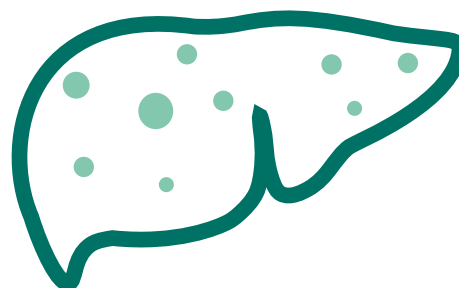


# DRINKING AND LIVER DISEASES

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## ABSTRACT

### PURPOSE

This review explores the relationship between alcohol consumption and incidence of overall liver disease, fatty liver disease, and cirrhosis in meta-analyses and cohort studies published between 2000 and 2023.

### CONCLUSIONS\*

- Increased risk of overall liver disease and cirrhosis was associated with higher alcohol intake.
- Reduced risk of fatty liver disease was associated with lower alcohol intake.

\*For all results and conclusions refer to full review.

## 25 STUDIES INCLUDED

8

fatty liver disease

2 meta-analyses and 6 cohort studies

5

cirrhosis

3 meta-analyses and 2 cohort studies

12

liver disease

3 meta-analyses and 9 cohort studies

### Risk of incidence associated with alcohol consumption in five meta-analyses

#### Fatty Liver Disease

Cao et al., 2016  
≤ 40 g/day vs abstaining (ref.)  
Women  
Men

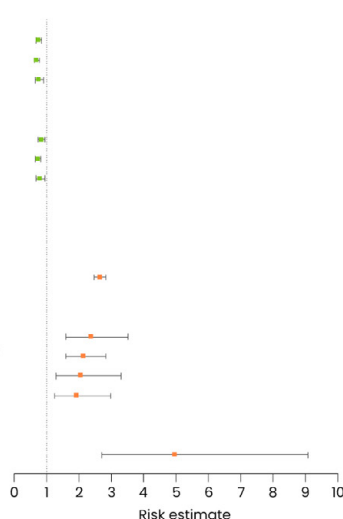
Roerecke et al., 2016  
≤ 20 g/day vs abstaining (ref.)  
Women  
Men

#### Liver Disease

Glyn-Owen et al., 2021  
> 16 g/day vs ≤ 16 g/day (ref)

Hutchinson et al., 2005  
30-37 g/day vs < 30 g/day (ref)  
30-80 g/day vs < 30 g/day (ref)  
40-72 g/day vs < 40 g/day (ref)  
≥ 80 g/day vs < 80 g/day (ref)

Zhang et al., 2022  
≥ 40 g/day vs < 40 g/day (ref)



Key: ref. - reference; ■ - increased risk; ■ - decreased risk;

### Risk of cirrhosis incidence associated with alcohol consumption in three meta-analyses

| Reference             | Sex | Lifetime abstaining | Average alcohol grams per day |      |      |    |      |      |      |       |    |    |     |       |
|-----------------------|-----|---------------------|-------------------------------|------|------|----|------|------|------|-------|----|----|-----|-------|
|                       |     |                     | 0                             | 2    | 12   | 14 | 24   | 36   | 38   | 48    | 60 | 96 | 156 | 160+  |
| Becker et al., 2002   | M   |                     |                               | 7.76 | ref. |    | 2.34 |      |      | 10.40 |    |    |     | 20.40 |
| Rehm et al., 2010     | W   | ref.                |                               | ns   | ns   |    | 2.40 | 1.90 |      | 5.90  |    |    |     | 6.10  |
| Rehm et al., 2010     | M   | ref.                |                               | 0.30 | 0.30 |    | ns   | 2.00 | 2.30 |       |    |    |     | 5.00  |
| Roerecke et al., 2019 | W   | ref.                |                               |      |      |    | ns   |      |      | ns    | ns |    |     | 8.70  |
| Roerecke et al., 2019 | M   | ref.                |                               |      |      |    | ns   |      |      | ns    | ns |    |     | 4.90  |

Key: ■ - increased risk; ■ - decreased risk; ■ - not assessed; ns - not significant; ref. - reference; M - Men, W - Women

### LIMITATIONS

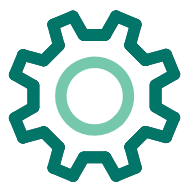
The review identified several limitations in the included studies, primarily involving inconsistencies that make synthesis and comparison of results difficult and a lack of studies that assess the full range of drinking levels and patterns.

There is a glossary of key terms used in this chapter on **page 20**.

Last literature review: **March 2025**

IARD Health Reviews offer a referenced overview of recent peer-reviewed, published research on the relationship between alcohol consumption and health outcomes. They are not necessarily intended to be exhaustive representations of all scientific research on a given subject and, as research is constantly evolving, they may not include the most recent findings. These materials do not necessarily reflect the views of IARD or its member companies. The reviews report the findings of the referenced studies and are not intended to advise individuals about their drinking. People with specific questions about their drinking are encouraged to consult a healthcare professional; together, they can determine what is best based on individual risk factors, including family history, genetics, and lifestyle. For some people, the better choice may be to not drink at all. IARD Health Reviews should be read in their entirety and not misrepresented or taken out of context.

***The International Alliance for Responsible Drinking (IARD)*** is a not-for-profit organization dedicated to reducing harmful drinking worldwide and promoting understanding of responsible drinking among those who choose to drink. IARD is supported by its member companies from all sectors of the regulated alcohol industry – beer, wine, and spirits – in their common purpose of being part of the solution to reducing the harmful use of alcohol.



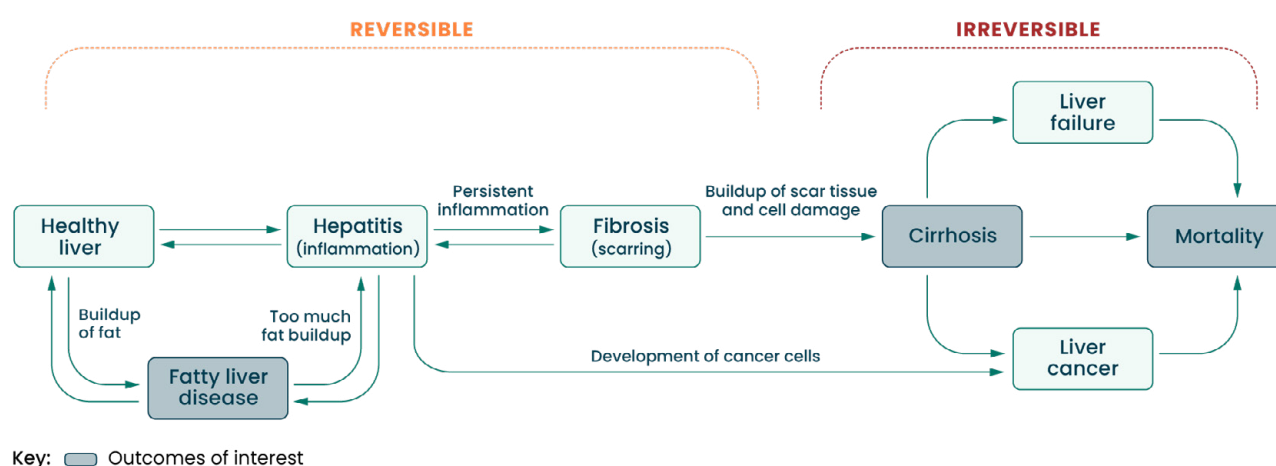
## Background

The liver performs many vital functions, including filtering out toxins from the blood, managing blood clots, regulating metabolism, and supporting the body's immune defense [1–4]. Liver disease refers to a group of conditions that may contribute to gradual liver damage and impair the organ's ability to function properly [5, 6]. The most common conditions are [1, 6, 7]:

