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# Modest alcohol consumption and risk of advanced liver fibrosis in nonalcoholic fatty liver disease: a systematic review and meta-analysis

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**Abstract**

**Background** Recent studies have suggested an association between modest alcohol consumption and a decreased risk of advanced liver fibrosis among patients with nonalcoholic fatty liver disease (NAFLD) although the results are inconsistent. The current systematic review and meta-analysis was conducted to comprehensively investigate this possible association by identifying all the relevant studies and combining their results.

**Methods** A comprehensive literature review was conducted utilizing the MEDLINE and EMBASE databases through February 2019 to identify all cross-sectional studies that compared the prevalence of advanced liver fibrosis among NAFLD patients who were modest alcohol drinkers to NAFLD patients who were non-drinkers. Effect estimates from each study were extracted and combined together using the random-effect, generic inverse variance method of DerSimonian and Laird.

**Results** A total of 6 studies with 8,936 participants fulfilled the eligibility criteria and were included in the meta-analysis. The risk of advanced liver fibrosis among patients with NAFLD who were modest alcohol drinkers was significantly lower compared to patients with NAFLD who were non-drinkers with a pooled odds ratio of 0.51 (95% confidence interval [CI] 0.35-0.75; $I^2$ 47%). The funnel plot was symmetric and was not suggestive of publication bias.

**Conclusion** A significantly lower risk of advanced liver fibrosis was observed among NAFLD patients who were modest alcohol drinkers compared to non-drinkers in this meta-analysis.

**Keywords** Hepatic steatosis, nonalcoholic steatohepatitis, alcohol, liver fibrosis, meta-analysis

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Conflict of Interest: None

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## Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide. Its estimated global prevalence is approximately 25-30% with the highest prevalence observed in the Middle East and South America [1]. Since stage of liver fibrosis is the strongest predictor for mortality in patients with NAFLD [2], interventions that can reduce the degree of liver fibrosis may also decrease mortality rate. However, there are still no medications approved for the treatment of liver fibrosis in NAFLD [3]. Few anti-fibrotic agents, such as simtuzumab and GR-MD-02, are being investigated and are currently in phase II clinical trials [4].

According to the current American Association for the Study of Liver Diseases guidance, the diagnosis of NAFLD indicates a lack of significant alcohol consumption, defined as more than 42 g of pure alcohol per day in men and more

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than 28 g of pure alcohol per day in women [3]. Significant alcohol consumption is a well-established risk factor for cirrhosis while modest alcohol consumption is not associated with a significantly increased risk of cirrhosis [5]. The effect of modest alcohol consumption on NAFLD is debatable as studies that investigated the association between modest alcohol consumption and the risk of advanced liver fibrosis have yielded inconsistent results [6-12]. This systematic review and meta-analysis was conducted to better characterize this association by comparing the prevalence of advanced liver fibrosis among NAFLD patients who were modest drinkers to NAFLD patients who were non-drinkers.

## Materials and methods

### Data sources and search strategy

We systematically searched and reviewed literature in MEDLINE and EMBASE databases starting from inception through February 2019 to identify original studies that compared the prevalence of advanced liver fibrosis between patients with NAFLD who were modest drinkers and patients with NAFLD who were non-drinkers. The search algorithms included the terms for "nonalcoholic fatty liver disease", "steatohepatitis", "alcohol consumption", "alcoholism" and "ethanol ingestion" as described in the Online Supplementary Data 1. Three authors (K.W., P.P., and P.U.) independently reviewed the titles and abstracts of the studies resulting from the search. No restrictions were applied in the systematic review. The reference lists in the full text of selected articles were reviewed to identify further relevant studies. This systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement as demonstrated in the Online Supplementary Data 2.

### Selection criteria

The eligible studies included were required to be cross-sectional studies of patients with NAFLD that compared the prevalence of advanced liver fibrosis among patients with NAFLD who were modest drinkers (generally defined as less than 28 g per day in men and less than 14 g per day in women although some variations were allowed) [13] to the prevalence of advanced liver fibrosis among patients with NAFLD who were non-drinkers. The eligible studies were required to provide odds ratio (OR) and 95% confidence interval (CI) for this comparison or enough raw data to calculate these data. We considered all articles irrespective of the study size or type of article, such as short reports or conference abstracts. In the case of multiple studies utilizing the same population or database, the most recent study or more comprehensive data set was included.

