pragmatic approach was adopted to selecting patients with plausible BMI values. Participants who recorded a height outside the range 140-210cm, or a weight outside the range 25-200kg, or where the BMI was outside the range 16-65 kgm-2 were excluded. The World Health Organisation’s definitions for BMI are: healthy weight (<25 kgm-2), overweight (25-<30 kgm-2) and obese (≥30 kgm-2). At follow up, participants were asked to estimate their weekly alcohol consumption as the number of drinks consumed per week according to the responses: none, less than 1, 1-3, 4-6, 7-10, 11-15, 16-20 or ≥ 21 drinks, assuming one drink is a glass of wine, half a pint of cider or a measure of spirits. These measures are equivalent to one standard UK unit of alcohol.

**Follow up.** All participants are followed through ‘flagging’ with the NHS Information Centre for Health and Social Care in England and Wales, and with the Central Services Agency and Cancer Registry in Northern Ireland who provided data on cancer registrations and deaths, with diagnosis/cause of death coded according to the International Classification of Diseases, version 10 (ICD-10). 99.98% of participants were successfully flagged. In addition, for women resident in England, hospital inpatient and outpatient episode data for 2001-10 was available through linkage to the Hospital Episodes Statistics (HES) database. Each HES record reports a main diagnosis and up to 13 further diagnoses and each death record reports the primary death code and additional diagnoses recorded on the death certificate.

**Outcome.** We defined a diagnosis of liver disease as first presentation with any of the following ICD-10 codes related to chronic liver disease and cirrhosis: K70 (alcoholic liver disease), K73 (chronic hepatitis), K74 (fibrosis and cirrhosis) and K76 (other diseases of liver, including fat) and codes relating to sequelae of decompensated liver disease: I85 (oesophageal varices), Z944 (liver transplant) and C22.0 (hepatocellular carcinoma). Inclusion of K76 widened the search for liver disease beyond cirrhosis to include fatty liver disease. In addition, death certificates were searched for any mention of alcoholic liver disease or fatty liver.

The main outcome measure was hazard ratio of first liver-related event (LRE) – defined as first presentation of either a hospital admission, outpatient appointment, cancer registration with, or death from an ICD-10 code of interest, or mention of alcoholic liver disease or fatty liver on the death certificate. Hazard ratios were calculated for all groups relative to the event rate observed in participants with a normal BMI and alcohol consumption <1-15 units/week.

*Statistical analysis*

The analysis was limited to participants resident in England as hospital admission data was only available for these women.

Standard descriptive statistics were used to describe variables. Incidence rates of all-cause mortality or first liver-related event were calculated using person-years of follow-up as the denominators, for each BMI group, each alcohol group and each BMI/alcohol combination. For each participant, person-years of follow-up were accrued from date of randomisation to the UKCTOCS trial until censor (February 1, 2013), date of first presentation with LRE, or death from any other cause.

Cox proportional hazards models were used to calculate HRs of all-cause mortality or first LRE in three categories of BMI (<25, 25-<30 and ≥30 kgm-2) using normal BMI as the reference. Similar analysis was performed with alcohol categories of none, <1-15, 16-21 and ≥21 units/week, with <1-15 units/week as the reference. The proportional hazards models were adjusted for age and BMI or alcohol as appropriate.

A univariate model (the “unadjusted model”) was also produced, and then adjusted for other risk factors (deprivation, smoking, age and alcohol or BMI) (the ”partially adjusted model”), then for factors associated with the metabolic syndrome (hypertension, hypercholesterolemia, heart disease, diabetes) and finally a “fully adjusted” model with all these covariates (data not shown – see appendix 1).

HRs were also calculated for nine BMI and alcohol combinations using the normal BMI/moderate drinkers category as the reference and adjusted as before.

Unadjusted and fully adjusted models (adjusted for age, smoking, deprivation and metabolic syndrome factors) were also produced (data not shown – see appendix 2).

The proportional hazards assumption was checked by examining the log minus log plot. All analyses were performed using SPSS (version 19, SPSS Inc, Chicago, IL, USA) and STATA statistical software (StataCorp 2007. Release 10. College Station, TX, USA: StataCorp LP).

To investigate any super-additive effect due to the interaction of BMI and alcohol, the synergy indices in the Cox models were calculated, with high BMI defined as ≥30kgm-2 and high alcohol as ≥21 units/week.

**RESULTS**

*Cohort*

202,638 women were recruited to UKCTOCS. Of the 157,996 resident in England, 48,254 were excluded (1,885 for implausible or no recorded BMI, 45,047 failure to return a questionnaire, 1,322 no answer to the alcohol consumption question). The final analysis included 109,742 women (appendix 3)

*Baseline characteristics*

Baseline characteristics of participants are shown in Table 1. Overall, 97.1% of the participants were white. Smoking was reported in 36% of respondents. 66% were overweight (37.3%) or obese (18.7%). 22.9% reported drinking no alcohol and 1.6% reported drinking more than 21 units per week. Increasing BMI correlated with the proportion of women drinking no alcohol, the proportion drinking 21 units per week or more, and the proportion reporting hypertension, heart disease, hypercholesterolemia and diabetes. A history of liver disease did not form part of the questionnaire.

