The combined effect of alcohol and body mass index on risk of chronic liver disease: systematic review and meta-analysis of cohort studies

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Title	The combined effect of alcohol and body mass index on risk of chronic liver disease: a systematic review and meta-analysis of cohort studies
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Conflict of interest disclosure

No conflicts of interest are declared.

Ethics approval statement

Ethical approval for this work was granted by the University of Southampton Research Ethics Committee (ID: 19594).

Patient and public involvement

Patients and the public were not involved in the design of this study. We would like to thank the participants of all the cohort studies included in this analysis.

Permission to reproduce material from other sources

The authors have permission to share the data supplied to them by other authors, for the purpose of performing this meta-analysis. This data is reproduced in supplementary material table S5.

Structured abstract

Background & Aims: Increasingly populations are both overweight/obese and consume alcohol. The risk of liver disease from the combination of these factors is unclear. We performed a systematic review and meta-analysis to address this important gap in evidence. Protocol registered with PROSPERO(CRD42016046508).

Methods: We performed electronic searches of Ovid Medline, Embase Classic + Embase, until 17th June 2020 for cohort studies of adults without pre-existing liver disease. Primary outcome was morbidity/mortality from chronic liver disease. Exposures were alcohol consumption categorised as within or above UK recommended limits (14 units/112g per week) and BMI categorised as normal, overweight or obese. Non-drinkers were excluded. A Poisson regression log-linear model was used to test for statistical interaction between alcohol and BMI and to conduct a one-stage meta-analysis.

Results: Searches identified 3,129 studies - 16 were eligible. Of these, nine cohorts (1,121,514 participants) had data available and were included in the analysis. The Poisson model showed no significant statistical interaction between alcohol consumption and BMI on risk of chronic liver disease. Compared to normal weight participants drinking alcohol within UK recommended limits, relative risk of chronic liver disease in overweight participants drinking above limits was 3.32 (95%CI 2.88 to 3.83) and relative risk in obese participants drinking above limits was 5·39 (95%CI 4.62 to 6·29).

Conclusions: This meta-analysis found the combination of alcohol consumption above recommended limits and overweight/obesity was associated with a significantly increased risk of chronic liver disease. This evidence should inform advice given to patients and risk stratification by healthcare professionals.

Key Points

- Alcohol and obesity are two of the main risk factors for chronic liver disease. A significant proportion of the population are both overweight/obese and drink above recommended limits of alcohol
- Individual studies have given inconsistent results about risk of chronic liver disease due to the combination of alcohol and overweight/obesity
- This meta-analysis demonstrates that overweight and obese patients drinking above 14 units/112g per week are at significantly increased risk of chronic liver disease
- This should be considered when advising patients, in clinical care and referral pathways and in public health policies for preventing chronic liver disease

INTRODUCTION

Global mortality from chronic liver disease is rising and it is now the 11th most common cause of death worldwide.[1] In the United Kingdom (UK), the mortality rate from liver disease has increased 400% since 1970 and it now represents the 3rd largest cause of premature mortality.[2] Alcohol consumption and obesity are leading causes of chronic liver disease.[3-5] Almost half of all global deaths from chronic liver disease are caused by alcohol-related liver disease (ALD).[6] The prevalence of obesity continues to rise, with associated Non-Alcoholic Fatty Liver Disease (NAFLD) now affecting one in four people in Western countries.[5 7]

Clustering of unhealthy behaviours is common.[8] A significant proportion of patients with liver cirrhosis are known to be multi-morbid at the time of diagnosis.[9] Those who are multi-morbid at the time of diagnosis are more likely to present with advanced disease and the presence of multi-morbidity is significantly associated with adverse outcomes.[9 10] The co-occurrence of risk factors for liver cirrhosis has been shown to increase the development and progression of liver disease. Specifically, the combination of Hepatitis C and harmful alcohol consumption significantly increases the rate of development of liver fibrosis and then progression to cirrhosis and hepatocellular carcinoma (HCC).[11] Several mechanisms for biological synergism between these risk factors have been proposed.[11] There is some evidence from individual studies of an increased risk of liver disease associated with a combination of elevated Body Mass Index (BMI) and alcohol. However, the potential biological mechanisms for this are unclear and findings from observational studies have been inconsistent.[12-15]

Understanding risk of the combination of elevated BMI and alcohol is important. Firstly, if clinicians are unaware of their patients' risk of developing liver disease they may not advise them to modify harmful behaviours and conduct targeted testing for liver disease. Secondly, if patients are unaware of the risks they are exposing themselves to, they may be less motivated to change these behaviours.[16] Behaviour modification and the early diagnosis of liver disease are important because weight loss and decreased alcohol consumption reduce progression of liver disease and early diagnosis of significant fibrosis and established cirrhosis can facilitate life-saving interventions.[2 17-19]

The interplay of alcohol and obesity on the risk of liver disease is not well understood, yet it is clear that accurately quantifying the combined risks of alcohol and obesity will empower both clinicians

and patients. To address this important gap in evidence we present a systematic review and meta-analysis that provides robust estimates for the increased risk of chronic liver disease associated with the combination of alcohol consumption and elevated BMI.