Three authors (K.W., P.P., and P.U.) independently reviewed the eligible studies; discrepancies were discussed and agreement was reached by the consensus. The modified Newcastle-Ottawa quality assessment scale was used to appraise the quality of the cross-sectional studies in 3 domains, including selection of the sample, comparability between the groups, and assessment of the outcomes [14].

### Data abstraction

The following data were extracted from each study: the citation data, the title of the study, the first author's last name, the publication year, the study design, the country where the study was conducted, the characteristics of the population, the number of the participants, methods used to quantify alcohol consumption, the definition of modest alcohol consumption, methods used to diagnose NAFLD, the methods used to diagnose advanced liver fibrosis, the adjusted effect estimates with 95%CI, and the confounding factors adjusted for in the multivariable analysis.

To ensure the accuracy, this data extraction process was independently performed by 2 investigators (K.W. and P.P.) and was reviewed by the senior investigator (P.U.).

### Statistical analysis

For the statistical analysis, we used the Cochrane Collaboration's Review Manager 5.3 software (London, United Kingdom). A P-value lower than 0.05 indicates statistical significance (except for the heterogeneity). Adjusted point estimates from each study were consolidated by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study for the pooled analysis based on its variance [15]. In light of the high probability of high between-study variance because of the different background populations and methods used to diagnose advanced liver fibrosis and definitions of modest alcohol consumption, random-effect model was chosen rather than fix-effect model. We also calculated the Cochran's Q test and $I^2$ statistic to quantify the percentage variation across the included studies due to heterogeneity. We used an $I^2$ cut-off of ≤25%, 26%-50%, 51%-75%, and >75% to represent insignificant, low, moderate and high heterogeneity, respectively [16]. We used funnel plot to assess for the presence of publication bias.

## Results

A total of 10,510 potentially eligible articles were identified using the described search strategy (3,957 from MEDLINE and 6,553 from EMBASE). After exclusion of 3,134 duplicate articles, the abstracts of 7,376 unique articles were reviewed. Seven thousand three-hundred and thirty-six manuscripts were then excluded given they were case reports, case series, correspondence items, review articles, *in vitro* studies, animal studies, or interventional studies. Forty articles met criteria for full-text review; however, 28 articles were excluded because they

did not report the outcome of interest and 5 articles were excluded because they were descriptive studies without comparative analysis. A total of 7 studies fulfilled the eligibility criteria [6-12]. However, one article was excluded since it used NAFLD fibrosis score of more than -1.455 as a cut off for advanced fibrosis [12]. We considered this cut-off to be inappropriate as it included both patients with intermediate and high probability of advanced fibrosis, instead of just high probability of advanced fibrosis. The final meta-analysis included 6 studies [6-11] with 8,936 participants. The literature retrieval, review, and selection process are shown in Fig. 1. The characteristics and quality appraisal of the included studies are presented in Table 1.

### Association between modest alcohol consumption and advanced liver fibrosis in NAFLD

The prevalence of advanced liver fibrosis among NAFLD patients who were modest drinkers was significantly lower than NAFLD patients who were non-drinkers with the pooled OR of 0.51 (95%CI 0.35-0.75). The between-study heterogeneity was low with an $I^2$ of 47%. The forest plot is shown in Fig. 2.

### Sensitivity analysis

Two sensitivity analyses were conducted. The first sensitivity analysis was conducted by including only studies that used histopathology to determine advanced liver fibrosis as histopathology is considered the gold-standard. A total of 4 studies were included [6-8,11]. The prevalence of advanced liver fibrosis among NAFLD patients who were modest drinkers was significantly lower than NAFLD patients who were non-drinkers with the pooled OR of 0.49 (95%CI 0.36-0.66). The between-study heterogeneity was negligible with an $I^2$ of 0%.

