Title: Characterising the risk interplay between alcohol intake and body mass index on cirrhosis morbidity

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List of abbreviations (order of appearance):

BMI, Body Mass Index; UKB, United Kingdom Biobank; CLD, Chronic Liver Disease; ICD, International Classifications of Disease; OPCS4, OPCS Classification of interventions and procedures version 4**.**

ABSTRACT:

BACKGROUND & AIMS:

It is thought that alcohol intake and BMI interact supra-additively to modulate the risk of cirrhosis; but evidence for this phenomenon is limited. We investigated the interrelationship between alcohol and BMI on the incidence of cirrhosis morbidity for participants of the United Kingdom Biobank study (UKB) study.

APPROACH & RESULTS:

The primary outcome was the cumulative incidence of cirrhosis morbidity, defined as a first-time hospital admission for cirrhosis (with non-cirrhosis mortality incorporated as a competing risk). All UKB participants without a previous hospital admission for cirrhosis were included in the analysis. We determined the ratio of the 10-year cumulative incidence in harmful drinkers versus safe drinkers according to BMI. We also calculated the excess cumulative incidence at 10 years for individuals with obesity and/or harmful alcohol compared to safe drinkers with a healthy BMI of 20-25.0 kg/m^2. 489,285 UK Biobank participants were included, with mean of 10.7 person-years follow-up. 2070 participants developed the primary outcome, equating to a crude cumulative incidence of 0.36% at 10years (95% CI:0.34-0.38). The 10-year cumulative incidence was 8.6 times higher for harmful (1.38%) versus safe drinkers (0.16%) if BMI was healthy. Conversely, it was only 3.6 times higher for obese participants (1.99% Vs 0.56%). Excess cumulative incidence was 1.22% (95% CI:0.89-1.55) for harmful drinkers with a healthy BMI, 0.40% (95% CI:0.34-0.46) for obese individuals drinking at safe levels, and 1.83%

(95% CI:1.46-2.20) for obese harmful drinkers (all compared to safe drinkers with a healthy BMI).

CONCLUSIONS:

Alcohol intake and obesity are independent risk factors for cirrhosis morbidity, but they do not interact supra-additively to modulate the cumulative incidence of this outcome.

KEY WORDS:

alcohol drinking; Liver cirrhosis; Middle Aged; Epidemiology; prognosis; risk factors; metabolic syndrome; obesity

INTRODUCTION

Chronic liver disease (CLD) is a major cause of mortality and morbidity, leading to an estimated 1.32 million deaths from cirrhosis every year. [1] In the UK and many other countries within Europe, the burden of liver disease is increasing over time.[2] Because of longstanding factors that stymie early CLD diagnosis [3,4], primary prevention initiatives – e.g minimum unit pricing and taxation of high energy content foods [5,6] –probably have the most potential to reduce this burden at present. But they require a robust understanding of the risk factors for adverse liver outcomes and their inter-relationships at a population level.

Harmful alcohol consumption and obesity have emerged as the strongest risk factors for cirrhosis incidence in population studies from Western countries. [7-10] At present, it is widely thought that these two risk factors interact supra-additively, meaning that the risk of cirrhosis for individuals with excess alcohol

and obesity is much greater than one would expect it to be if these risk factors were operating independently of one another.[7,10] Biologically, this has been interpreted as obesity priming the liver to the deleterious effect of harmful alcohol use [11], whereas statistically, it has been interpreted as the hepatotoxic effect of two bottles of wine being equivalent to four for individuals with obesity.[2]

However, previous studies investigating the alcohol-BMI risk relationship on cirrhosis exhibit numerous methodological limitations. These include: a) BMI being measured either partly or entirely on self-reported data [7,9]; b) small sample sizes, with only a very small number of liver events in persons with obesity & excess alcohol use [7,8,10]; c) Not adopting a competing risk perspective [7-10], which is crucial given that alcohol and obesity are also strong risk factors for a myriad of others adverse health conditions that cause death[12,13]; and d) focusing only on the relative risk of cirrhosis and how this varies according to alcohol and BMI (i.e. ignoring absolute risk differences, which may be more pertinent from a public-health perspective[14]).