METHODS

The protocol for this systematic review and meta-analysis was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews, no. CRD42016046508). Covidence (www.covidence.org) was used by the review team for all stages of the review process.

Search Strategy

The search strategy is described in full in PROSPERO (CRD42016046508).[17] We performed electronic searches of Ovid Medline from 1946 and Embase Classic + Embase from 1947, until 17th June 2020. We manually searched clinical guidelines and reference lists of all included papers for other relevant research. Study authors were contacted where required. Search terms for liver disease were combined alternately with search terms for alcohol and obesity or BMI. Search terms are described in full in Table S1.

Inclusion criteria

Criteria for studies included in the review are described fully in the study protocol.[20] Briefly inclusion criteria were: cohort studies of adults without pre-existing liver disease, where data were collected on BMI and a quantifiable measure of alcohol consumption. Outcomes were incident morbidity or mortality due to chronic liver disease (with cirrhosis or HCC as a minimum requirement), diagnosed by any of: appropriate diagnostic imaging, histology, cancer registry, ICD code, or clinician's diagnosis.

Studies that only involved participants with a specific liver, or non-liver disease were excluded. Studies that did not adjust for Hepatitis B (HBV) or Hepatitis C (HCV) and were conducted in areas with a high (>2%) background prevalence of HBV or HCV (from published epidemiological data) were also excluded.

Study Selection

At each stage of the review process, two team members (KGO and RB) independently reviewed the studies. In cases of disagreement, the papers were discussed with neither reviewer aware of what their initial decision had been. If agreement could not be reached, a third reviewer (JP) would have made the final decision but this was not necessary.

Studies were initially screened by title and abstract, and then by full text, to determine which studies met the a priori selection criteria. We considered all cohort studies with outcome data on incidence of or mortality due to chronic liver disease (with cirrhosis or HCC as a minimum requirement), which also included quantifiable data on participants' alcohol consumption and BMI. We included studies if BMI or alcohol consumption had been measured, but data were not presented in the published paper. Where otherwise eligible studies had not presented data on BMI or alcohol consumption, or data were not in the required format for the meta-analysis, we contacted authors directly, via email, to request data. All authors were emailed a second time if no response had been received from the first contact. Where data from the same cohort was used for more than one published study that met the eligibility criteria, only one study was included.

Data extraction and risk of bias assessment

For each study included in the meta-analysis, one review team member (KGO) extracted the data using a standardised template. A second team member (RB) checked the data extraction. Any inconsistencies were resolved through discussion, with a third review team member (JP) ready to arbitrate but this was not necessary. Data collected were:

a) General study information (authors, year, country, study design, enrolment period, inclusion and exclusion criteria, measures to reduce bias, and funding source)

b) Study population details (sample and setting, participants, age, sex)

c) Exposure details (Alcohol measurement method and how recorded; BMI measurement method and how recorded; measurement of or measures taken to account for viral hepatitis)

d) Outcome details (outcome measures collected, method of ascertainment, steps taken to ensure outcome measure not present at baseline, method of follow-up, duration of follow-up, and loss to follow-up)

Quality assessment and risk of bias was assessed using the Newcastle-Ottawa Quality Assessment scale for cohort studies, using information presented in the published study and/or published protocols and methods.[21]

Data preparation

The available data and/or extra data where provided by authors, were used to cross tabulate numbers of participants in five categories of BMI and alcohol consumption. BMI categories were normal (<25), overweight (≥25 to <30) and obese (≥30) and were not ethnicity-specific. Alcohol categories were within recommended limits (>0 to 14 units/112 grams per week) and above recommended limits (>14 units/112 grams per week). The number of cases and the total number of exposed participants in each category were also entered.

Alcohol data were presented in a variety of formats and were re-categorised where necessary. We did not include participants who recorded zero alcohol consumption.