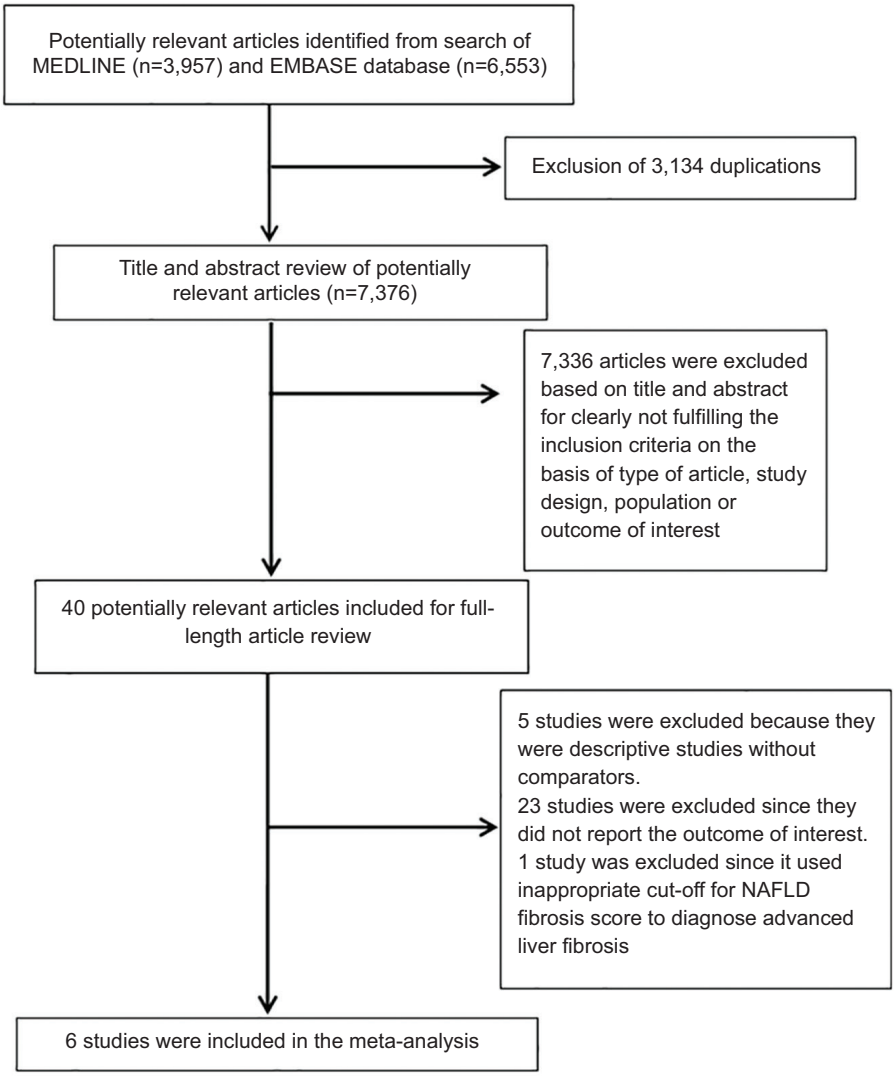


**Figure 1** Literature review process
*NAFLD, nonalcoholic fatty liver disease*

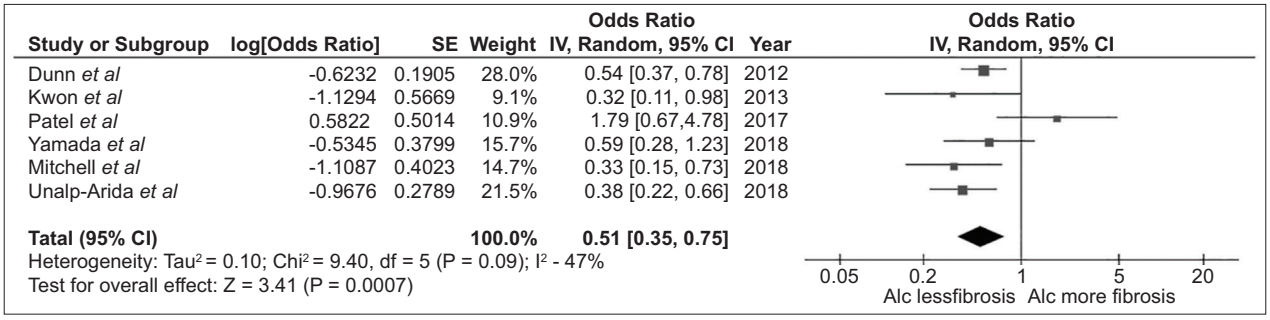


**Figure 2** Forest plot of all studies
*SE, standard error; CI, confidence interval*

**Table 1** Main characteristics of the studies included in this meta-analysis

| Study | Dunn *et al* [6] | Kwon *et al* [7] | Patel *et al* [9] |
|---|---|---|---|
| Country | United States | United States | Australia |
| Study design | Cross-sectional study | Cross-sectional study | Cross-sectional study |
| Year | 2012 | 2013 | 2017 |
| Total number of participants | 583 (331 modest alcohol drinkers and 252 non-drinkers) | 77 (52 modest alcohol drinkers and 25 non-drinkers) | 116 (70 modest alcohol drinkers and 46 non-drinkers) |
| Study participants | Participants were patients with NAFLD aged ≥21 years enrolled in one of the 2 NASH CRN studies (the NAFLD Database and the PIVENS study). Only patients who underwent liver biopsy were included | Participants were patients with histologically-confirmed NAFLD recruited from the hepatology clinic of the University of Michigan from March 2003 to November 2004 | Participants were patients with NAFLD who also had T2DM. They were recruited from the endocrine clinic of the Princess Alexandra Hospital, Brisbane, Australia and primary care practices within the Metro South Hospital and Health Services Districts from October 2015 to November 2016 |
| Definition of modest alcohol consumption | History of alcohol consumption was obtained from questionnaire. Modest drinkers were defined as currently drinking with average alcohol consumption of <20 g daily during the 2 years before entry | History of alcohol consumption was obtained from direct interview. Modest drinkers were defined as currently drinking with average alcohol consumption of <24 g-years | History of alcohol consumption was obtained from questionnaire. Modest drinkers were defined as currently drinking with average alcohol consumption ≤20 g daily and never drink alcohol >20 g per day |