615 (0.056%) women had a first presentation with a liver-related event over a mean follow up of 9.2 years, equivalent to 0.6 first events per 1000 person years (2.98 first events per 1000 women over 5 years). There were 3,150 deaths from any cause. As the alcohol question was asked at the follow up questionnaire, analysis will start from the questionnaire date. Of the 615 events, 261 occurred prior to returning the follow up questionnaire. These participants were excluded from further analysis. The analysis group therefore comprises 109,742 – 261 = 109,481 participants. When the questionnaire date is used as the date from which follow up begins, the mean follow up period is 5.1 years. There were therefore 354 events in the analysis cohort. There were 3,121 deaths from any cause in this cohort.

*BMI and risk of liver-related events and all-cause mortality*

Rates of LRE and all-cause mortality increased with rising BMI. Using a univariate model, the HRs for LRE were significantly higher in both overweight (1.46, 95% CI; 1.13-1.90) ~~(1.46; 95% CI 1.20-1.77)~~ and obese (2.27, 95% CI; 1.73-2.99) ~~(2.40; 95% CI 1.96-2.93)~~ categories compared to the normal BMI group (Table 2 and Figure 1). However the HRs for all-cause mortality, compared to normal BMI, were insignificantly lower for overweight, and significantly higher (1.20, 95% CI; 1.09-1.31) ~~(HR=1.10; 95% CI 1.09-1.11)~~ for obesity.

*Alcohol consumption and risk of liver-related events and all-cause mortality*

Crude rates of LRE and all-cause mortality both demonstrated a J-shaped relationship with alcohol consumption (LREs were lowest in the group drinking <1-15 units weekly and all-cause mortality was lowest in the group drinking 16-20 units weekly). When age and BMI were adjusted for, the J-shaped relationships between events and alcohol consumption were preserved, with lowest hazard ratios in the <1-15 units/week group. This indicates that alcohol is an independent risk factor for LRE and all-cause mortality, with moderate alcohol consumption providing protection compared to abstinence. (Table 2 and Figure 2).

*Interaction between alcohol and BMI and risk of liver-related events*

Participants were grouped according to BMI and alcohol combinations. Table 3 shows the rates of liver-related events and all-cause mortality for participants with normal BMI, overweight and obesity, according to alcohol consumption. A multivariate model adjusted for age, deprivation and smoking shows that the lowest risk is in moderate drinkers (<1–15 units/week) with normal weight (<25kgm-2), and compared to this group, abstinence or drinking >16 units/week (with a normal weight) increases the risk of LRE (Table 4).

Higher BMI (and moderate alcohol consumption) increases the risk of LRE. Overweight increases risk by 30% ~~41%~~, and obesity increases risk of LRE by 97% ~~118%~~, whereas higher alcohol consumption (>21 units/week) results in an increased HR of 2.16 ~~1.85~~, suggesting that ALCOHOL ~~BMI~~ is the greater risk for LRE.

Higher BMI and abstinence increases risk of LRE further, as does the combination of higher BMI and greater alcohol consumption. The highest risk of LRE was found in those who are obese and drink more than 21 units weekly – HR is 3.55 ~~3.66~~. This risk is higher than the moderate drinkers with high BMI (HR 1.97) ~~(HR 2.18)~~ and higher than the heavy drinkers with normal weight (HR 2.16) ~~(HR 1.85)~~.

After adjustment for confounding for factors associated with the metabolic syndrome the pattern of risk remains the same. However, the hazard associated with drinking heavily and obesity increases to 5.25 ~~5.30~~, indicating a supra-additive effect (Table 4 and Figure 3) suggesting that the contribution to risk attributable to BMI is not entirely accounted for by hypertension, hypercholesterolemia or diabetes, but may be attributable to fatty liver disease.

~~(~~**~~In drinkers~~**~~, event rate is greater with higher BMI (normal to obese) and with greater alcohol consumption (1-15 compared to 21+). Further, when the lowest and highest alcohol drinking groups (1-15 and 21+) are compared, both the absolute risk (0.36 and 0.89 events per 1000 person years) and the relative risk (2.47 and 3.45) increases with a higher BMI from normal to obese~~.

In those who drink alcohol, the event rate increases with increasing alcohol consumption, and in all categories of drinkers the event rate is higher in the obese compared to the normal BMI groups.

Using the methodology of Anderson to calculate synergy indices, there was evidence of a super-additive effect of BMI and alcohol after adjustment for hypertension, hypercholesterolaemia and diabetes, (factors associated with the metabolic syndrome) (synergy index = 2.1 (0.5-8.3)). The synergy index in the univariate (unadjusted) model was 1.9 (0.5-7.1). There was no super-additive effect demonstrated in the model “partially adjusted” for deprivation, smoking and age or in the fully adjusted model that incorporated these factors and metabolic risk factors.

Other covariates also demonstrated independent association with liver-related events. In the fully adjusted Cox model, variables with significant HRs were; smoking (HR 1.53, 95% CI 1.29-1.82), highest IMD tertile (HR 1.48, 95% CI 1.19-1.84), heart disease (HR 1.48, 95% CI 1.12-1.97), and diabetes (HR 2.28, 95% CI 1.76-2.94) (appendix 4) suggesting that each of these factors contributes independently to the risk of liver disease.