- ▶ **Fatty liver disease** – Buildup of fat cells in the liver [8, 9].
- ▶ **Hepatitis** – Inflammation triggered by the build-up fat cells or by infections or toxins. Uncontrolled inflammation may lead to reduced liver function and scarring [5, 10, 11].
- ▶ **Fibrosis** – Reversible accumulation of scar tissue due to chronic inflammation leads to liver stiffening, inability to regenerate cells, and loss of blood flow [12].
- ▶ **Cirrhosis** – Untreated fibrosis may lead to severe and irreversible scarring of the liver, as it is no longer able to repair itself [12, 13].
- ▶ **Liver failure** – A decrease in liver function due to ongoing inflammation, tissue damage, and scarring may lead to liver failure and death [1, 14].
- ▶ **Liver cancer** – Uncontrolled growth of abnormal cells in the liver that replace healthy tissue and interfere with normal function [15, 16].

This Health Review focuses on the following outcomes: incidence and mortality of liver disease, fatty liver disease, and cirrhosis. Information on liver cancer can be found in the [IARD Health Review: Drinking and liver cancer](#) chapter.

**Figure 1.** The natural course of liver disease progression



Source: American Liver Foundation [5, 7, 12], Cancer Australia [15], Cleveland Clinic [1, 11], Hyun et al., 2021 [14], Liver Foundation [17], National Institute of Diabetes and Digestive and Kidney Diseases [18], and Yan et al., 2012 [19].

According to the Global Burden of Disease (GBD) 2023 study, liver disease is the 12th leading cause of death. It accounts for approximately 2% of all deaths worldwide [20]. Globally, higher rates of liver disease were reported in low and low-to-middle income countries and affect men more than women. Regionally, liver disease incidence (new cases diagnosed within a given year) and mortality rates were highest in the Eastern Mediterranean region and the African region, respectively (see Appendix A: Tables A1–A3 for liver disease rates stratified by World Bank income, sex, and region) [21].

High overall incidence and mortality rates across different regions reflect various liver disease conditions (see Table 1). The GBD categorizes liver disease into five conditions: non-alcoholic fatty liver disease (NAFLD), cirrhosis due to alcohol, cirrhosis due to other causes, and chronic hepatitis B and C infection (see Appendix A: Table A4 liver disease definitions). For example, NAFLD accounts for 85% of new cases of liver disease in the Eastern Mediterranean region, while hepatitis B infections contribute to 38% of liver-related deaths in the African region (see Appendix A Tables A3 for liver disease rates stratified by region) [21].

**Table 1.** Global age-standardized incidence and mortality rates per 100,000 in 2023

|                                  | Incidence rate | Mortality rate |
|----------------------------------|----------------|----------------|
| Overall liver disease            | 733.4          | 14.3           |
| Nonalcoholic fatty liver disease | 582.6          | 1.0            |
| Liver cirrhosis due to alcohol   | 4.6            | 3.4            |
| Liver cirrhosis due to other     | 4.2            | 1.8            |
| Chronic hepatitis C              | 56.2           | 3.7            |
| Chronic hepatitis B              | 85.7           | 4.4            |

Source: Institute for Health Metrics Evaluation. Used with permission. All rights reserved [21].

## RISK FACTORS FOR LIVER DISEASE

Multiple risk factors can influence the risk of liver disease and may vary depending on the stage or type of liver disease. Risk factors include alcohol consumption—primarily heavy consumption—obesity, viral infections, genetics, and metabolic conditions [1, 7, 22, 23]. These factors may interact in different ways, with some directly causing liver disease and others increasing susceptibility or accelerating its progression (see Figure 2) [1, 22, 24].

**Figure 2.** Risk factors for liver disease conditions

| Risk factors*                                          | Fatty liver disease | Hepatitis | Fibrosis | Cirrhosis |
|--------------------------------------------------------|---------------------|-----------|----------|-----------|
| Autoimmune disease                                     |                     |           | ✓        | ✓         |
| Chronic conditions                                     | ✓                   | ✓         | ✓        | ✓         |
| Exposure to environmental toxins                       |                     | ✓         | ✓        | ✓         |
| Genetic disorders                                      |                     |           | ✓        | ✓         |
| Heart disease                                          |                     |           | ✓        | ✓         |
| Heavy alcohol use                                      | ✓                   | ✓         |          | ✓         |
| High blood pressure                                    | ✓                   |           |          |           |
| High cholesterol                                       | ✓                   |           |          |           |
| Inflammation                                           |                     |           |          | ✓         |
| Lack of physical exercise                              | ✓                   |           |          |           |
| Metabolic syndrome                                     | ✓                   |           |          | ✓         |
| Obesity                                                | ✓                   | ✓         | ✓        | ✓         |
| Older than 50 years of age                             |                     |           |          | ✓         |
| Overuse of prescription or over-the-counter medication | ✓                   | ✓         |          |           |
| Type 2 diabetes                                        | ✓                   |           |          |           |
| Viral infection                                        |                     | ✓         | ✓        | ✓         |

Source: Cleveland Clinic [25], Grant & Purres., 2025 [26], Liver Foundation [17], National Library of Medicine [27], and Correll., 2015 [28].

\* Items are not listed according to importance or magnitude of risk.

The importance (that is, magnitude or prevalence) of any given risk factor relative to other risk factors may differ by population due to environmental, socioeconomic, behavioral, or genetic differences.

## BIOLOGICAL MECHANISM OF LIVER DISEASE

Researchers are still exploring several plausible biological mechanisms that may explain the role of alcohol in liver disease.

### Liver disease and alcohol

The liver is the primary organ responsible for metabolizing alcohol (ethanol) [14, 29–31]. Ethanol is first converted into acetaldehyde (a toxin), then further broken down into acetate (a non-toxic compound) and finally eliminated from the body [30]. Studies have shown that acetaldehyde may harm the liver by causing DNA damage, fat build-up, inflammation, and fibrosis [14, 29].

- ▶ Acetaldehyde can attach to proteins and DNA in liver cells, potentially changing protein structure and disrupting liver cell function, which may lead to liver injury [14, 29].