Statistical analysis

Original count data were used from all nine studies for which adequate data were available. A direct approach was used to perform a one-stage meta-analysis, estimating the relative risk from each study individually and for all studies combined. This is in contrast to the two-stage analysis, which is used where only summary statistics are available.

A Poisson regression, log linear model, was used to generate coefficients for each category of BMI and alcohol against the reference categories, which were normal weight (BMI<25) and within limits alcohol consumption (>0 to 14 units (112g)/wk). The model used random effects to account for baseline study heterogeneity and a fixed parameter to estimate the exposure effect. The model was run for each study individually, and for all studies combined in a random effects summary

analysis. The log-linear model relates the logarithmic count of cases with the factors alcohol consumption and BMI. Study (as random effect) and sample size (as offset) were entered in to the model to adjust for confounding effects. The model was run with and without an interaction term for BMI and alcohol.

Relative risks were then calculated from the exponential of the coefficients. For individual categories, RR = exp (coefficient). For combinations of categories, RR= exp (coefficient category A + coefficient cat B). The relative risks of chronic liver disease in different BMI and alcohol consumption categories, and combinations of categories, were illustrated with Forest Plots.

Sensitivity analyses (not pre-specified) were performed, to check for any undue effects from the following:

1. excluding data from the paper (Setiawan 2018) in which the alcohol consumption data was most different to the categories used in the meta-analysis
2. excluding data from the paper (Persson 2013) which was rated 'poor' in the quality assessment

The summary statistics from the Poisson model were entered in to a further analysis, using the two-stage meta-analysis technique, in order to produce conventional estimates of heterogeneity. Publication bias and small study effects were assessed by visual inspection of funnel plots and Egger's test.[22] We tested for statistical heterogeneity using I-squared.[23]

Data were analysed using STATA version 14.2.

RESULTS

The search results are summarised in Figure 1. The initial search returned 3129 papers, of which 401 were duplicates. 2,651 records were excluded by review of title and/or abstract. Full text review of 77 papers was conducted and 61 were excluded. Of the 16 eligible studies, two studies included the required data in the published paper. The further 13 eligible studies did not publish the required data for the analysis. These authors were contacted and seven responded providing the necessary data. Therefore, nine studies were included in the data analysis.

These nine studies are summarised in Table 1 (the remaining seven studies are summarised in Tables S2 and S3). The nine studies included in the data analysis had 1,121,514 participants, from nine cohorts - seven European cohorts and two from the USA. The cohorts varied in size (1458 to 477,178 participants) and gender (four were mixed, three women only and two men only). Table 2 summarises the exposures and outcomes in each of the included studies. In keeping with the inclusion criteria all studies reported BMI and alcohol as exposures and all recorded cases of cirrhosis as a minimum. Some studies also included ICD codes encompassing a broader spectrum of chronic liver disease (see table 2). Most studies also recorded cases of HCC.

Prevalence of obesity ranged from 6% to 25% and alcohol consumption above recommended limits ranged from 5% to 38%.

Table S4 shows the risk of bias assessment. Overall, six studies were rated 'good', two were 'fair' and one was 'poor'.