**DISCUSSION**

**Principal findings**

The most striking finding of this study is the level of liver disease attributable to overweight/obesity in middle-aged women. While the association between alcohol consumption and liver disease is widely recognized, the association between obesity and liver disease is not widely recognized and strategies for preventing and detecting liver disease should be developed accommodating these findings.

This study shows that in women aged 50-74, those who are overweight or obese have an increased risk of liver disease. Women who drink moderate amounts of alcohol are at the lowest risk of liver disease, compared to those who drink more alcohol or those who abstain. ~~Surprisingly, of the two risk factors, BMI presented~~ Although BMI presents a significant risk, alcohol still appears to present the greater risk. For example, compared to the baseline group (normal BMI or moderate alcohol), obesity is associated with a 127% ~~140%~~ increase in risk whereas drinking ≥21 units/week increases risk by 159% ~~101%~~. Abstinence is associated with a higher risk than being overweight. It is possible that some abstainers had previously been heavy drinkers and had become abstinent because they were aware of the risks of heavy drinking.

When combinations of risk are considered, compared to a baseline category (normal BMI and moderate alcohol) higher alcohol consumption (to ≥21 units) confers a greater risk than higher BMI (to ≥30).. The presence of two risk factors is generally more hazardous than having a single risk factor.

After adjustment for confounding due to metabolic risk factors, the hazard ratios attributable to BMI and alcohol consumption decreased, suggesting that these factors may be contributing to the risk of liver disease associated with greater than normal BMI. It is biologically plausible that diabetes, hypercholesterolaemia and hypertension may contribute to liver disease over and above that caused by fatty liver disease and alcoholic liver toxicity. The corollary is that obesity can cause liver morbidity and mortality in the absence of the metabolic syndrome, providing evidence that case ascertainment cannot be restricted to those overweight or obese patients with features of the metabolic syndrome. In this model, a supra-additive effect on risk was demonstrated in the presence of obesity and consumption of alcohol ≥21 units/week.

**Strengths and limitations**

This was a large study with a relatively long follow up period. Data were available for smoking, deprivation and co-morbidities. Clinical outcome data were collected from three independent data sources (HES, cancer registry, deaths), which enhanced case-finding, further strengthened by the availability of both inpatient and outpatient data from the HES database. Rather than use only cirrhosis ICD-10 codes, we selected codes that represented a clinically relevant group of diseases related to CLD, including both codes for CLD and those relating to the consequences of decompensated liver disease. This selection was designed to maximize the ability to detect liver disease because liver disease can sometimes be difficult to identify until a decompensation event has occurred. By including such events in the search, the ‘pick up’ rate of liver disease in the study population was enhanced.

Limitations of the study include reliance on self-reporting to document alcohol consumption, co-morbidities, height and weight. As discussed, a pragmatic approach was taken to exclude BMI values considered to be implausible. This study included only postmenopausal women aged 50-74 with 97% of the cohort being white. Volunteers for prevention or screening trials tend to be healthier than the overall population, due to the ‘healthy volunteer effect’ (HVE). [5](#_ENREF_5) The UKCTOCS study design aimed to ensure that participants were representative of the general population. [6](#_ENREF_6) Participants were not allowed to self-refer as it is thought that the HVE is largely related to socioeconomic status and that these more ‘health conscious’ individuals are more likely to participate in trials. However, there was evidence of a HVE on both overall and cause-specific mortality, which again may have an effect on the generalizability of findings. [4](#_ENREF_4)

We cannot exclude the possibility of bias due to exclusion of participants who did not answer the alcohol question. These participants were slightly older (median age 62), but with a similar spread of BMI values and proportions of comorbidities to the analysis group.

Viral hepatitis, although an important cause of liver disease, does not in itself signify liver disease, and viral hepatitis codes were not included as an outcome in this study. The prevalence of viral hepatitis however may help to assess the representativeness of the group to the general population. Chronic hepatitis C and chronic hepatitis B were recorded in 20 and 6 participants respectively, equivalent to a study population prevalence of 0.02% and 0.005% respectively. The prevalence of chronic hepatitis C in England and Wales has been estimated at 0.53%. The lower prevalence found in this study population may be representative of this population, i.e. white females aged 50-74 with a relatively high socioeconomic status. 9 of the 20 participants with chronic hepatitis C and 1 of the 6 participants with chronic hepatitis B also incurred a first presentation of a code of interest.

Sensitivity analysis comparing HRs for liver-related events according to BMI groups and alcohol groups, censoring at 3 years, showed changes in HRs of 2-7% for BMI and 2-20% for alcohol groups (data not shown – appendix 5). The largest discrepancy was in the ≥21units/week group, where the number of events was smallest.