There is a third product of metabolizing alcohol: reactive oxygen species (ROS). Excess ROS molecules trigger oxidative stress, which may cause tissue damage, inflammation, and cell dysfunction [14, 32, 33].

Alcohol increases intestinal permeability, allowing bacteria and the toxins produced when bacteria are broken down by the body to enter the bloodstream, triggering inflammation in the liver and worsening tissue damage [32, 34].

For in-depth information on the role alcohol plays in liver disease and liver cancer, please see the [IARD Health Review: Drinking and liver cancer](#).

### Interaction of alcohol with hepatitis and obesity

The development of liver disease may also result from the joint effect of alcohol consumption with hepatitis, obesity, or both. However, researchers are still studying how these factors may interact with regard to liver health in humans [35–42].

#### Hepatitis

- ▶ As Dolganiuc describes in a 2015 review, alcohol-exposed liver cells are prone to several changes that make them more susceptible to hepatitis B and C infection [35].
- ▶ Prevalence of hepatitis C is three to 30 times higher among patients with alcoholism than in the general population, as Singal and Anand describe in their 2007 review [36].
- ▶ Chronic heavy drinking may compromise the body's immune response and aggravate damage from hepatitis infection, accelerating disease progression [37, 38, 42].
- ▶ Patients with both hepatitis C and alcohol abuse may develop more severe fibrosis and experience higher rates of cirrhosis and other liver diseases compared with those who do not drink [36, 38].

#### Obesity

- ▶ A 2021 meta-analysis found a multiplicative effect between obesity and alcohol consumption [39].

- ▷ Overweight individuals (BMI 25–29.9) and those with obesity (BMI  $\geq$  30) had a 1.25 and 2.03 higher risk of chronic liver disease, respectively, compared to normal-weight participants.
  - ▷ Those who drank greater than 16 g/day had a 2.65 higher risk compared to those who drank less than or equal to 16 g/day.
  - ▷ When combined, overweight individuals and those with obesity who drank greater than 16 g/day were 3.3 and 5.4 times more likely, respectively, to develop chronic liver disease compared to normal-weight participants who drank less than or equal to 16 g/day.
- Obesity and alcohol consumption likely contribute to liver disease through complex interactions involving adipose tissue, the gut, and the liver [40, 41].
- ▷ Obesity increases the production of proinflammatory cytokines, which may amplify alcohol-induced liver damage [41].
  - ▷ Obesity and alcohol both induce CYP2E1, an enzyme linked to oxidative stress and liver injury. This activation may contribute to inflammation, mitochondrial dysfunction, and increased gut permeability, further exacerbating liver damage [43]. Frequent binge drinking, especially combined with a high-fat diet, promotes fat storage in adipose tissue, increasing inflammation and worsening liver fibrosis. Chronic alcohol use alongside obesity may impair liver recovery and accelerate disease progression [41, 43].



## Summary of recent liver disease research

The *IARD Health Review: Drinking and liver disease* includes studies that examine the association between alcohol consumption and the risk of liver disease incidence and related mortality. Information on liver cancer can be found in the [IARD Health Review: Drinking and liver cancer](#) chapter.

The following criteria were used to select studies following a systematic literature search using the IARD Research Database and PubMed (see Appendix B for search strategies and the PRISMA flow diagram).

**Study designs:** Meta-analyses, pooled cohort (a type of study that pools data from multiple studies), prospective or retrospective cohort studies

**Publication dates:** from 2000 through 2023

**Outcomes:** Non-alcoholic fatty liver disease, alcoholic fatty liver disease (steatosis/hepatic steatosis), alcoholic cirrhosis, and non-alcoholic cirrhosis (incidence and mortality), liver disease (overall)

**Exposure:** At least two defined levels of alcohol consumption

**Sample size:** 1,000+

When a study presented multiple analyses, we included results from models that were fully adjusted, used lifetime alcohol consumption assessments (versus a single assessment), and separated former drinkers from lifetime abstainers. Results from meta-analyses and pooled cohort studies are presented first, followed by individual cohort studies to allow comparison of risk estimates across study designs.

Note: The time frame of alcohol exposure assessment varies from study to study (for example, researchers may assess a study participant's lifetime, recent past, or current consumption), making it difficult to determine whether risk estimates reflect recent drinking patterns or cumulative lifetime drinking patterns.

To facilitate synthesis and reporting, this review organizes and reports the findings of individual studies according to three liver-related outcomes:

- ▶ fatty liver disease,
- ▶ liver cirrhosis, and
- ▶ liver disease (used as a broad or composite outcome in some studies, potentially including fatty liver disease, cirrhosis, or other chronic liver conditions)

Results are presented by outcome and type of analysis (meta-analyses and prospective cohort studies) to clarify how risk estimates were derived and compared across studies.

### SUMMARY OF RECENT FATTY LIVER DISEASE RESEARCH

Two meta-analyses [44, 45] and six individual cohort studies [46–51] consistently reported reduced risk estimates of fatty liver disease incidence for alcohol consumption compared to no alcohol consumption when assessed as a binary variable and grams per day (see Figure 3 and Table 2; Appendix C: Table C2 and C3 for study descriptions). However, assessment of heavy alcohol consumption was limited in both meta-analyses: Cao et al. [44] reported > 40 g/day estimates only for select countries (for example, Japan, shown here for comparability) but not for the overall analysis, while Roerecke et al., 2016 [45] did not include heavy consumption categories due to limited eligible studies.

**Figure 3.** Forest plot of relative risk of fatty liver disease incidence associated with alcohol consumption in two meta-analyses