Table 1: Baseline data for the nine cohort studies included in the analysis

Author and year	Country	Sample & setting	Participants	Gender	Age	Ethnicity	Follow up duration‡	Follow up method	Stated primary aim of study
Aberg 2018[24]	Finland	General population cohort.	6519	44% men	≥30yrs Mean 54yrs.	No information.	Mean 11·4yrs (SD 3·3yrs)	National Hospital Discharge Register, Finnish Cancer Registry and Statistics Finland databases.	Investigate which metabolic factors predict liver disease, stratified by alcohol consumption
Carter 2019[25]	Denmark	General population cohort.	91,552	55% men	>20yrs Mean 58yrs.	White, Danish descent only.	Mean 6.8yrs.§ Range 2yrs to 11.5yrs	National Danish Patient Registry. Danish Causes of Death Registry.	To investigate the joint association of BMI and alcohol consumption with liver injury biomarkers and liver disease
Hart 2010[13]	UK	Working population cohort.	9559	Men only	Range 14-92yrs.	No information.	Median 29yrs.	NHS Central Register and Scottish Morbidity Records data.	Explore whether alcohol and obesity act together to increase the risk of liver disease
Liu 2010†± [26]	UK	Middle-aged women in England and Scotland.	748,658¥	Women only	50-64yrs. Mean age 56yrs	No information.	Mean 6.2yrs.	NHS health records for data on hospital admissions, deaths, cancer diagnoses and emigration.	Investigate association between BMI and incidence/mortality from liver cirrhosis and whether association is modified by other factors including alcohol
Persson 2013[27]	USA	American Association of Retired Persons (AARP) members	477,178	59% men	50 to 71 years	Majority were white, non-Hispanic (91%).	Median 10·5yrs.	State cancer registries (HCC). US Social Security Administration Death Master File and National Death Index Plus.	Investigate association of alcohol consumption and folate intake, independently and together, on HCC incidence and liver disease mortality
Schult 2018[28]	Sweden	General population sample.	1458	Women only	38-60yrs Mean 46·5yrs.	No information.	33yrs§	Hospital Discharge Registry and Central Bureau of Statistics.	Analyse the association of overweight with risk of liver cirrhosis
Schwartz 2013[29]	Finland	General population sample of smokers.	27,094	Men only	50-69years	No information.	22·5yrs§	Finnish Cancer Registry. Finnish Register of Causes of Death.	Assess the effect of alcohol consumption and one-carbon metabolite intake on liver cancer incidence and liver disease mortality
Setiawan 2016[30]	USA	General population cohort.	36,864	50% men	45-75yrs	Hispanic and Latino only.	Median 19·6yrs.	Cancer surveillance program for Los Angeles County. California State Cancer Registry. Linkage to state death certificates in California and the National Death Index.	Examine whether risk of incident HCC and CLD mortality differed by birth place among Hispanics and whether known risk factors could account for the differences
Trembling 2017[31]	UK	Post-menopausal women living in England.	95,126	Women only	50-74yrs	No information.	5·1yrs§	NHS information centre for health and social care in England and Wales. HES data linkage 2001-10. Death certificate data.	Investigate incidence of CLD and its relationship to BMI and alcohol, and examine the interaction between these two risk factors

† A paper published by Liu et al in 2009 also met the eligibility criteria but the data were from the same cohort of women as the 2010 paper. As per protocol, to avoid duplication of data, we assessed both papers and the 2010 paper only was included in the review and meta-analysis.
‡ Median or mean follow-up duration if stated. If not stated, calculated depending on available information as a) mid-point of possible range of follow-up durations or b) total person years of follow-up time divided by number of participants.
§ Indicates that follow-up duration has been calculated.
± A paper published by Simpson in 2019[32], identified in an update of the original search, also met the eligibility criteria. Data were from the same cohort of women as the Liu 2010 paper. The updated data from the 2019 paper had already been supplied by the Million Women study authors, therefore the paper itself was not added to the review.
¥ Does not include any data on women who reported zero alcohol consumption
UK – United Kingdom, USA – United States of America, SD – Standard Deviation, HCC – Hepatocellular carcinoma, HES – Hospital Episode Statistics.

Table 2: Exposure and outcome summary data for the nine cohort studies included in the analysis