The United Kingdom Biobank (UKB) study, which integrates a wide range of individual patient data for a cohort of half a million middle-aged people in the UK, provides an unique opportunity to investigate this question further.[15] Thus, using UKB data, our goal was to characterise the relationship between alcohol and BMI with respect to the cumulative incidence of cirrhosis morbidity.

METHODS AND METHODS

Objective

The goal of this study was to characterise the relationship between alcohol and BMI with respect to the cumulative incidence of cirrhosis morbidity.

Data source

The United Kingdom biobank (UKB) is a community cohort study of 502,492 individuals in the UK. Participants were interviewed in May 2006 to July 2010 from 22 UKB assessment centres located throughout the UK. All individuals aged 40-69 years and living within 25 miles of an assessment centre (approximately 9 million persons in total) were sent an invitation letter for the study. During the interview, participants completed a comprehensive health questionnaire, a physical examination and donated biological specimens. Follow-up data on subsequent health outcome events are supplied through record linkage to UK mortality, hospital and cancer registries. [15]

Study population

All 502,492 participants recruited to UK biobank were eligible for inclusion. However, 12,520 individuals missing data for one or more key covariates were excluded (i.e. BMI, alcohol intake, age, sex, Townsend deprivation index; diagnosis of diabetes mellitus; waist circumference, and hip circumference).

We also excluded 687 participants who had developed cirrhosis morbidity (the primary outcome event; see below) prior to UK interview. This included 579 individuals who had an in-patient hospital admission for cirrhosis prior to UKB interview. Further, we excluded 108 participants who had a cirrhosis hospital admission in the first 12 months of follow-up. These participants are likely to have already had cirrhosis morbidity at the time of UKB interview and their inclusion could lead to reverse-causality bias [16]. Thus, the final sample in our main analysis was 489,285 participants (Figure 1).

Primary outcome event

The primary outcome event was a first-time in-patient hospital admission for liver cirrhosis. Hospital admissions for cirrhosis were identified by the presence of specific International classification of Disease (ICD) & Operations/procedure codes version 4 (OPCS4) codes. We used the code set proposed previously by Ratib et al for cirrhosis (see Table S1 for more details)[17].

By this definition, there were 2006 participants with an incident hospital admission for cirrhosis in our final sample. In addition, we included a small number of participants who died from cirrhosis without a prior hospitalisation episode (n=64). For these participants, the date of death was used as a proxy for the date cirrhosis morbidity onset. Thus, the total number of participants in our final sample who developed the primary outcome event was 2070.

Follow-up

Follow-up time was commenced at the date of UKB interview, and stopped at date of cirrhosis morbidity, date of death or censor date (which ever came first). Censoring was applied at the date of hospital registry completion; 30-Jun-2020, 31-Oct-2016, and 1-Mar-2016, for participants in England, Scotland and Wales, respectively.

Measurement of BMI and alcohol intake

The primary exposure variables in this study were BMI and alcohol intake. BMI was determined from each participant's height and weight at the time of their assessment visit. Standing height was measured via the Seca202 height measure, whilst body weight was measured from the Tanita BC-418 MA body composition analyser[10]. BMI was grouped into four categories: <20 kg/m^2; 20

to<25.0 kg/m^2; 25.0 to<30; and ≥30 kg/m^2. Participants in the 20 to <25.0kg/m^2 BMI category were regarded as having a "healthy" BMI.

Information on alcohol intake was elicited through a computer-assisted touchscreen system at UKB interview. Participants were asked to report their average alcohol intake per week/month in terms of the number of: glasses of red wine (Field IDs: 1568, 4407), glasses of champagne/white wine (Field IDs: 1578, 4418), pints of beer/cider (Field IDs: 1588, 4429), measures of spirits (Field IDs: 1598, 4440), glasses of fortified wine (Field IDs: 1608, 4451), and glasses of "other" types of alcoholic drinks (Field IDs: 5364, 4462). Non-weekly and occasional drinkers were asked to report consumption in an "average month" to generate more reliable estimates for infrequent drinkers. For each participant, we calculated the average number of alcohol units consumed per week, assuming there are 2 units (16g) of pure alcohol in a pint of beer/cider; 1.5 units (12g) in a glass of red wine, champagne, white wine, fortified wine, and "other" alcoholic drink; and 1 unit (8g) in a measure of spirits. These conversions are comparable to those used in the Health Survey for England methods protocol [18]. We then categorised alcohol intake into three consumption levels adopted in UK guidelines [19]: (i) "safe" consumption, if intake <22 units per week for males and <15 units for females; (ii) "hazardous" consumption, if intake was 22-49 units per week for males, and 15-35 for females; and (iii) "harmful" consumption, if intake >50 units per week for males, and >35 units per week for females. Townsend deprivation score was categorised into quintiles, with quintile 1 and 5 corresponding to the most affluent 20% and most deprived 20%, respectively.