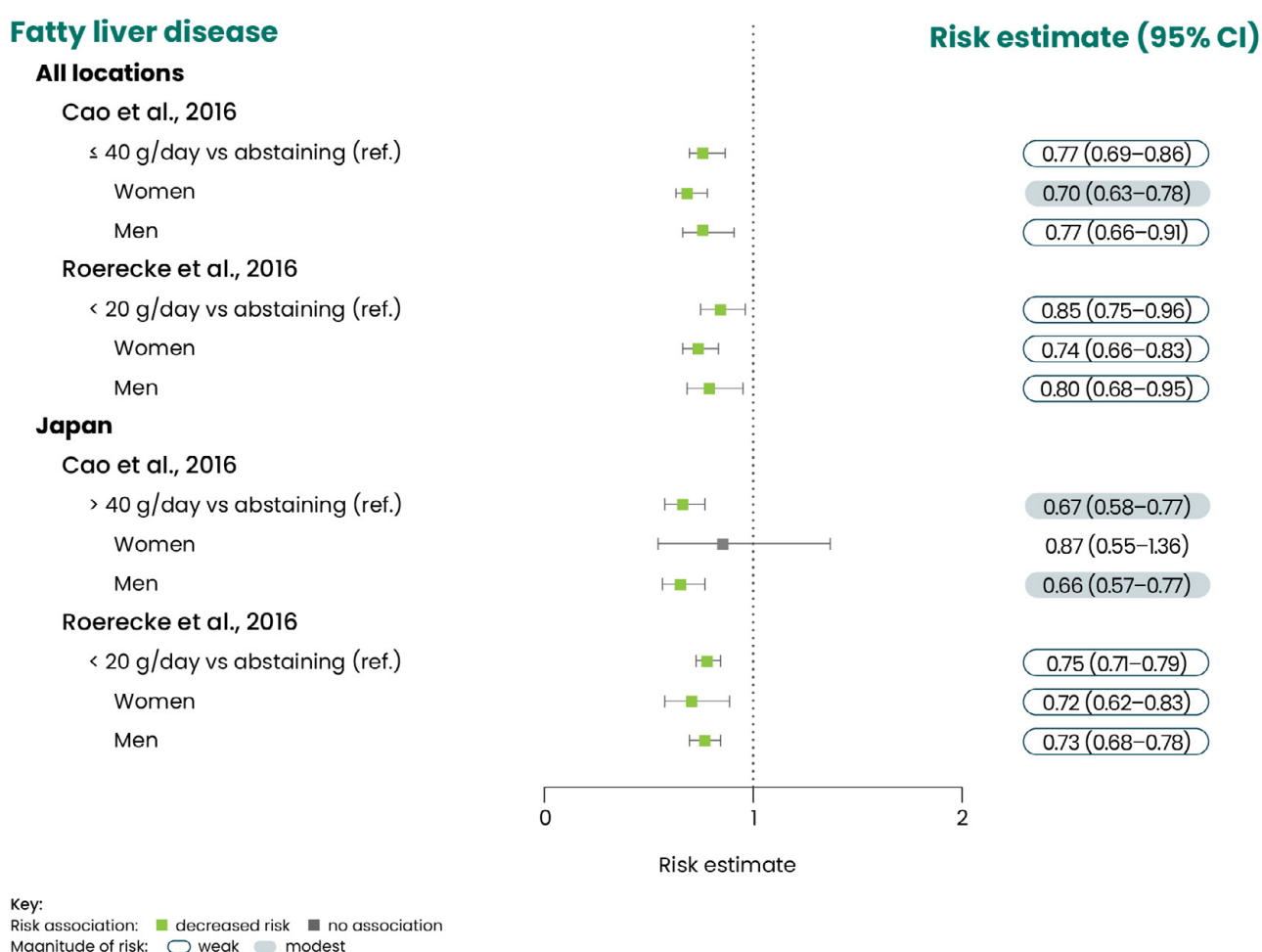


Figure Notes:

| Authors               | All locations                                        |
|-----------------------|------------------------------------------------------|
| Cao et al., 2016      | Argentina, Brazil, Germany, Hong Kong, Japan, and US |
| Roerecke et al., 2016 | China, Finland, Germany, Japan, Spain, and US        |

- See Appendix C: Figure C1 for assistance on how to read and interpret results of a forest plot.

**Table 2.** Relative risk estimates of individual cohort studies on fatty liver disease incidence by sex associated with average volume of alcohol consumption\*

| Average alcohol grams per day      |                   |                     |                  |                  |                  |                  |                  |                  |                  |                  |  |  |
|------------------------------------|-------------------|---------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|--|--|
| Study reference                    | Abstaining        | Occasional drinking |                  |                  |                  |                  |                  |                  |                  |                  |  |  |
| Combined                           |                   |                     |                  |                  |                  |                  |                  |                  |                  |                  |  |  |
| Peeraphatdit et al., 2020          | ref. <sup>†</sup> |                     | 1.09 (0.90–1.33) |                  |                  |                  |                  | 2.19 (1.54–3.06) |                  |                  |  |  |
| Men                                |                   |                     |                  |                  |                  |                  |                  |                  |                  |                  |  |  |
| Hashimoto et al., 2015             | ref. <sup>†</sup> |                     | 0.72 (0.60–0.86) |                  | 0.69 (0.57–0.84) |                  |                  | 0.80 (0.57–1.00) |                  |                  |  |  |
| Chang et al., 2020 <sup>‡</sup>    | ref. <sup>†</sup> |                     | 0.93 (0.90–0.95) |                  | 0.90 (0.87–0.92) |                  |                  |                  |                  |                  |  |  |
| Yamada et al., 2010                | ref. <sup>†</sup> | 0.95 (0.77–1.17)    | 0.72 (0.58–0.89) |                  |                  |                  | 0.65 (0.50–0.85) |                  |                  |                  |  |  |
| Sogabe et al., 2023                | ref. <sup>†</sup> |                     | 0.76 (0.53–1.08) |                  | 1.15 (0.84–1.58) |                  | 0.87 (0.65–1.15) |                  |                  | 1.60 (0.85–2.99) |  |  |
| Sugiyama et al., 2021 <sup>‡</sup> | ref. <sup>†</sup> |                     |                  |                  |                  | 1.00 (0.90–1.10) |                  |                  |                  | 1.20 (1.00–1.40) |  |  |
| Women                              |                   |                     |                  |                  |                  |                  |                  |                  |                  |                  |  |  |
| Chang et al., 2020 <sup>‡</sup>    | ref. <sup>†</sup> |                     | 0.93 (0.90–0.95) |                  | 0.90 (0.87–0.92) |                  |                  |                  |                  |                  |  |  |
| Yamada et al., 2010                | ref. <sup>†</sup> | 0.81 (0.63–1.04)    | 0.71 (0.44–1.16) |                  |                  |                  | 0.74 (0.25–2.17) |                  |                  |                  |  |  |
| Sogabe et al., 2023                | ref.              |                     | 1.14 (0.79–1.65) |                  | 1.16 (0.70–1.94) |                  | 1.35 (0.74–2.45) |                  |                  |                  |  |  |
| Hashimoto et al., 2015             | ref. <sup>†</sup> |                     |                  | 0.86 (0.52–1.42) |                  | 1.23 (0.62–2.41) |                  |                  | 1.12 (0.35–3.55) |                  |  |  |
| Sugiyama et al., 2021 <sup>‡</sup> | ref. <sup>†</sup> |                     |                  |                  |                  | 1.00 (0.90–1.10) |                  |                  | 1.20 (1.00–1.40) |                  |  |  |

\*This table includes prospective and retrospective individual cohort studies that were published between January 2000 and July 2023 and reported risk estimates for drinking at multiple levels.

<sup>†</sup> Drinking category may include former drinking, or occasional drinking, or both.

<sup>‡</sup> Risk estimates for men and women are the same, but definitions of alcohol categories are different.

**Table Notes:**

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study, converted, if necessary, to grams of pure alcohol per day.
- Tangerine shading indicates a statistically significant increase in relative risk compared to the reference group.
- Green shading indicates a statistically significant decrease in relative risk compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- White shading indicates that the risk for that drinking level was not statistically different from the risk for the reference group.