**Other studies**

The present study highlights the interaction between BMI and alcohol consumption. The National Health and Nutritional Examination Survey used data from 11,465 US participants and reported a cirrhosis rate of 0.59 per 1000 person-years, similar to our study, with increasing risk of event with increasing BMI.[7](#_ENREF_7) Although a strong association between overweight / obesity and cirrhosis was seen in abstainers, there was only a weak association in drinkers of up to 0.3 drinks a day, and no association in drinkers of >0.3 drinks / day. A Scottish prospective study found that liver disease was associated with increasing BMI in men, but no significant association was observed in 10,216 women of which 35% were overweight and 14% obese.[2](#_ENREF_2) Further analysis of the males found the lowest risk of LRE in the abstainers with normal BMI and the risk increased with higher levels of alcohol consumption, with increased BMI and with both increased alcohol and BMI. This is in contrast to our study where although risk increased with increased BMI, a clear U-shaped relationship was seen between risk of LRE and alcohol consumption in all BMI groups. Interestingly there were no events in the Scottish obese abstainers while 13% of events in our study were in this group.[8](#_ENREF_8) The UK based Million Women Study with shorter average follow-up period of 6.2 years reported an incidence of first hospital admission with cirrhosis, or death from cirrhosis of 1.2 per 1000 women over 5 years. Increased BMI was associated with increased risk of event, and the highest risk was seen in obese drinkers of ≥150g/week (HR 6.53 compared to those with normal BMI drinking <70 g alcohol/week). However the authors did not report the risk in non-drinkers by BMI and found no evidence of a synergistic interaction between alcohol and BMI, possibly due to the shorter follow-up and younger average age of the participants in their study.[1](#_ENREF_1) The magnitude of risk in obese heavy drinkers may be attributable to the higher levels of alcohol consumption reported in the Million Women Study compared to the UKCTOCS cohort.

A prospective cohort study in men and women with 12 year follow up analysed risk of alcohol-induced liver disease and alcohol-induced cirrhosis. The nadir was in those self-reporting 1-6 drinks per week, with a steep increase in relative risk above this level. In this study, the J-shaped relationship, with an increase in risk in abstainers was seen in men only[9](#_ENREF_9).

**Implications**

Compared to other studies our results suggest a substantial influence of both above normal BMI and alcohol on risk of liver disease. In addition we found a supra-additive effect when both risks were present suggesting a synergistic interaction between alcohol and fat in causing liver disease. Liver disease often remains asymptomatic until cirrhosis has developed, with clinical consequences including hepatocellular carcinoma and sequeale of portal hypertension including oesphageal varices. Identification of people at risk of these events at an early stage of the natural history of the disease would allow targeted risk modification and more efficient use of resources. Much is made of the risks associated with heavy alcohol consumption but these data emphasize the importance of disseminating awareness of the risks of liver disease associated with overweight/obesity, particularly in light of the growing prevalence of overweight and obesity throughout the world [10](#_ENREF_10). Public health policy and health education should take these facts into account.

**Summary**

In summary this study shows that above-normal BMI and high alcohol intake are independent risk factors for liver disease. Conditions associated with the metabolic syndrome may contribute to the risk due to BMI but overweight and obesity in the absence of the metabolic syndrome confers significant risk of liver disease. There is evidence of an interaction between alcohol and BMI resulting in a supra-additive effect at the high extremes of BMI and alcohol consumption. Strategies for detecting liver disease and public health strategy should recognize the importance of BMI as well as alcohol when confronting the growing burden of liver disease.

**Table 1.** Baseline characteristics and number of first events according to BMI category and in all participants

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristic | BMI category (kgm-2) | | | All participants | Using questionnaire as start date |
| <25 | 25 - <30 | ≥30 |
| Number (%) | 48,694 (44.0) | 40,566 (37.3) | 20,482 (18.7) | 109,742 | 109,481 |
| Median age (years) | 60.0 | 61.0 | 60.0 | 60.0 | 60.0 |
| Smoker – data available (%)  Missing | 14,774 (30.3)  6,150 | 12,657 (31.2)  5,396 | 6.650 (32.5)  2,799 | 34,081 (35.7)  14,345 | 33,996 (35.7)  14,295 |
| Hypertension (%) | 10,962 (22.5) | 14,024 (34.6) | 9,889 (48.3) | 34,875 (31.8) | 34,777 (31.8) |
| Heart disease (%) | 2,006 (4.1) | 2,512 (6.2) | 1,707 (8.3) | 6,225 (5.7) | 6,199 (5.7) |
| Hypercholesterolemia (%) | 9,322 (19.1) | 10,792 (26.6) | 6,448 (31.5) | 26,562 (24.2) | 26,479 (24.2) |
| Diabetes (%) | 962 (2.0) | 2,022 (5.0) | 2,724 (13.3) | 5,708 (5.2) | 5,661 (5.2) |
| Mean IMD (SD) | 17.2 (13.1) | 18.8 (14.1) | 21.3 (15.2) | 18.5 (14.0) | 18.5 (14.0) |
| Alcohol consumption (units/week) |  |  |  |  |  |
| None | 9,453 | 9,265 | 6,402 | 25,120 | 25,028 |
| <1 – 15 | 36,558 | 29,395 | 13,370 | 79,323 | 79,163 |
| 16 – 20 | 1,802 | 1,294 | 450 | 3,546 | 3,540 |
| ≥21 | 881 | 612 | 260 | 1,753 | 1,750 |
| First events | | | | |  |
| Alcohol consumption (units/week) |  |  |  |  |  |
| None | 50 | 72 | 79 | 201 | 109 |
| <1 – 15 | 121 | 146 | 110 | 377 | 217 |
| 16 – 20 | 11 | 7 | 3 | 21 | 15 |
| ≥21 | 5 | 6 | 5 | 16 | 13 |
| Total | 187 | 231 | 197 | 615 | 354 |