| Diagnosis of NAFLD | NAFLD Database: Diagnosis of NAFLD required histology plus imaging suggestive of NAFLD without any other causes of liver disease and significant alcohol consumption (average alcohol consumption >20 g daily during the 2 years before entry). PIVENS study: Criteria for diagnosis were similar to NAFLD Database plus histological evidence of NASH without cirrhosis and diabetes | Diagnosis of NAFLD required histology without any other causes of liver disease and significant alcohol consumption (>40 g per week) | NAFLD was diagnosed based on the presence of fatty liver on US without any other causes of liver disease and significant alcohol consumption (>20 g per day) |
| Definition of advanced liver fibrosis | Advanced fibrosis was defined by histopathology showing fibrosis stage 3-4 | Advanced fibrosis was defined by histopathology showing fibrosis stage 3-4 | Advanced fibrosis was defined as liver stiffness of >8.2 kPa from transient elastography |
| Confounder adjusted in multivariate analysis | None | None | Age, sex and BMI |
| Quality assessment (Newcastle-Ottawa scale) | Selection: 4<br>Comparability: 1<br>Outcome: 3 | Selection: 4<br>Comparability: 1<br>Outcome: 3 | Selection: 3<br>Comparability: 2<br>Outcome: 3 |

*NAFLD, nonalcoholic fatty liver disease; IHTG, intrahepatic triglyceride; H-MRS, proton-magnetic resonance spectroscopy; NASH, nonalcoholic steatohepatitis; CRN, Clinical Research Network; Peth, phosphatidyl ethanol; NAS, nonalcoholic fatty liver disease activity score; SAF, steatosis activity fibrosis; FLIP, fatty liver inhibition of progression; DM, diabetes mellitus; HTN, hypertension; BMI, body mass index; US, ultrasonography; FIB-4, fibrosis-4*