- Five of the six prospective cohort studies included focused on sex-stratified results [47–51]. Most reported no significant associations [47, 49–51] particularly among women [47, 49], and a reduced risk of fatty liver disease incidence at lower levels of alcohol consumption mostly among men [47–49] (see Table 2).

### **SUMMARY OF RECENT LIVER CIRRHOSIS RESEARCH**

Two meta-analyses [52, 53], one pooled cohort [54], and two prospective cohort studies [19, 55] reported risk estimates for cirrhosis incidence and mortality (see Table 3; Appendix C: Table C2 and C3 for study descriptions). The available evidence on cirrhosis was limited, with some overlap among studies included in the meta-analyses. Most studies included in the meta-analyses were older, cross-sectional or prevalence-based, or had relatively small sample sizes ( $n < 1000$ ), and few assessed alcohol consumption in volume (quantity and frequency).

- Risk estimates for cirrhosis incidence were more variable than those for mortality, though higher alcohol consumption was broadly associated with increased risk.
- Mortality risk for women was higher than men even at lower levels of alcohol consumption [52, 53].

**Table 3.** Relative risk of cirrhosis incidence and mortality associated with average volume of alcohol consumption in meta-analyses and prospective cohort studies\*

| Average alcohol grams per day            |          |                     |                                  |                     |                     |                     |                     |                       |                        |                     |                     |                    |                    |  |  |                  |                      |  |  |  |  |
|------------------------------------------|----------|---------------------|----------------------------------|---------------------|---------------------|---------------------|---------------------|-----------------------|------------------------|---------------------|---------------------|--------------------|--------------------|--|--|------------------|----------------------|--|--|--|--|
| Study reference                          | Sex      | Lifetime abstaining | Currently abstaining             | Occasional drinking |                     |                     |                     |                       |                        |                     |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Incidence                                |          |                     |                                  |                     |                     |                     |                     |                       |                        |                     |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Liu et al., 2009<br>(Prospective study)  | Women    |                     | 1.23<br>(0.74–2.06) <sup>†</sup> |                     | ref.<br>(1.04–2.86) | 1.92<br>(1.15–3.21) | 5.38 (3.02–9.58)    |                       |                        |                     |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Becker et al., 2002                      | Men      |                     |                                  |                     | † ref.              | 2.34 (1.18–4.62)    |                     |                       | 10.40 (5.40–19.90)     |                     | 20.40 (10.80–38.80) |                    |                    |  |  |                  |                      |  |  |  |  |
| Rehm et al., 2010                        | Women    | ref.                |                                  |                     | 0.40<br>(0.10–1.20) | 1.00<br>(0.50–1.90) | 2.40<br>(1.80–3.20) | 1.90<br>(1.40–2.60)   | 5.90<br>(3.70–9.30)    | 6.10 (4.60–8.00)    |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Rehm et al., 2010                        | Men      | ref.                |                                  |                     | 0.30<br>(0.10–0.90) | 0.30<br>(0.20–0.40) | 0.70<br>(0.50–1.00) | 2.00<br>(1.50–2.70)   | 2.30<br>(1.70–3.20)    | 5.00 (3.90–6.40)    |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Roerecke et al., 2019                    | Combined | ref.                |                                  |                     |                     | 1.19 (0.58–2.43)    |                     |                       | 3.42 (1.31–8.96)       |                     |                     |                    | 7.36 (1.91–28.34)  |  |  |                  | 5.71<br>(2.87–11.33) |  |  |  |  |
| Roerecke et al., 2019                    | Women    | ref.                |                                  |                     |                     | 0.96 (0.24–3.86)    |                     |                       | 3.27 (0.63–16.92)      |                     |                     |                    | 7.05 (0.94–52.94)  |  |  |                  | 8.70<br>(2.30–32.95) |  |  |  |  |
| Roerecke et al., 2019                    | Men      | ref.                |                                  |                     |                     | 1.56 (0.80–3.02)    |                     |                       | 3.66 (0.67–20.06)      |                     |                     |                    | 7.90 (0.56–111.90) |  |  |                  | 4.90<br>(2.20–10.91) |  |  |  |  |
| Mortality                                |          |                     |                                  |                     |                     |                     |                     |                       |                        |                     |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Yang et al., 2012<br>(Prospective study) | Men      |                     | ref. <sup>†</sup>                |                     | 1.12 (0.76–1.64)    |                     |                     | 0.84 (0.59–1.21)      |                        | 1.16 (0.85–1.56)    |                     | 1.22 (0.83–1.79)   |                    |  |  | 1.74 (1.22–2.48) |                      |  |  |  |  |
| Rehm et al., 2010                        | Women    | ref.                |                                  |                     | 1.90<br>(1.10–3.10) | 5.60<br>(4.50–6.90) | 7.70<br>(6.30–9.50) | 10.10<br>(7.50–13.50) | 14.70<br>(11.00–19.60) | 22.70 (17.20–30.10) |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Rehm et al., 2010                        | Men      | ref.                |                                  |                     | 1.00<br>(0.60–1.60) | 1.60<br>(1.40–2.00) | 2.80<br>(2.30–3.40) | 5.60<br>(4.50–7.00)   | 7.00<br>(5.80–8.50)    | 14.00 (11.70–16.70) |                     |                    |                    |  |  |                  |                      |  |  |  |  |
| Roerecke et al., 2019                    | Combined | ref.                |                                  | 1.11<br>(0.77–1.59) | 1.40<br>(1.00–1.97) | 3.02 (1.95–4.70)    |                     |                       | 3.27<br>(0.90–11.87)   | 6.26 (2.38–16.50)   |                     | 10.70 (2.95–38.78) |                    |  |  |                  |                      |  |  |  |  |
| Roerecke et al., 2019                    | Women    | ref.                |                                  | 0.88<br>(0.77–1.00) | 1.33<br>(1.19–1.48) | 3.59 (2.58–4.99)    |                     |                       | 2.00<br>(0.99–4.03)    | 8.73 (2.96–25.76)   |                     | 15.20 (5.81–39.76) |                    |  |  |                  |                      |  |  |  |  |
| Roerecke et al., 2019                    | Men      | ref.                |                                  | 1.23<br>(0.46–3.28) | 0.91<br>(0.31–2.64) | 1.97 (0.89–4.37)    |                     |                       | 2.62<br>(0.42–16.21)   | 3.80 (0.85–17.02)   |                     | 6.93 (1.07–44.99)  |                    |  |  |                  |                      |  |  |  |  |

\*This table includes all meta-analyses, pooled, and prospective cohorts that were published between January 2000 and July 2023 and reported risk estimates for drinking at multiple levels.

† Drinking category may include former drinking, or occasional drinking, or both.

‡ The risk estimate and confidence interval for men consuming < 2 g/day is 7.76 (3.35–18.00) which includes participants who do not drinking and may include former drinking, occasional drinking, or both.

**Table Notes:**

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study, converted, if necessary, to grams of pure alcohol per day.
- Tangerine shading indicates a statistically significant increase in relative risk compared to the reference group.
- Green shading indicates a statistically significant decrease in relative risk compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- White shading indicates that the risk for that drinking level was not statistically different from the risk for the reference group.