**Table 2.** Rates of all-cause mortality and first liver-related events, and hazard ratios of all-cause mortality and first liver-related event, according to BMI category and according to alcohol category

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | Event rate (per 1000 person years) | | Hazard ratio (95% confidence intervals)\* | |
| All-cause mortality | First event | All-cause mortality | First event |
| BMI category (kgm-2) | <25 | ~~2.94~~  5.30 | ~~0.41~~  0.45 | 1  (reference) | 1  (reference) |
| 25 - <30 | ~~2.98~~  5.39 | ~~0.61~~  0.65 | ~~0.95~~  ~~(0.88-1.03)~~  0.95  (0.88-1.03) | ~~1.46~~  ~~(1.20-1.77)~~  1.46  (1.13-1.90) |
| ≥30 | ~~3.65~~  6.60 | ~~1.04~~  1.05 | ~~1.10~~  ~~(1.09-1.11)~~  1.20  (1.09-1.31) | ~~2.40~~  ~~(1.96-2.93)~~  2.27  (1.73-2.99) |
| Alcohol category (units/week) | None | ~~4.46~~  8.06 | ~~0.86~~  0.86 | ~~1.45~~  ~~(1.35-1.57)~~  1.43  (1.32-1.54) | ~~1.54~~  ~~(1.30-1.83)~~  1.43  (1.12-1.81) |
| <1 – 15 | ~~2.69~~  4.87 | ~~0.51~~  0.54 | 1  (reference) | 1  (reference) |
| 16 – 20 | ~~2.34~~  4.18 | ~~0.63~~  0.81 | ~~1.04~~  ~~(0.83-1.30)~~  1.04  (0.83-1.31) | ~~1.32~~  ~~(0.85-2.05)~~  1.42  (0.81-2.49) |
| ≥21 | ~~2.91~~  5.27 | ~~0.97~~  1.43 | ~~1.36~~  ~~(1.02-1.81)~~  1.37  (1.03-1.83) | ~~2.01~~  ~~(1.22-3.32)~~  2.59  (1.45-4.65) |

\* adjusted for age and for BMI or alcohol category as appropriate

**Table 3.** Rates of all-cause mortality and first liver-related events according to combinations of BMI and alcohol consumption

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | First event rate (per 1000 person years) | | | |
|  | Alcohol (units/week) | | | |
| BMI group  (kgm-2) | None | <1 – 15 | 16 – 20 | ≥21 |
| All-cause mortality | | | |
| <25 | ~~4.42~~  8.00 | ~~2.59~~  4.68 | ~~2.19~~  3.97 | ~~2.89~~  5.23 |
| <25 - <30 | ~~4.20~~  7.56 | ~~2.62~~  4.76 | ~~2.63~~  4.72 | ~~2.60~~  4.69 |
| ≥30 | ~~4.90~~  8.90 | ~~3.10~~  5.62 | ~~2.13~~  3.43 | ~~3.72~~  6.76 |
|  | First event | | | |
| <25 | ~~0.57~~  0.52 | ~~0.36~~  0.50 | ~~0.65~~  0.75 | ~~0.60~~  1.53 |
| <25 - <30 | ~~0.84~~  0.81 | ~~0.53~~  0.65 | ~~0.57~~  0.89 | ~~1.04~~  1.56 |
| ≥30 | ~~1.34~~  1.43 | ~~0.89~~  0.97 | ~~0.71~~  0.86 | ~~2.07~~  3.01 |