Author and year	BMI assessment	BMI<25 N (%)	BMI 25 to <30 N (%)	BMI≥30 N (%)	Alcohol assessment	Alcohol within UK limits‡ N (%)	Alcohol above UK limits‡ N (%)	Total cases N (%)	Outcome	ICD codes used to define CLD and HCC
Aberg 2018[24]	Measured	2458 (37·7%)	2603 (39·9%)	1458 (22·4%)	Self-reported	2956 (45·3%) >0 to 16 g/day	1255 (19·3%) ≥17g/day	84 (1·3%)	CLD hospitalisation or mortality HCC incidence	ICD8/9: 570-573 ICD10: K70-K77 and C22
Carter 2019[25]	Measured	40065 43.8%	36787 40.2%	14700 16.1%	Self-reported	59136 (64.6%) 1-14 units/week	23986 (26.2%) ≥15 units/week	616 (0.6%)	CLD incidence or mortality HCC incidence or mortality	ICD8: 570-571.9, 573-573.9, 155.09-155.89, 785.19-785.39 ICD10: K70, 74.0, 74.6, 75.8, 75.9, 76.0, 76.9, C22, R18
Hart 2010[13]	Main study: self-reported Collaborative study: measured	5033 (52·7%)	4000 (41·9%)	526 (5·5%)	Self-reported	3583 (37·5%) 1-14 units/week	2621 (27·4%) ≥15 units/week	146 (1·5%)	CLD mortality HCC mortality	ICD9: 155, 570-573 ICD10: C22, K70-77
Liu 2010 § [26]	Self-reported	187980 (50·0%)ł	139441 (37·1%)ł	48743 (13·0%)ł	Self-reported	700,857 (n/a)ł <150g/week	47,801 (n/a)ł ≥150g/week	1443 (0·4%)	CLD hospitalisation or mortality	ICD10: K70, K73, K74
Persson 2013[27]	Self-reported	169047 (35·4%)	204818 (42·9%)	103313 (21·7%)	Self-reported	253178 (53·1%) <1 drink/day	110288 (23·1%) ≥1 drink/day	1165 (0·2%)	CLD mortality HCC incidence	ICD9: 571.0-571.9 ICD10: K70, K73, K74
Schult 2018[28]	Measured	974 (66·8%)	373 (25·6%)	111 (7·6%)	Structured interview	919 (63·0%) 1-16g/day	182 (12·5%) >16g/day	11 (0·8%)	CLD hospitalisation or mortality HCC hospitalisation or mortality	ICD8/9: 571.00-571.01, 571.90-99, 571C, 571F-G, 572C-E, 456.0, 456A-C, 185.0-9, 198.2-3, 155.01, 155A ICD10: K70.2-4, K71.7, K72.0-9, K74.0-6, K76.6-7, C22.0
Schwartz 2013[29]	Measured	10428 (38·5%)	12556 (46·3%)	4110 (15·2%)	Food frequency questionnaire	13777 (50·9%) <17 g/day	10294 (38·0%) ≥17 g/day	410 (1·5%)	CLD mortality HCC incidence	ICD8/9: 571 ICD10: K70-K77
Setiawan 2016[30]	Self-reported	10320 (28·0%)	17301 (46·9%)	9243 (25·1%)	Food frequency questionnaire	15109 (41·0%) <2 drinks/day	3353 (9·1%) ≥2 drinks/day	487 (1·3%)	CLD mortality HCC incidence	ICD-O3¥: C22.0, 8170-8175 ICD9: 571 ICD10: K70-K76
Trembling 2017[31]	Self-reported	42452 (44·6%)	35073 (36·9%)	17601 (18·5%)	Self-reported	68608 (72·1%) >0 to 15 units/wk	4303 (4·5%) ≥16 units/wk	325 (0·3%)	CLD incidence HCC incidence	ICD10: K70, K73, K74, K76, 185, Z94.4, C22.0

‡ Assumes 1 drink = 2 units = 16 grams of alcohol. Measurement of alcohol is either how presented in original paper, if data from original paper were used, or how presented to us, if data were provided directly by authors.
§ Updated data provided by Simpson et al 2019[32]
ł Cannot calculate percentage of all participants, as data only available for alcohol consumers
¥ International Classification of Diseases for Oncology, 3rd edition

Count data from the nine studies included in the analysis are shown cross tabulated by BMI and alcohol in table S5. The Poisson model showed no significant statistical interaction between categories of alcohol consumption and BMI, on risk of chronic liver disease. This was tested for each study independently, and for all studies combined. For all studies combined, testing for interaction between above limits alcohol consumption and overweight the coefficient was -0·07 (95%CI -0·22 to 0·08, p=0·35) and for interaction between above limits alcohol consumption and obesity the coefficient was -0·14 (95%CI -0·31 to 0·04, p=0·12). The AIC and BIC for the model were lower when interaction was removed from the model, confirming that the model was a better fit without interaction.

However, even in the absence of interaction, the risks of BMI and alcohol consumption are multiplicative, as per the properties of the log linear model. The results of sensitivity analyses performed are shown in Table S6. None showed effects which were compelling enough to require studies to be excluded from the final analysis.

The relative risks of chronic liver disease for different levels of BMI and alcohol consumption in the individual studies, and for all studies combined, are presented in Table 3. For all studies combined, compared to normal weight participants, the relative risk associated with being overweight was 1·25 (95%CI 1·16-1·35) and the relative risk associated with being obese was 2·03 (95%CI 1·87-2·21). Compared to participants drinking alcohol within recommended limits, the relative risk associated with drinking alcohol above limits was 2·65 (95%CI 2·48-2.84).

The relative risks of chronic liver disease for combinations of BMI and alcohol consumption in individual studies, and for all studies combined, are presented in Table 3, Figure 2 and Figure 3. For all studies combined, compared to normal weight participants drinking within recommended limits, the relative risk associated with the combination of overweight and consumption of alcohol above limits, was 3.32 (95%CI 2.88, 3.83). The relative risk associated with the combination of obesity and consumption of alcohol above limits was 5.39 (95%CI 4.62, 6.29).