**SUMMARY OF RECENT LIVER DISEASE RESEARCH**

Twelve studies included in this review examined the relationship between alcohol consumption and risk of liver disease incidence and mortality (*studies may define liver disease differently; the most commonly reported ICD-10 codes were K70–K77, as listed on the CDC [ICD-10-CM](#) website*) [39, 56–66]. Three meta-analyses [39, 60, 66] assessed alcohol consumption as a binary variable combining nondrinking with lighter drinking categories and nine individual cohort studies (see Figure 4) [56–59, 61–65] assessed alcohol consumption using a measure of average volume of alcohol consumption (quantity multiplied by frequency), a measure that can be quantified in grams of ethanol (see Table 4; Appendix C: Table C2 and C3 for study descriptions).

Results from both meta-analyses and prospective studies indicate that liver disease risk increased at heavier drinking levels for both incidence and mortality compared to lower drinking levels [39, 56–66].

**Figure 4.** Forest plot of the risk of liver disease incidence associated with alcohol consumption in three meta-analyses**Liver disease**

Glyn-Owen et al., 2021

&gt; 16 g/day vs ≤ 16 g/day (ref.)

Hutchinson et al., 2005

30–37 g/day vs &lt; 30 g/day (ref.)

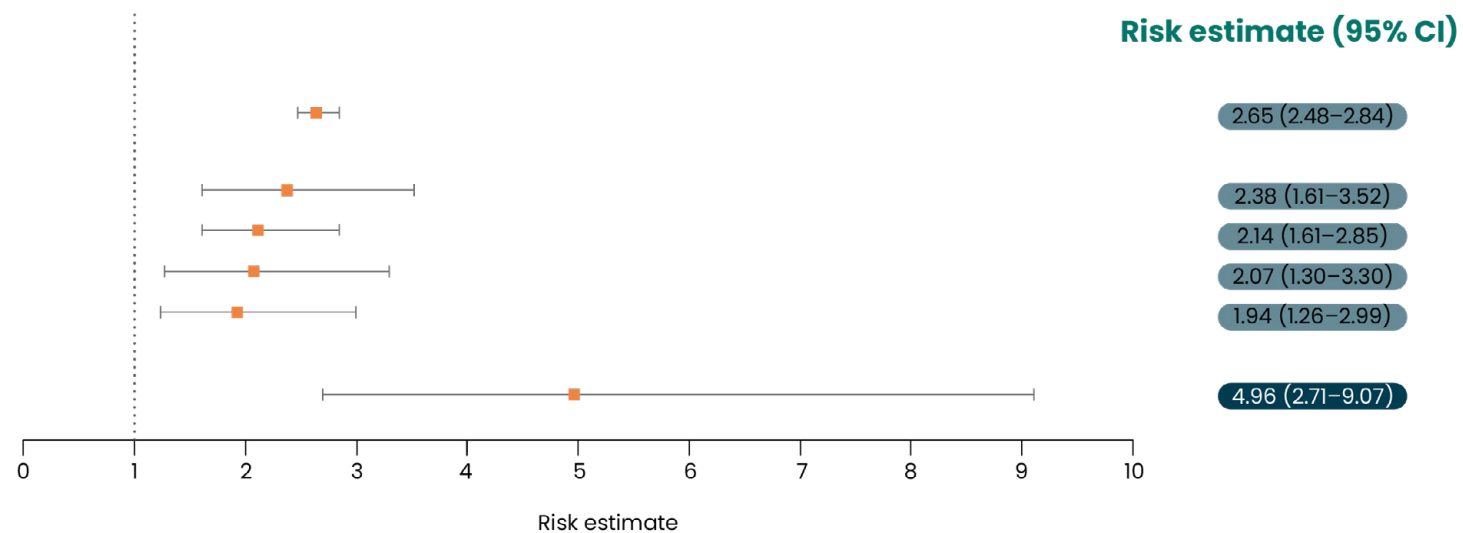
30–80 g/day vs &lt; 30 g/day (ref.)

40–72 g/day vs &lt; 40 g/day (ref.)

≥ 80 g/day vs &lt; 80 g/day (ref.)

Zhang et al., 2022

≥ 40 g/day vs &lt; 40 g/day (ref.)

**Key:**

Risk association: ■ increased risk

Magnitude of risk: ■ moderate ■ strong

**Figure Notes:**

- See Appendix C: Figure C1 for assistance on how to read and interpret results of a forest plot.

**Table 4.** Relative risk of liver disease incidence and mortality associated with average volume of alcohol consumption in prospective cohort studies\*

| Average alcohol grams per day                    |          |                     |                               |                     |                     |                      |                     |                     |                    |                    |                  |                      |                  |                   |  |
|--------------------------------------------------|----------|---------------------|-------------------------------|---------------------|---------------------|----------------------|---------------------|---------------------|--------------------|--------------------|------------------|----------------------|------------------|-------------------|--|
| Study reference                                  | Sex      | Lifetime abstaining | Abstaining                    |                     |                     |                      |                     |                     |                    |                    |                  |                      |                  |                   |  |
| Incidence                                        |          |                     |                               |                     |                     |                      |                     |                     |                    |                    |                  |                      |                  |                   |  |
| Carter et al., 2019                              | Combined |                     | ref. <sup>†</sup>             | 0.84 (0.62–1.13)    |                     |                      |                     |                     |                    | 1.58 (1.16–2.14)   |                  |                      |                  |                   |  |
| Hagstrom et al., 2018                            | Men      |                     | ref. <sup>†</sup>             | 1.39<br>(0.74–2.59) | 1.50<br>(0.79–2.87) | 1.33<br>(0.67–2.65)  | 1.58<br>(0.77–3.24) | 2.03<br>(0.98–4.23) | 195<br>(0.87–4.35) | 2.32 (1.06–5.05)   | 2.99 (1.28–7.00) | 4.83<br>(2.07–11.29) | 3.66 (1.65–8.11) |                   |  |
| Mortality                                        |          |                     |                               |                     |                     |                      |                     |                     |                    |                    |                  |                      |                  |                   |  |
| Patra et al., 2021                               | Combined | ref.                | 0.90 (0.43–1.89)              | 0.49 (0.26–0.94)    |                     |                      |                     | 1.44 (0.47–4.44)    |                    |                    |                  | 6.17 (2.32–16.44)    |                  | 4.46 (1.23–15.83) |  |
| Setiawan et al., 2016<br>(US-born Hispanic)      | Combined |                     | ref. <sup>†</sup>             | 0.66 (0.47–0.94)    |                     |                      |                     | 2.23 (1.52–3.29)    |                    |                    |                  |                      |                  |                   |  |
| Setiawan et al., 2016<br>(Foreign-born Hispanic) | Combined |                     | ref. <sup>†</sup>             | 1.07 (0.68–1.70)    |                     |                      |                     | 2.74 (1.53–4.91)    |                    |                    |                  |                      |                  |                   |  |
| Persson et al., 2013                             | Combined |                     | 1.88 (1.55–2.28) <sup>‡</sup> | ref.                |                     | 2.03 (1.63–2.52)     |                     |                     |                    | 5.84 (4.81–7.10)   |                  |                      |                  |                   |  |
| Schwartz et al., 2013                            | Men      |                     | ref. <sup>†</sup>             | 2.06 (1.22–3.50)    |                     |                      | 6.68 (4.16–10.71)   |                     |                    |                    |                  |                      |                  |                   |  |
| Hart et al., 2008                                | Men      |                     | ref. <sup>†</sup>             | 1.06 (0.18–6.37)    | 1.72<br>(0.34–8.56) | 7.28<br>(1.86–28.50) | 7.44 (1.88–29.40)   |                     |                    | 15.50 (4.13–58.60) |                  |                      |                  |                   |  |
| Sinn et al., 2021 <sup>‡</sup>                   | Men      |                     | ref. <sup>†</sup>             | 1.03 (0.82–1.29)    |                     |                      |                     | 1.78 (1.42–2.23)    |                    |                    |                  |                      |                  | 3.33 (2.34–4.75)  |  |
| Fan et al., 2022                                 | Men      | ref.                | 1.37 (0.70–2.69)              | 1.61 (0.84–3.10)    |                     |                      |                     | 2.77 (1.42–5.40)    |                    |                    |                  |                      |                  |                   |  |
| Sinn et al., 2021 <sup>‡</sup>                   | Women    |                     | ref. <sup>†</sup>             | 1.03 (0.82–1.29)    | 1.78 (1.42–2.23)    |                      |                     |                     | 3.33 (2.34–4.75)   |                    |                  |                      |                  |                   |  |
| Fan et al., 2022                                 | Women    | ref.                | 1.11 (0.67–1.83)              | 1.06 (0.63–1.76)    |                     |                      | 2.09 (1.20–3.64)    |                     |                    |                    |                  |                      |                  |                   |  |