**Table 4.** Hazard ratio of first liver-related event according to different BMI and alcohol combinations

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Hazard ratio (95% confidence intervals)  Adjusted for age, smoking, deprivation | | | | Hazard ratio (95% confidence intervals)  Adjusted for hypertension, heart disease, hypercholesterolemia, diabetes | | | |
| BMI category  (kgm-2) | Alcohol category (units/week) | | | | | | | |
| None | <1 – 15 | 16 – 20 | ≥21 | None | <1 – 15 | 16-20 | ≥21 |
| <25 | ~~1.52~~  ~~(1.07-2.15)~~  1.31  (0.70-1.83) | 1  (reference) | ~~1.70~~  ~~(0.86-3.35)~~  1.12  (0.41-3.08) | ~~1.85~~  ~~(0.75-4.53)~~  2.16  (0.79-5.94) | ~~1.54~~  ~~(1.11-2.14)~~  1.17  (0.73-1.88) | 1  (reference) | ~~1.88~~  ~~(1.02-3.49)~~  1.70  (0.74-3.92) | ~~1.73~~  ~~(0.71-4.23)~~  2.29  (0.84-6.28) |
| 25 - <30 | ~~2.00~~  ~~(1.46-2.75)~~  1.76  (1.16-2.65) | ~~1.41~~  ~~(1.09-1.82)~~  1.30  (0.94-1.18) | ~~1.72~~  ~~(0.80-3.70)~~  1.81  (0.73-4.50) | ~~3.14~~  ~~(1.38-7.16)~~  3.82  (1.54-9.48) | ~~2.10~~  ~~(1.56-2.81)~~  1.79  (1.20-2.67) | ~~1.43~~  ~~(1.12-1.82)~~  1.34  (0.98-1.84) | ~~1.60~~  ~~(0.75-3.43)~~  1.88  (0.76-4.64) | ~~2.89~~  ~~(1.27-6.57)~~  3.93  (1.59-9.74) |
| ≥30 | ~~3.69~~  ~~(2.74-4.96)~~  3.07  (2.08-4.52) | ~~2.18~~  ~~(1.65-2.88)~~  1.97  (1.38-2.81) | ~~2.09~~  ~~(0.66-6.60)~~  2.03  (0.50-8.30) | ~~3.66~~  ~~(1.15-11.46)~~  3.55  (0.82-14.79) | ~~2.95~~  ~~(2.19-3.97)~~  2.76  (1.86-4.09) | ~~2.17~~  ~~(1.67-2.83)~~  1.86  (1.30-2.66) | ~~1.83~~  ~~(0.58-5.75)~~  2.03  (0.50-2.89) | ~~5.30~~  ~~(2.16-12.99)~~  5.25  (1.65-16.71) |

**Figure 1**. Liver-related event rate according to BMI category

**Figure 2.** Liver-related event rate according to alcohol consumption category

**Figure 3.** Hazard ratio of first liver-related event according to different BMI and alcohol combinations

Adjusted for age, smoking, deprivation

Adjusted for hypertension, heart disease, hypercholesterolemia, diabetes

BMI <25 kgm-2

BMI 25-<30 kgm-2

BMI ≥30 kgm-2

Reference

**Appendix 1**

Hazard ratio of first liver-related event according to BMI and according to alcohol consumption, adjusted for various covariates

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | Hazard ratio (95% confidence intervals) | | | | |
| Unadjusted | Adjusted for alcohol or BMI | Adjusted for age, smoking, deprivation and alcohol or BMI | Adjusted for hypertension, hypercholesterolemia, heart disease, diabetes | Adjusted for age, smoking, deprivation and alcohol or BMI, and hypertension, hypercholesterolemia, heart disease, diabetes |
| BMI category (kgm-2) | <25 | 1  (reference) | 1  (reference) | 1  (reference) | 1  (reference) | 1  (reference) |
| 25 - <30 | ~~1.48~~  ~~(1.22-1.80)~~  1.47  (1.14-1.90) | ~~1.46~~  ~~(1.20-1.77)~~  1.46  (1.13-1.89) | ~~1.37~~  ~~(1.11-1.68)~~  1.39  (1.06-1.81) | ~~1.40~~  ~~(1.15-1.70)~~  1.38  (1.07-1.79) | ~~1.30~~  ~~(1.06-1.60)~~  1.32  (1.01-1.73) |
| ≥30 | ~~2.51~~  ~~(2.06-3.07)~~  2.35  (1.79-1.08) | ~~2.40~~  ~~(1.96-2.93)~~  2.27  (1.73-2.99) | ~~2.23~~  ~~(1.80-2.77)~~  2.17  (1.64-2.87) | ~~2.10~~  ~~(1.70-2.60)~~  2.01  (1.52-2.67) | ~~1.90~~  ~~(1.52-2.38)~~  1.89  (1.41-2.54) |
| Alcohol category (units/week) | None | ~~1.69~~  ~~(1.43-2.01)~~  1.55  (1.22-1.96) | ~~1.54~~  ~~(1.30-1.83)~~  1.43  (1.13-1.81) | ~~1.54~~  ~~(1.28-1.86)~~  1.35  (1.05-1.72) | ~~1.51~~  ~~(1.27-1.80)~~  1.40  (1.10-1.78) | ~~1.44~~  ~~(1.20-1.74)~~  1.27  (0.99-1.63) |
| <1 – 15 | 1  (reference) | 1  (reference) | 1  (reference) | 1  (reference) | 1  (reference) |
| 16 – 20 | ~~1.24~~  ~~(0.80-1.93)~~  1.36  (0.78-2.39) | ~~1.32~~  ~~(0.85-2.05)~~  1.42  (0.81-2.48) | ~~1.34~~  ~~(0.84-2.14)~~  1.22  (0.66-2.25) | ~~1.30~~  ~~(0.84-2.01)~~  1.42  (0.81-2.49) | ~~1.38~~  ~~(0.64-2.19)~~  1.25  (0.68-2.30) |
| ≥21 | ~~1.92~~  ~~(1.16-3.16)~~  2.55  (1.42-4.55) | ~~2.01~~  ~~(1.22-3.32)~~  2.58  (1.46-4.62) | ~~1.95~~  ~~(1.14-3.33)~~  2.35  (1.28-4.33) | ~~1.97~~  ~~(1.20-3.25)~~  2.61  (1.46-4.67) | ~~1.96~~  ~~(1.14-3.36)~~  2.37  (1.29-4.36) |