Absolute risk of chronic liver disease (ICD codes used to define CLD in individual studies are shown in table 2), over the follow-up periods of the studies, ranged from 0.2% to 0.9% in the reference group (BMI < 25 and alcohol consumption >0 ≤ 14 units/112g per week).

Table 3: Relative risk of chronic liver disease, for each study individually and all studies combined, in participants with differing combinations of alcohol consumption and BMI. Relative risks calculated using a one-stage meta-analysis. All expressed as Risk Ratio with 95% confidence intervals.

	Normal weight	Overweight	Obese	Alcohol within limits	Alcohol above limits	Overweight and alcohol above limits	Obese and alcohol above limits
Aberg 2018	Ref	1.21 (0.67, 2.16)	1.21 (0.60, 2.46)	Ref	4.63 (2.70, 7.94)	5.58 (1.82, 17.18)	5.63 (1.62, 19.54)
Carter 2019	Ref	1.11 (0.91, 1.35)	1.76 (1.40, 2.21)	Ref	1.85 (1.56, 2.20)	2.06 (1.42, 2.97)	3.26 (2.19, 4.85)
Hart 2010	Ref	1.89 (1.29, 2.78)	3.76 (2.16, 6.52)	Ref	2.85 (1.96, 4.15)	5.41 (2.53, 11.55)	10.72 (4.25, 27.06)
Liu 2010 §	Ref	1.28 (1.13, 1.44)	2.30 (2.01, 2.63)	Ref	3.10 (2.75, 3.50)	3.95 (3.12, 5.02)	7.12 (5.51, 9.20)
Persson 2013	Ref	1.17 (0.99, 1.37)	1.99 (1.66, 2.38)	Ref	2.81 (2.45, 3.22)	3.27 (2.42, 4.42)	5.58 (4.07, 7.65)
Schult 2018 †	Ref	1.87 (0.53, 6.64)	n/a	Ref	3.25 (0.92, 11.5)	6.09 (0.48, 76.47)	n/a
Schwartz 2013	Ref	1.25 (0.99, 1.58)	1.73 (1.31, 2.29)	Ref	2.28 (1.85, 2.81)	2.86 (1.84, 4.44)	3.95 (2.42, 6.45)
Setiawan 2018	Ref	1.22 (0.89, 1.67)	1.72 (1.22, 2.42)	Ref	3.14 (2.45, 4.03)	3.83 (2.19, 6.71)	5.39 (2.98, 9.75)
Trembling 2017	Ref	1.40 (1.03, 1.90)	2.09 (1.49, 2.94)	Ref	1.79 (1.15, 2.78)	2.50 (1.19, 5.26)	3.74 (1.72, 8.16)
All studies combined	Ref	1.25 (1.16, 1.35)	2.03 (1.87, 2.21)	Ref	2.65 (2.48, 2.84)	3.32 (2.88, 3.83)	5.39 (4.62, 6.29)

Normal weight defined as BMI < 25
Overweight defined as BMI ≥25 <30
Obese defined as BMI ≥ 30
Alcohol within limits defined as >0 to 14 units/112g per week
Alcohol above limits defined as > 14 units/112g per week
§ Updated data provided by Simpson et al 2019[32]
† It was not possible to calculate relative risk of obesity from the Schult data, as there were no cases who were obese.

The two-stage meta-analysis gave a relative risk in those who were overweight and drinking above limits alcohol, compared to normal weight and drinking within limits, of 3.31 (95%CI 2.99 to 3.67). Relative risk in those who were obese and drinking above limits alcohol, compared to normal weight and drinking within limits, of 5·44 (95%CI 4.88 to 6·08).

The I^2 statistic was 67.8% (p = 0.002) for the combination of overweight and above limits and 76.6% (p<0.001) for the combination of obese and above limits. We saw consistently large joint effects of overweight/obesity and drinking above limits alcohol, but the effect sizes varied across studies.

Egger's test (p = 0.66 for overweight/above limits and p=0.60 for obese/above limits) was non-significant. On visual inspection the funnel plots for both combinations were symmetrical, indicating low chance of small study effects. For overweight/above limits there was one small study outlier.

DISCUSSION

This is the first meta-analysis to quantify the combined risk of chronic liver disease with increasing BMI and alcohol intake above recommended levels. We found significantly increased risks with a combination of risk factors. This included individuals who were drinking above recommended limits and were overweight (BMI >25 and <30).