Statistical analysis:

Competing risks survival analysis methods were used to investigate the time to first presentation with cirrhosis morbidity. In preliminary analyses, we calculated the ten-year cumulative incidence for the total cohort, and according to BMI category, alcohol intake, Townsend deprivation quintile, age group and gender. We also calculated the ten-year cumulative incidence of non-cirrhosis mortality to provide context regarding competing health risks.

The alcohol-BMI inter-relationship was assessed in two different, but complementing, ways. Firstly, we determined the ratio of the ten-year cumulative incidence in harmful drinkers versus ten-year cumulative incidence safe drinkers – and assessed how this varied according to BMI category (if at all). Vice versa, we calculated the ratio of cumulative incidence in obese participants versus those with a healthy BMI – and determined how this varied according to alcohol intake (if at all). A Fine-Gray regression model, incorporating non-cirrhosis mortality as a competing risk, was used to ascertain whether adjustment for basic confounders altered this picture. The model included age category, BMI category, alcohol intake category, gender, and Townsend deprivation quintile, as covariates. Interaction terms between alcohol intake and BMI were also included to ascertain the inter-relationship between these two risk factors.

Secondly, we determined the alcohol-BMI inter-relationship in terms of the absolute risk of cirrhosis morbidity. We did this by calculating the excess cumulative incidence at ten years for three groups of participants; namely, participants with: 1) safe alcohol intake and obesity; 2) harmful alcohol intake and a healthy BMI; 3) harmful alcohol intake and obesity. The excess cumulative incidence was calculated by taking the 10-year cumulative incidence in each group and subtracting it from the 10-year cumulative incidence in participants

with safe alcohol intake and a healthy BMI of 20.0-25.0 kg/m^2. These estimates were also stratified according to age, gender and Townsend deprivation score.

In all analyses, cumulative incidence estimates at specific times points (e.g. 10 years) were generated non-parametrically, using the "stcomlist" command within Stata v.16. [20] Cumulative incidence curves were also determined non-parametrically using the "stcompet" command. [21]

Sensitivity analyses

Sensitivity analyses were performed to assess if our conclusions were altered by: a) modifications to our study inclusion criteria; b) the handling of competing risks; and c) stratification by genetic factors. Detailed information regarding each sensitivity analysis is provided in Appendix A.

RESULTS

Participant characteristics

In the final sample of 489,285 participants, the mean age was 57.0 years (sd:8.1) and 45.4% were male (Table 1). The mean BMI was 27.4 kg/m2 (sd:4.8), and one quarter (24.3%) were obese with a BMI exceeding 30 kg/m2. The majority of participants (76.5%) were consuming alcohol at "safe" levels. Hazardous and harmful drinking was reported for 19.7% (n=96,388) and 3.8% (n=18,755) participants, respectively. 5,249 (1.1%) were harmful drinkers who also had a BMI ≥30 kg/m2 and 21,649 (4.4%) were hazardous drinkers with a BMI≥30 kg/m2. Further in-depth data on the characteristics of the cohort are provided in Table S2.

Cumulative incidence of cirrhosis morbidity

The 489,285 participants included in this analysis were followed for a mean of 10.7 years (median: 11.1 years). There were 2070 (0.42%) participants who presented with incident cirrhosis morbidity during this follow-up period, equating to a crude incidence rate of 3.94 events per 10,000 person years (95% CI:3.77-4.11). The cumulative incidence of cirrhosis after 10 years of follow-up was 0.36%(95%CI:0.34-0.38). The cumulative incidence for the competing risk of non-cirrhosis mortality was considerably higher at 4.6% (Table 2).