| Study | Mitchell *et al* [8] | Unalp-Arida *et al* [10] | Yamada *et al* [11] |
|---|---|---|---|
| Country | Australia | United States | Japan |
| Study design | Cross-sectional study | Cross-sectional study | Cross-sectional study |
| Year | 2018 | 2018 | 2018 |
| Total number | 146 (72 modest alcohol drinkers and 74 non-drinkers) | 7,836 (4,879 modest alcohol drinkers and 2,957 non-drinkers) | 178 (77 modest alcohol drinkers and 101 non-drinkers) |
| Study participants | Participants were patients with histologically-confirmed NAFLD recruited from the hepatology clinic or bariatric surgery clinic of the Sir Charles Gairdner Hospital, Australia | Participants were patients with NAFLD identified from the cohort of HCHS/SOL from 2008-2011 | Participants were patients with histologically-confirmed NAFLD recruited from the Graduate School of Medicine of the Kanazawa University Hospital, Japan, from 1998-2013 |
| Definition of modest alcohol consumption | History of alcohol consumption was obtained from questionnaire plus direct interview. Modest drinkers were defined as currently drinking with average alcohol consumption of <70 g per week | History of alcohol consumption was obtained from questionnaire. Modest drinkers were defined as currently drinking with average alcohol consumption of 1-14 drinks/week in females and 1-21 drinks/week in males | History of alcohol consumption was obtained from direct interview. Modest drinkers were defined as currently drinking with average alcohol consumption of ≤20 g/day |
| Diagnosis of NAFLD | Diagnosis of NAFLD required histology without any other causes of liver disease and significant alcohol consumption (>21 drinks per week for males and >14 drinks per week for females) | NAFLD was diagnosed based on the presence of fatty liver on magnetic resonance spectroscopy (liver fat score ≥1.257) without any other causes of liver disease and significant alcohol consumption (>14 drinks/week in females and >21 drinks/week in males) | Diagnosis of NAFLD required histology without any other causes of liver disease and significant alcohol consumption (>21 g per day) |
| Definition of advanced liver fibrosis | Advanced fibrosis was defined by histopathology showing fibrosis stage 3-4 | Advanced fibrosis was defined by NAFLD fibrosis score of >0.676 | Advanced fibrosis was defined by histopathology showing fibrosis stage 3-4 |
| Confounder adjusted in multivariate analysis | Age, BMI and DM | Age, sex, heritage group, education, BMI and physical activity | None |
| Quality assessment (Newcastle-Ottawa scale) | Selection: 4<br>Comparability: 2<br>Outcome: 3 | Selection: 5<br>Comparability: 2<br>Outcome: 3 | Selection: 4<br>Comparability: 1<br>Outcome: 3 |

*NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; CRN, Clinical Research Network; BMI, body mass index; DM, diabetes mellitus; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; US, ultrasonography*

The second sensitivity analysis was conducted by excluding the study published as conference abstract and does not undergo peer-review yet [10]. Exclusion of this study did not significantly alter the pooled result as the prevalence of advanced liver fibrosis among NAFLD patients who were modest drinkers was still significantly lower than NAFLD patients who were non-drinkers with the pooled OR of 0.56 (95%CI 0.35-0.89). The between-study heterogeneity was low with an $I^2$ of 50%.

### Evaluation for publication bias

A funnel plot was constructed based on the effect estimate and accuracy of each study to assess for the presence of publication bias (Fig. 3). The funnel plot was symmetric and not suggestive of publication bias.

## Discussion

The current study is the first systematic review and meta-analysis that summarizes all available studies on the association between modest alcohol consumption and risk of advanced liver fibrosis among patients with NAFLD. Interestingly, we found that modest alcohol consumption is inversely associated with advanced liver fibrosis among patients with NAFLD. The reasons for this suggested protective effect of modest alcohol consumption on presence of advanced fibrosis are not known [17]. It seems contradictory that alcohol consumption may provide a beneficial effect to the liver when excessive alcohol consumption is a well-established cause of chronic liver disease [18].

There are many possible explanations for why modest alcohol disease may be protective. The first explanation is related to insulin resistance. Studies have demonstrated that moderate alcohol consumption is associated with increased peripheral

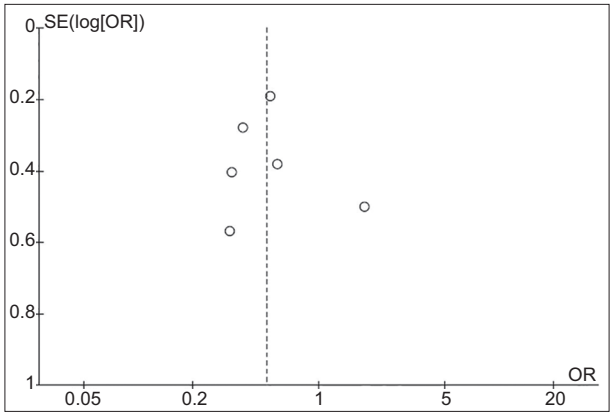


**Figure 3** Funnel plot of all studies
*OR, odds ratio*

insulin sensitivity, decreased basal insulin secretion rate, and lower fasting plasma glucagon concentrations in healthy subjects [19,20]. In fact, several epidemiological studies have demonstrated a significantly lower risk of incident diabetes mellitus among moderate drinkers [21,22]. Since insulin resistance plays an important role in the development of hepatic steatosis, modest alcohol consumption may help slow down this process and thus, lower the chance of progression to liver fibrosis.