\*This table includes prospective individual cohort studies that were published between January 2000 and July 2023 and reported risk estimates for drinking at multiple levels.

<sup>†</sup> Drinking category may include former drinking, or occasional drinking, or both.

<sup>‡</sup> Risk estimates for men and women are the same, but definitions of alcohol categories are different.

#### Table Notes:

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study, converted, if necessary, to grams of pure alcohol per day.
- Tangerine shading indicates a statistically significant increase in relative risk compared to the reference group.
- Green shading indicates a statistically significant decrease in relative risk compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- White shading indicates that the risk for that drinking level was not statistically different from the risk for the reference group.

All individual cohort studies reported an increased risk of liver disease at higher levels of alcohol consumption compared to low levels of drinking or abstaining [56–59, 61–65]. These results held true when assessed among women and men separately [57, 59, 63] (see Table 4).

### **RISK FACTOR INTERACTIONS**

Five cohort studies examined the joint association of body mass index (BMI) and alcohol consumption with liver disease outcomes [46, 48, 56, 57, 61]. These studies assessed fatty liver disease incidence [46, 48] and liver disease incidence [56] and mortality [57, 61] across different categories of BMI (underweight, healthy weight, overweight, obesity) and varying levels of alcohol intake (see Table 6).

#### **Incidence of liver disease**

- Low alcohol consumption was associated with a reduced risk of liver disease across BMI categories compared with overweight and obese individuals with high alcohol consumption [56]. The strength of these associations ranged from weak to moderate [67].

#### **Incidence of fatty liver disease**

- In one cohort study [48], no significant associations were observed for light drinking among healthy-weight individuals compared to non-drinking, and risk was lower in those with obesity. Moderate drinking was associated with increased risk in healthy-weight individuals and reduced risk in those with obesity compared to non-drinking.
- Peeraphatdit et al., 2020 however, found that consumption of less than or equal to 26 g/day was associated with reduced risk in underweight individuals but increased risk in those with obesity compared to non-drinking. Higher intake (> 26 g/day) was consistently associated with a higher risk of fatty liver disease across all BMI groups [46].

#### **Mortality of liver disease**

- Moderate to very strong associations [67] were found for increased liver disease mortality risk and higher alcohol intake in underweight individuals compared to healthy-weight individuals who always abstained from drinking. Among individuals with obesity, the lowest consumption category was associated with reduced mortality risk, while higher categories showed higher risks. Past drinking, however, was not significantly associated with liver disease mortality in either group [61].
- Fan et al., 2022 found moderate drinking increased risk of liver disease mortality among healthy-weight individuals, with heavy drinking associated with higher risk across all BMI categories, especially in obesity [57].

**Table 5.** Relative risk of incidence and mortality associated with joint effect of average volume of alcohol consumption and BMI, by outcome.

| Author, date                            | Alcohol Consumption/BMI<br>(as defined by study)                      | Underweight<br>< 18 kg/m <sup>2</sup> | Healthy<br>18–25 kg/m <sup>2</sup> | Overweight<br>25–30 kg/m <sup>2</sup> | Obesity<br>≥ 30 BMI kg/m <sup>2</sup> |
|-----------------------------------------|-----------------------------------------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|---------------------------------------|
| <b>Incidence of liver disease</b>       |                                                                       |                                       |                                    |                                       |                                       |
| Carter et al., 2019                     | Low alcohol consumption (mean alcohol consumption - 15.2 g/day)       | 0.60 (0.45–0.75)                      |                                    | 0.73 (0.57–0.90)                      |                                       |
|                                         | High alcohol consumption (mean alcohol consumption + 15.2 g/day)      | 0.82 (0.64–1.01)                      |                                    | ref.                                  |                                       |
| <b>Incidence of fatty liver disease</b> |                                                                       |                                       |                                    |                                       |                                       |
| Chang et al., 2020                      | Nondrinkers<br>0 g/day                                                |                                       | ref.                               |                                       | ref.                                  |
|                                         | Light drinkers<br>1.0–9.9 g/day                                       |                                       | 0.98 (0.95–1.01)                   |                                       | 0.81 (0.77–0.85)                      |
|                                         | Moderate drinkers: 10.0–20.0 g/day for women; 10.0–30.0 g/day for men |                                       | 1.06 (1.03–1.10)                   |                                       | 0.74 (0.70–0.77)                      |
| Peeraphatdit et al., 2020               | Nondrinker                                                            |                                       | ref.                               | ref.                                  | ref.                                  |
|                                         | ≤ 26.0 g/day                                                          | 0.48 (0.26–0.90)                      |                                    | 0.86 (0.58–1.26)                      | 1.31 (1.03–1.67)                      |
|                                         | > 26.0 g/day                                                          | 3.12 (1.32–7.41)                      |                                    | 2.06 (1.13–3.77)                      | 1.94 (1.21–3.09)                      |
| <b>Mortality of liver disease</b>       |                                                                       |                                       |                                    |                                       |                                       |
| Patra et al., 2021                      | Lifetime abstaining                                                   |                                       | ref.                               |                                       |                                       |
|                                         | Past drinking                                                         | 1.54 (0.79–2.99)                      |                                    |                                       | 1.08 (0.49–2.38)                      |
|                                         | < 19.9 g/day                                                          | 1.50 (0.83–2.73)                      |                                    |                                       | 0.40 (0.16–0.97)                      |
|                                         | 20.0–39.9 g/day                                                       | 3.54 (1.61–7.79)                      |                                    |                                       | 4.11 (1.38–12.22)                     |
|                                         | 40.0–59.9 g/day                                                       | 8.27 (3.74–18.33)                     |                                    |                                       | 4.08 (0.83–19.93)                     |
|                                         | ≥ 60.0 g/day                                                          | 14.89 (6.86–32.39)                    |                                    |                                       | 12.33 (3.85–39.46)                    |
| Fan et al., 2022                        | Nondrinkers                                                           |                                       | ref.                               |                                       | ref.                                  |
|                                         | Former drinkers                                                       |                                       | 1.36 (0.78–2.43)                   |                                       | 1.10 (0.64–1.89)                      |
|                                         | Moderate drinkers: ≤ 14.0 g/day for women; ≤ 28.0 g/day for men       |                                       | 1.79 (1.03–3.12)                   |                                       | 0.89 (0.50–1.59)                      |
|                                         | Heavy drinkers: > 14.0 g/day for women; > 28.0 g/day for men          |                                       | 2.70 (1.52–4.77)                   |                                       | 2.35 (1.26–4.38)                      |