In our analysis we did not show evidence of a statistical interaction between BMI and alcohol consumption and therefore our findings do not support biological synergism, as suggested by other authors.[13 14 33] Instead the statistical effects were multiplicative such that the risk from alcohol and increased BMI is the product of the two individual risks. This adds clarification to biological studies, which have been inconclusive about the hepatotoxic interaction between fat and alcohol.[34]

These findings are important for three reasons. Firstly, they indicate that the risks of chronic liver disease may be under-estimated for the proportion of the global population who are both overweight and drink above recommended levels of alcohol. In some areas this is a very large number of individuals - for example one quarter of the general population of England have at least two risk factors for liver disease (alcohol consumption above UK limit, BMI ≥25 or diabetes).[35]

Secondly, the results imply that a proportion of individuals at significant risk of chronic liver disease may be missed in conventional referral pathways. This may occur because they are drinking too

much alcohol to meet the criteria for NAFLD pathways, but they are not drinking enough alcohol to be considered at risk of ALD.[36-39]

This complexity is recognised in the recently proposed change in nomenclature from Non-Alcoholic Fatty Liver Disease (NAFLD) to Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD).[40 41] Moving away from a diagnosis of exclusion may support clinicians to recognise the role of alcohol in the development of liver disease in people at risk of NAFLD.[42] Our results also highlight the important reverse scenario where being overweight increases the likelihood of developing liver disease in people who also consume alcohol above recommended limits.[43] It is important to ensure that people with a combination of risk factors are correctly identified as being at increased risk of chronic liver disease, so that prevention strategies can be appropriately targeted.

Thirdly, by quantifying the complex interplay between co-factors on the development of chronic liver disease, the results contribute to our understanding of the epidemiology of chronic liver disease. For example, the most deprived individuals suffer disproportionate harm from alcohol consumption.[44 45] One hypothesis for this is that it is due to the associated suite of co-morbid conditions in more deprived populations, including obesity.[44] The results of this meta-analysis would support this hypothesis and quantify the additional risks.

This study used data from prospective cohort studies and included a total of more than one million participants. In our analysis we were able to include nine of the sixteen eligible studies identified in the systematic review. Unfortunately, the necessary data was not available from the remaining seven studies. These seven cohorts were similar in size to the included studies and followed up participants across a similar time horizon. However, they were more ethnically diverse. They included a cohort from Japan,[46] Singapore[47] and Korea.[48] The nine cohorts analysed were all western populations. This may impact the generalisability of our findings.

For seven of the nine studies in the analysis data were obtained directly from the study authors. Many of these studies had primary outcomes which were not looking at combined effects of alcohol and BMI. Therefore, the risk of publication bias and selective reporting bias is low. With the data provided, we were able to conduct a one-stage meta-analysis.[49] This provides more accurate estimates of effect size, as the original count data from each study are combined in analysis, to determine the relative risk structure. However, in the analysis it was not possible to adjust for any variables other than BMI and alcohol, as individual participant data on other variables were not

available. This reduces the risk of statistical heterogeneity due to different studies adjusting for different variables, but there may be unseen confounding effects.

The ICD codes used to measure liver disease outcomes in the included studies varied. Diagnosis of cirrhosis or HCC were the minimum requirements to meet the study inclusion criteria. However some studies included a number of additional chronic liver disease outcomes. This may explain some of the heterogeneity seen between studies. All studies apart from one included patients with HCC in their outcome data. However, as HCC is a late complication of cirrhosis and incidence of HCC is low, this should not have unduly influenced results and any effect would lead to an underestimate of risk.

The data in the included studies describing alcohol consumption was largely self-reported and categorical. We excluded participants who reported zero alcohol consumption, as this group is known to be highly heterogeneous and has been shown to include a large proportion of previously alcohol-dependent individuals.[32] This approach is consistent with other studies, and limits potential biases which might arise from factors influencing liver disease outcomes in this group.[32 50] From the available data we could also make no differentiation between moderate risk and higher risk drinkers. We were therefore limited in our ability to measure the dose response effect of alcohol on risk of chronic liver disease across BMI categories.

In conclusion, we present the first meta-analysis to test the effect of alcohol consumption and elevated BMI on risks of chronic liver disease. We have shown that a combination of risk factors significantly increases risk and that this risk increases at BMI >25 and alcohol consumption >14 units/112g per week. This evidence should inform advice given to patients and we advocate for a move towards multi-morbid risk stratification of chronic liver disease. Current UK guidelines for safe alcohol consumption may not be appropriate for overweight and obese patients.