Alcohol-BMI relationship

The cumulative incidence of cirrhosis morbidity increased with alcohol intake. (Table 2). The 10-year cumulative incidence was 5.0 times higher in harmful drinkers (1.51%) versus safe drinkers (0.30%). However, this ratio varied according to BMI. For example, the 10-year cumulative incidence was 8.6 times higher for harmful (1.38%) versus safe drinkers (0.16%) where BMI was healthy. Conversely, it was only 3.6 times higher for those with obesity (1.99% Vs 0.56%); Figure 2.

Equally, the cumulative incidence of cirrhosis morbidity varied strongly with BMI (Table 2). The 10-year cumulative incidence was 3.1 times higher in participants with obesity (0.65%) versus those with a healthy BMI (0.21%). However, this ratio varied strongly with alcohol intake. For example, the 10-year cumulative incidence was 3.7 times higher for individuals with obesity (0.56%) versus a healthy BMI (0.15%) if alcohol intake was at safe levels. Conversely, it was only 1.4 times higher where alcohol intake was harmful (1.99% versus Vs 1.38%); see Figure 3.

Fine-Gray regression modelling confirmed a sub-additive relationship between obesity and harmful alcohol intake for relative cumulative incidence. For

example, modelling indicated that, after controlling for differences in age, gender and deprivation, the cumulative incidence was 6.84 times higher in harmful drinkers versus safe drinkers where BMI was healthy (sHR:6.84;95%CI:5.24-8.93). Conversely, the cumulative incidence was only 3.14 times higher for harmful drinkers versus safe drinkers where BMI ≥30 kg/m2 (sHR:3.14; 95%CI:2.59-3.81) (Figure 4 and Table S3). These differences were statistically significant at $P_{interaction}=3.5X10^{-6}$.

In the total cohort and subgroup analysis, the excess cumulative incidence in obese harmful drinkers was roughly equivalent to the excess cumulative incidence in obese safe drinkers + excess cumulative incidence in harmful drinkers with a healthy BMI. (Figure 5). For example, overall, the excess cumulative incidence was 1.22% (95%CI: 0.89-1.55) for harmful drinkers with a healthy BMI, 0.40% (95%CI:0.34-0.46) for obese individuals drinking at safe levels, and 1.83% (95%CI:1.46-2.20) for obese harmful drinkers (Figure 5). Excess cumulative incidence was higher for older (Figure S1), male (Figure S2), and more deprived participants (Figures S3).

Sensitivity analyses

The alcohol-BMI relationship remained unchanged in all sensitivity analyses conducted (Tables S4-S5; Figures S4-S9).

DISCUSSION:

PRINCIPAL FINDINGS:

Cirrhosis is a prominent global health problem, causing approximately 1.3 million deaths every year world-wide.[1] The present study of 489,285 UKB participants

underlines the importance of obesity and harmful alcohol intake as independent risk factors for cirrhosis morbidity in a community setting. However, in contrast to some previous studies, we found little evidence that these two risk factors interacted supra-additively to modulate the risk of cirrhosis morbidity. On the contrary, through a relative risk lens, the association between alcohol intake and cirrhosis morbidity was actually weaker for individuals with obesity than for individuals with a healthy BMI (indicating a sub-additive relationship). From an absolute risk perspective, there was similarly no strong indication of a supra-additive alcohol-BMI relationship. For example, overall, the excess cumulative incidence in obese harmful drinkers was about equivalent to the excess cumulative incidence in obese safe drinkers plus the excess cumulative incidence in harmful drinkers with a healthy BMI (all relative to safe drinkers with a healthy BMI), suggesting an additive inter-relationship. Developing our understanding of the alcohol-BMI inter-relationship is critical for designing effective public-health interventions needed to counter rising incidence of cirrhosis in some settings. To reduce the incidence of cirrhosis morbidity, broad interventions are needed that target obesity *and* harmful alcohol intake, because, in the absence of a supra-additive relationship, a focus on mitigating one or the other (i.e. obesity or alcohol) will have only a fractional impact.