The second possible mechanism is related to adiponectin, a hormone that regulates hepatic stellate cells (HSC). Adiponectin inhibits proliferation and migration of HSC by decreasing matrix metalloproteinases-1 and increasing the expression of tissue inhibitor of metalloproteinase-1 [23]. Studies have found the increased levels of adiponectin among alcohol drinkers [24,25], which may reduce HSC proliferation and migration, the essential steps in the development of liver fibrosis [23].

Antioxidants found in wine may also play a protective role against inflammation and subsequent fibrosis [26-28]. Red wine has been shown to have a greater anti-inflammatory effect when compared to white wine, thought to be due to higher polyphenol content [29]. In addition, work by Yamada *et al* suggests that modest alcohol consumption may suppress the activity of nonalcoholic steatohepatitis by reducing the expression of genes involved in immune response [11].

On the other hand, this association may not be causal. It is possible that NAFLD patients with advanced liver fibrosis (F3) or cirrhosis (F4) may have been strongly encouraged by their physicians to quit alcohol completely and, thus, a higher prevalence of non-drinkers among those with advanced liver fibrosis/cirrhosis.

Although the quality of included studies was high, as reflected by the high Newcastle-Ottawa scores, and the literature identification process was comprehensive, this meta-analysis has some limitations and therefore, the results should be interpreted with caution. First, most of the included studies only minimally adjusted their results for potential confounders and several important confounders, such as sex, body mass index, diabetes, smoking, and comorbid conditions, were not appropriately adjusted for. Therefore, it is possible that confounders associated with alcohol consumption and behavior, not the modest alcohol consumption itself, were responsible for this apparent protective effect. Second, statistical heterogeneity was not low in the meta-analysis. We believe that the differences in study populations and methodologies were the main sources of the between-study variation. Third, almost all of the included studies were conducted in Western countries. Studies have shown that there are significant racial and ethnic disparities in NAFLD prevalence and severity [30-32]. Therefore, the generalizability of the results to other populations may be limited. Another limitation is that many of these studies have defined modest alcohol consumption without taking into account different thresholds for women vs. men.

In conclusion, this study demonstrated a significant association between modest alcohol consumption and a decreased risk of advanced liver fibrosis among patients with NAFLD. However, further studies are required to determine whether this association is causal or causative.

**Summary Box**

**What is already known:**

- Heavy alcohol consumption or binge drinking is a risk factor for developing cirrhosis in nonalcoholic fatty liver disease (NAFLD)
- Previous studies showed that modest of alcohol consumption in patients with NAFLD may associated with decreased risk of liver fibrosis; however, the results from those studies varied considerably

**What the new findings are:**

- This meta-analysis from 6 cross-sectional studies with 8,936 participants showed that the risk of advanced liver fibrosis among patients with NAFLD was lower than those without modest alcohol consumption
- However, the included studies have defined modest alcohol consumption without taking into account different thresholds for women vs. men

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## Supplementary material

**Online Supplementary Data 1** Search Strategy

Database: Ovid MEDLINE

1. Nonalcoholic fatty liver.mp. or exp Nonalcoholic fatty liver disease/
2. fatty liver.mp. or exp fatty liver/
3. nonalcoholic steatohepatitis.mp.
4. steatohepatitis.mp.
5. or/1-4
6. alcohol consumption.mp. or exp Alcohol Drinking/
7. alcoholism.mp. or exp Alcoholism/
8. alcohol abuse.mp.
9. exp Ethanol/ or ethanol ingestion.mp.
10. or/6-9
11. 5 and 10

Database: EMBASE

1. 'Nonalcoholic fatty liver' or 'Nonalcoholic fatty liver'/exp
2. 'fatty liver'/exp OR 'fatty liver'
3. 'steatohepatitis'/exp OR 'steatohepatitis'
4. 'nonalcoholic' AND ('steatohepatitis'/exp OR steatohepatitis)
5. or/1-4
6. 'alcohol consumption'/exp OR 'alcohol consumption'
7. 'alcoholism'/exp OR 'alcohoism'
8. 'alcohol abuse'/exp OR 'alcohol abuse'
9. ('ethanol'/exp OR ethanol) AND ('ingestion'/exp OR ingestion)
10. or/6-9
11. 5 and 10

**Online Supplementary Data 2** PRISMA checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |
| METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3-4 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3-4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4-5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Table 1 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 5 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Not applicable |
| RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 6 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table 1 |

(*Contd*...)

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Fig. 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 6 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Not applicable |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 7-8 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 8 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 8 |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 9 |

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