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Figure legends:

Figure 1: PRISMA study selection flow diagram

Figure 2: Results of one-stage meta-analysis. Relative risk of chronic liver disease in participants who are overweight and drinking above recommended limits of alcohol (>14 units/112g per week), compared to those who are normal weight and drinking within recommended limits (>0 ≤ 14 units/112g per week). Box size indicates weight study contributes.

Figure 3: Results of one-stage meta-analysis. Relative risk of chronic liver disease in participants who are obese and drinking above recommended limits of alcohol (>14 units/112g per week), compared to those who are normal weight and drinking within recommended limits (>0 ≤14 units/112g per week). Box size indicates weight study contributes.

Visual abstract: Infographic conveying key messages for healthcare professionals, patients and the public

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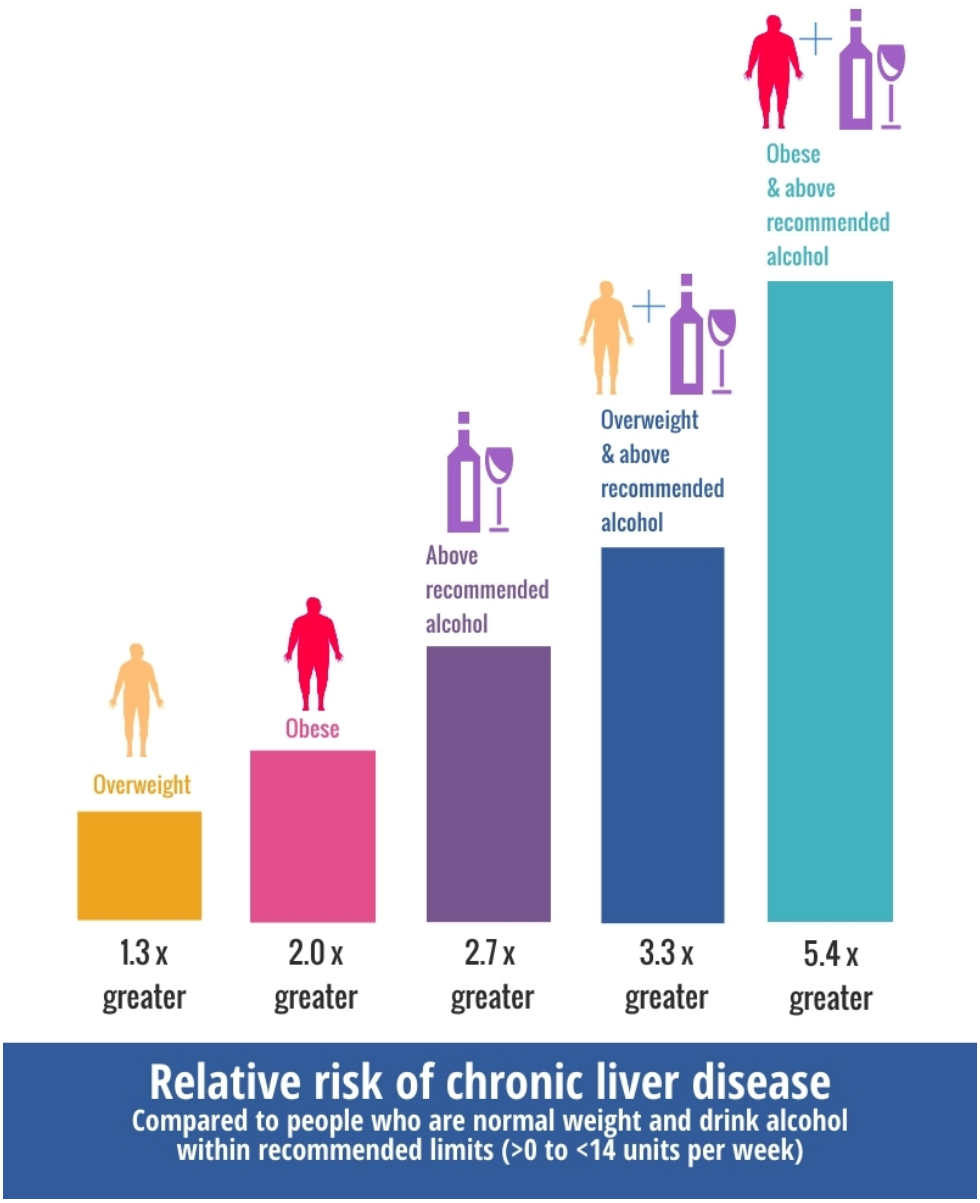

Visual Abstract

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