CONSISTENCY WITH PREVIOUS STUDIES

Currently, the prevailing perception is that alcohol and BMI interact supra-additively to modulate the risk of cirrhosis. [2,7,10,11,] One influential study supporting this relationship was an analysis of the Midspan cohort, which includes 9559 Scottish workers with almost thirty years of mortality follow-up data. [7] Here, participants with obesity who were drinking >15 units/week at baseline had a 16.2 (95%CI:7.22-36.4) times greater risk of dying of liver

disease versus non-drinkers with a normal/low BMI – but most strikingly, Hart et al reported that half of the excess risk in this group was attributable to a supra-additive relationship between obesity and excess alcohol intake. However, limitations of this study included that BMI was partly based on self-reported data, and that the number of outcomes in this study was relatively small (i.e. there were no liver deaths in the "obesity + no excess alcohol" participant group for instance). Also, in a systematic review of the literature, Aberg identified 15 primary studies investigating the alcohol-BMI relationship, of which 10 appeared to show evidence of supra-additivity (with respect either to cirrhosis morbidity risk or other liver disease outcomes including liver blood test values, steatosis or hepatocellular carcinoma).[10] However, the definition for supra-additivity used in this review is questionable insofar as at least one study was reported to show evidence of supra-additivity even though it did not actually perform the requisite interaction tests (e.g. Liu et al [9]). There are also other studies that appear to directly contradict a supra-additive relationship. For example, an analysis of 11,465 participants from the NHANES I survey, found that the association between obesity and cirrhosis mortality/hospitalisation was actually stronger in non-drinkers (HR:4.10; 95% CI: 1.4-11.4) versus individuals drinking >0.3 drinks per day (HR:0.80; 95% CI: 0.3-2.1).[22] More recently, Glyn-Owen et al assessed the inter-relationship between alcohol and BMI on chronic liver disease by performing a systematic review and meta-analysis on data published through to June 2020. From 16 eligible cohort studies identified, they found no evidence to support a supra-additive relationship between harmful alcohol use and obesity. [23] Our analysis is therefore consistent with this recent synthesis of the literature.

Finally, the present study only examined the inter-relationship between alcohol and BMI on the risk of cirrhosis morbidity. It is important to emphasise that our conclusions may not be generalisable to other liver-related phenotypes. In particular, previous studies have reported that alcohol and BMI interact supra-additively with respect to the risk of hepatocellular carcinoma [24,25], and also serum aminotransferases levels [26]. Our results are not necessarily in conflict with these studies.

STRENGTHS AND LIMITATIONS:

The four major strengths of this study are: 1) large sample size and hence greater statistical power to ascertain interaction effects, 2) objectively determined BMI data for all participants, 3) a focus on the cumulative incidence of cirrhosis morbidity, thus taking account of competing health risks; and 4) a focus not just on the relative risk of cirrhosis morbidity, but the absolute risk too. These strengths differentiate our study from previous attempts to characterise the alcohol-BMI inter-relationship [7-10].

However, this study has a number of limitations too. Firstly, the UKB cohort is not representative of the broader UK general population. On average, UKB participants are more likely to be female, older in age and live in less socio-economically deprived areas than non-participants.[27] There is a possibility that selection bias may have influenced our results, but we think that any such impact is likely to be modest or negligible. Second, this study is predicated on measurements of BMI and alcohol intake data collected at a single point in time. In reality, BMI and alcohol intake may change over time and our analysis did not this into account. Nevertheless, in the UK, BMI and alcohol intake are relatively stable over time for a middle-aged demographic [28,29], and so we would not