**Appendix 2.**

Hazard ratio of first liver-related event according to various BMI/alcohol combinations

a) unadjusted

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Hazard ratio (95% confidence intervals) | | | |
| BMI category (kgm-2) | Alcohol category (units/week) | | | |
| None | <1 – 15 | 16 - 20 | ≥21 |
| <25 | ~~1.61~~  ~~(1.56-2.23)~~  1.23  (0.77-1.96) | 1 | ~~1.84~~  ~~(0.99-3.42)~~  1.66  (0.72-3.12) | ~~1.71~~  ~~(0.70-4.19)~~  2.27  (0.83-6.20) |
| 25 - <30 | ~~2.36~~  ~~(1.76-3.16)~~  2.01  (1.35-2.99) | ~~1.50~~  ~~(1.18-1.91)~~  1.42  (1.03-1.94) | ~~1.63~~  ~~(0.76-3.49)~~  1.92  (0.77-4.74) | ~~2.95~~  ~~(1.30-6.70)~~  4.04  (1.63-10.00) |
| ≥30 | ~~3.76~~  ~~(2.83-4.99)~~  3.42  (2.34-4.98) | ~~2.49~~  ~~(1.93-3.23)~~  2.11  (1.49-2.98) | ~~2.02~~  ~~(0.64-6.34)~~  2.28  (0.55-9.07) | ~~5.85~~  ~~(2.39-14.30)~~  5.80  (1.83-18.39) |

b) adjusted for age, smoking, deprivation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Hazard ratio (95% confidence intervals) | | | |
| BMI category (kgm-2) | Alcohol category (units/week) | | | |
| None | <1 – 15 | 16 - 20 | ≥21 |
| <25 | ~~1.52~~  ~~(1.07-2.15)~~  1.31  (0.70-1.83) | 1 | ~~1.70~~  ~~(0.86-3.35)~~  1.23  (0.41-3.08) | ~~1.85~~  ~~(0.75-4.53)~~  2.16  (0.79-5.94) |
| 25 - <30 | ~~2.00~~  ~~(1.46-2.75)~~  1.76  (1.16-2.65) | ~~1.41~~  ~~(1.09-1.82)~~  1.30  (0.94-1.80) | ~~1.72~~  ~~(0.80-3.70)~~  1.81  (0.73-4.50) | ~~3.14~~  ~~(1.38-7.16)~~  3.82  (1.54-9.48) |
| ≥30 | ~~3.69~~  ~~(2.74-4.96)~~  3.07  (2.08-4.52) | ~~2.18~~  ~~(1.65-2.88)~~  1.97  (1.38-2.81) | ~~2.09~~  ~~(0.66-6.60)~~  2.03  (0.50-8.30) | ~~3.66~~  ~~(1.15-11.46)~~  3.55  (0.87-14.48) |

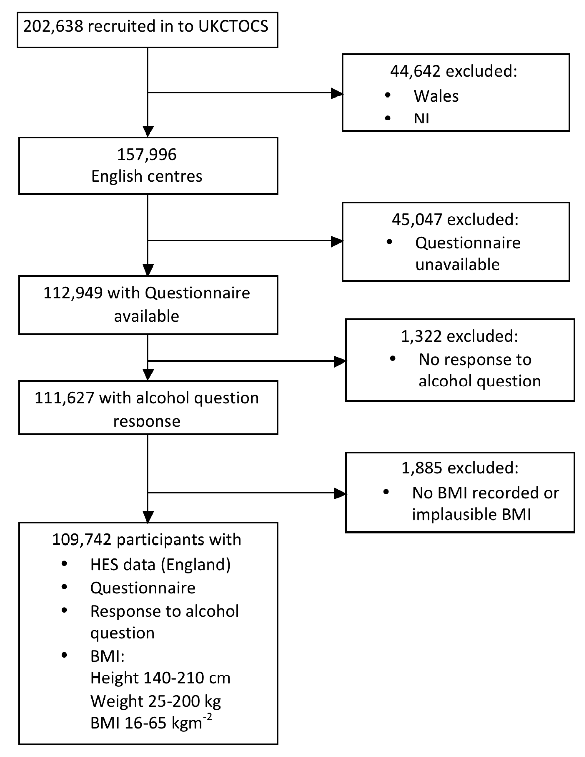
c) adjusted for hypertension, heart disease, hypercholesterolemia, diabetes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Hazard ratio (95% confidence intervals) | | | |
| BMI category (kgm-2) | Alcohol category (units/week) | | | |
| None | <1 – 15 | 16 - 20 | ≥21 |
| <25 | ~~1.54~~  ~~(1.11-2.14)~~  1.17  (0.73-1.88) | 1  (reference) | ~~1.88~~  ~~(1.02-3.49)~~  1.70  (0.74-3.92) | ~~1.73~~  ~~(0.71-4.23)~~  2.29  (0.84-6.28) |
| 25 - <30 | ~~2.10~~  ~~(1.56-2.81)~~  1.79  (1.20-2.67) | ~~1.43~~  ~~(1.12-1.82)~~  1.34  (0.98-1.84) | ~~1.60~~  ~~(0.75-3.43)~~  1.88  (0.76-4.64) | ~~2.89~~  ~~(1.27-6.57)~~  3.93  (1.59-9.74) |
| ≥30 | ~~2.95~~  ~~(2.19-3.97)~~  2.76  (1.86-4.09) | ~~2.17~~  ~~(1.67-2.83)~~  1.86  (1.30-2.66) | ~~1.83~~  ~~(0.58-5.75)~~  2.03  (0.50-8.29) | ~~5.30~~  ~~(2.16-12.99)~~  5.25  (1.65-16.71) |