expect this issue to cause major bias. Third, the primary outcome of this study was incidence of cirrhosis morbidity as opposed to the incidence of cirrhosis per se. As a result, cases of compensated cirrhosis will not necessarily be captured in our primary outcome event. Nevertheless, our focus on the incidence of cirrhosis morbidity – i.e. severe disease stemming from cirrhosis – is arguably a more relevant endpoint from a clinical, patient and public health perspective. Our primary outcome event also allows comparability with previous studies that have investigated the risk interplay between alcohol and BMI. [7-10] Fourth, our sensitivity analysis exploring if the alcohol-BMI inter-relationship varied according to genetic factors was relatively rudimentary. Only a single polymorphism was considered (i.e. rs738409 in the *PNPLA3* gene). This analysis could be developed further in the future by employing polygenic risk scores for cirrhosis.[30] Finally, BMI is only one of a number of metabolic risk factors that influence risk of cirrhosis. In this study we did not consider metabolic risk factors that are correlated with BMI, such as type 2 diabetes, abdominal obesity or dyslipidaemia. The risk-interplay between the different components of the metabolic syndrome, and how each interacts with other risk factors to modulate the risk of incident cirrhosis is extremely complex; delineating this was beyond the scope of this study. Instead, we focused on the relationship between alcohol and BMI which has been a key topic in previous research. [7-10] Recent studies have begun to look more broadly at the interaction between alcohol intake and the different feature of metabolic syndrome [30] – but more detailed work is needed in this area.

CONCLUSION:

Alcohol intake and obesity are independent risk factors for cirrhosis morbidity; yet, in contrast to previous studies, we show that they do not interact supra-

additively to modulate the risk of cirrhosis morbidity. This finding has bearing on the design of public health interventions that are urgently needed to counter rising incidence of cirrhosis in some settings.

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FIGURE AND TABLE LEGENDS:

TABLE 1: Characteristics of final sample, according to alcohol intake and BMI.

Values are means (standard deviation in brackets) unless indicated otherwise. For units/week of alcohol, which is not normally distributed, the median is shown (with IQR in brackets).

TABLE 2: Cumulative incidence of cirrhosis morbidity and non-cirrhosis mortality after 10 years (N=489,285)

FIGURE 1: Derivation of final sample.

Key covariates refer to age, gender, townsend deprivation score, alcohol intake, BMI, Type 2 diabetes and waist-hip ratio.

FIGURE 2: Cumulative incidence of cirrhosis morbidity according to alcohol intake, stratified by BMI.

Cumulative incidence curves are generated non-parametrically used the "stcompet" user written module for Stata. The numbers displayed in the graph represent the cumulative incidence at 10 years, which were also generated non-parametrically using the "stcomlist" user written module for stata. Cumulative incidence is expressed as a percentage. Thus a cumulative incidence of 2.78 indicates that 2.78% of participants developed the primary outcome event (i.e. hospitalisation for cirrhosis morbidity) within 10 years of UK biobank interview.

FIGURE 3: Cumulative incidence of cirrhosis morbidity by BMI, stratified by alcohol intake.

Cumulative incidence curves are generated non-parametrically used the "stcompet" user written module for Stata. The numbers displayed in the graph

represent the cumulative incidence at 10 years, which were also generated non-parametrically using the "stcomlist" user written module for stata. Cumulative incidence is expressed as a percentage. Thus, a cumulative incidence of 2.78 indicates that 2.78% of participants developed the primary outcome event (i.e. hospitalisation for cirrhosis morbidity) within 10 years of UK biobank interview.

FIGURE 4: Adjusted association between A) BMI and cumulative incidence, stratified by alcohol intake; and B) alcohol intake and cumulative incidence, stratified by BMI.

Cumulative incidence refers to the cumulative incidence of cirrhosis morbidity. sdHR refers to subdistribution hazard ratio. Panel A shows that the sdHR association between BMI>30 is greater for individuals with safe alcohol intake (sdHR:3.07) versus harmful alcohol intake (sdHR: 1.41). Vice versa, panel B shows that the sdHR association between harmful alcohol intake and cirrhosis morbidity is greater for individuals with a BMI of 20-25 (6.84) versus those with BMI>30 (3.14). These differences are significant at $P=3.5 \times 10^{-6}$. All sdHR estimates are derived from a Fine-Gray regression model, including adjustment for age, sex and deprivation index (see Table S3).

FIGURE 5: Excess cumulative incidence of cirrhosis morbidity after ten years.

The excess cumulative incidence of cirrhosis morbidity for a given alcohol-BMI group is calculated by subtracting the cumulative incidence observed in that group from the cumulative incidence observed in the reference group. The reference group is participants with safe alcohol intake and healthy BMI. The dashed black line represents the sum of the cumulative incidence in groups #2 and #3 . Red lines represent 95% confidence intervals.