d) adjusted for adjusted for age, smoking, deprivation, hypertension, heart disease, hypercholesterolemia, diabetes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Hazard ratio (95% confidence intervals) | | | |
| BMI category (kgm-2) | Alcohol category (units/week) | | | |
| None | <1 – 15 | 16 - 20 | ≥21 |
| <25 | ~~1.47~~  ~~(1.04-2.08)~~  1.10  (0.68-1.78) | 1 | ~~1.72~~  ~~(0.87-3.40)~~  1.14  (0.42-3.13) | ~~1.83~~  ~~(0.75-4.50)~~  2.15  (0.78-5.91) |
| 25 - <30 | ~~1.80~~  ~~(1.31-2.49)~~  1.60  (1.05-2.43) | ~~1.35~~  ~~(1.05-1.75)~~  1.25  (0.90-1.73) | ~~1.69~~  ~~(0.79-3.64)~~  1.78  (0.72-4.43) | ~~3.04~~  ~~(1.33-6.94)~~  3.70  (1.49-9.19) |
| ≥30 | ~~2.90~~  ~~(2.13-3.96)~~  2.51  (1.68-3.77) | ~~1.89~~  ~~(1.42-2.52)~~  1.75  (1.21-2.52) | ~~1.89~~  ~~(0.60-5.97)~~  1.86  (0.46-7.62) | ~~3.25~~  ~~(1.03-10.26)~~  3.20  (0.78-13.09) |

Appendix 3



**Appendix 4**

Hazard ratios for first liver-related event for various characteristics in a) separate unadjusted models and b) in a fully adjusted model

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | | Hazard ratio (95% confidence intervals) | |
| Univariate | Fully adjusted\* |
| Smoking | No | 1 | 1 |
| Yes | 1.58  (1.33-1.87) | 1.53  (1.29-1.82) |
| IMD tertile | 1 | 1 | 1 |
| 2 | 1.30  (1.05-1.61) | 1.23  (0.98-1.55) |
| 3 | 1.84  (1.51-2.25) | 1.48  (1.19-1.84) |
| Hypertension | No | 1 | 1 |
| Yes | 1.37  (1.66-1.61) | 0.96  (0.79-1.17) |
| Heart disease | No | 1 | 1 |
| Yes | 2.02  (2.61) | 1.48  (1.12-1.97) |
| Hypercholesterolemia | No | 1 | 1 |
| Yes | 1.55  (1.31-1.83) | 1.20  (0.98-1.46) |
| Diabetes | No | 1 | 1 |
| Yes | 3.20  (2.56-4.00) | 2.28  (1.76-2.94) |

\* adjusted for BMI category, alcohol category, age, deprivation, smoking, hypertension, diabetes, hypercholesterolemia, heart disease as appropriate

**Appendix 5.**

Sensitivity analysis comparing hazard ratios for first liver-related event, according to BMI category and according to alcohol category (censored at 3 years)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | Number of events | | Hazard ratio (95% confidence intervals)\* | |
| Censored | Main analysis | Censored | Main analysis |
| BMI category (kgm-2) | <25 | ~~137~~  94 | ~~187~~  111 | 1  (reference) | 1  (reference) |
| 25 - <30 | ~~168~~  108 | ~~231~~  134 | ~~1.44~~  ~~(1.15-1.80)~~  1.44  (1.09-1.91) | ~~1.46~~  ~~(1.20-1.77)~~  1.46  (1.13-1.90) |
| ≥30 | ~~136~~  90 | ~~197~~  109 | ~~2.23~~  ~~(1.75-2.83)~~  1.98  (1.46-2.67) | ~~2.40~~  ~~(1.96-2.93)~~  2.27  (1.73-2.99) |
| Alcohol category (units/week) | None | ~~153~~  95 | ~~201~~  109 | ~~1.68~~  ~~(1.37-2.06)~~  1.43  (1.10-1.85) | ~~1.54~~  ~~(1.30-1.83)~~  1.43  (1.12-1.81) |
| <1 – 15 | ~~264~~  179 | ~~377~~  217 | 1  (reference) | 1  (reference) |
| 16 – 20 | ~~15~~  11 | ~~21~~  15 | ~~1.35~~  ~~(0.80-2.27)~~  1.30  (0.66-2.54) | ~~1.32~~  ~~(0.85-2.05)~~  1.42  (0.81-2.49) |
| ≥21 | ~~9~~  7 | ~~16~~  13 | ~~1.62~~  ~~(0.83-3.15)~~  1.77  (1.02-1.07) | ~~2.01~~  ~~(1.22-3.32)~~  2.59  (1.45-4.65) |

\* adjusted for age and for BMI or alcohol category as appropriate

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