**Table Notes:**

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study, converted, if necessary, to grams of pure alcohol per day.
- Tangerine shading indicates a statistically significant increase in relative risk compared to the reference group.
- Green shading indicates a statistically significant decrease in relative risk compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- White shading indicates that the risk for that drinking level was not statistically different from the risk for the reference group.

**LIVER DISEASE OUTCOMES SUMMARY**

- ▶ Higher levels of alcohol consumption were consistently associated with increased risk of both liver disease and cirrhosis incidence and mortality. At lower levels of alcohol consumption, results were mixed.
- ▶ There was either no association between alcohol consumption and fatty liver disease incidence or a reduced risk at lower levels of consumption (primarily among men) in the vast majority of studies.
- ▶ A small number of studies attempted to explore the joint effect of BMI and alcohol use on various liver disease outcomes. These appeared to indicate that heavy alcohol consumption, regardless of BMI, consistently increased liver disease risk, which echoes the main findings, however, the effect of BMI at different levels of alcohol consumption was inconsistent.
- ▶ Drawing conclusions about alcohol and liver disease outcomes is limited by study design, few studies assessing alcohol consumption by volume (quantity and frequency), more studies examining incidence than mortality, and variation in outcome definitions across studies (for example, measurement methods and ICD-10 codes).
- ▶ These factors may limit the generalizability and comparability of some study results and the overall strength of evidence from currently available research.

We assessed the relationship between alcohol consumption and liver disease progression within the scope of this review. Outcomes of interest included progression from fatty liver disease to hepatitis, fibrosis, and cirrhosis. Of the 2,477 studies screened, only one study, a meta-analysis, met the inclusion criteria [68]. The authors reported conflicting findings regarding light-to-moderate alcohol consumption and progression of NAFLD. Fibrosis was the most frequently studied outcome; however, findings were inconsistent and varied according to study design and outcome assessed.



## Future Research

Liver disease has been widely studied in relation to alcohol use, but variation in study design, reference groups, and outcome definitions complicates efforts to draw firm conclusions. While many studies report increased risks of liver disease incidence and mortality at higher levels of alcohol consumption, fewer have examined the effects at lower levels. This gap creates uncertainty about the levels of alcohol consumption above which risk begins to increase and whether the relationship between consumption and liver disease differs by disease severity. Although it appears from this review that light to moderate drinking is not associated with incidence of early-stage liver disease, that is, fatty liver disease, but may be associated with cirrhosis. Additionally, an inconsistency in study definitions for liver disease and in the reporting of results by sex complicate synthesis of the evidence from this literature.

Future research would benefit from a more consistent assessment of alcohol intake across studies as average volume and definition of liver disease to enable clearer comparisons across studies. Additional studies are also needed to explore how liver disease risk differs by sex and disease subtypes such as fatty liver disease and cirrhosis, as current evidence in these areas is limited.



## Glossary

- ▶ **Acetaldehyde** is a product of ethanol metabolism, which takes place in the liver and other tissues and may lead to DNA damage.
- ▶ **Acetate** is the non-toxic product of acetaldehyde metabolism and can be further metabolized into carbon dioxide and water for energy.
- ▶ **Acetaldehyde dehydrogenase (ALDH)** is an enzyme that breaks down acetaldehyde into smaller molecules such as acetate, which are further broken down into carbon dioxide and water molecules.
- ▶ **Alcohol dehydrogenase (ADH)** is an enzyme that converts ethanol into acetaldehyde molecules.
- ▶ **Carcinogen** is any agent or substance that may cause cancer.
- ▶ **CYP2E1** is a protein that is induced by ethanol, diabetes, and starvation and metabolizes ethanol and other endogenous and exogenous substances.
- ▶ **Endotoxins** are toxic components of the outer membrane of certain bacteria (such as Gram-negative bacteria) that can trigger inflammation and immune responses when released into the body.
- ▶ **Hepatitis B** is a viral infection spread through blood and bodily fluids that affects the liver and can cause both acute and chronic inflammation. Preventable with a vaccine.
- ▶ **Hepatitis C** is a viral infection spread primarily through blood that affects the liver and can cause both acute and chronic inflammation. Treated with antiviral medications, but no vaccine.
- ▶ **Oxidative stress** occurs when there is an imbalance between the accumulation of reactive oxygen species (see below for definition) and the body's ability to detoxify and eliminate these molecules through an antioxidant (for example, glutathione, vitamin C, vitamin E) defense.
- ▶ **Reactive oxygen species** are a group of highly-reactive molecules containing oxygen that, at low levels, are an important part of metabolism and inflammatory response. An excess of reactive oxygen species can damage cellular proteins, lipids, or DNA, and has been linked with chronic diseases, such as cancer, diabetes, and cardiovascular disease.
- ▶ **Relative risk** is a measure that compares the probability of a given outcome (for example, breast cancer) among a group of people with a given risk factor (for example, alcohol consumption) with the probability of that outcome among a group of people without the risk factor (for example, nondrinkers).

A risk estimate above one ( $RR > 1$ ) indicates an increased risk of the outcome associated with the exposure and a risk estimate below one ( $RR < 1$ ) indicates a reduced risk of the outcome associated with the exposure. If the risk estimate is equivalent to one ( $RR = 1$ ) then there is no association between the outcome and the exposure.

- ▶ The **magnitude of relative risk** describes the strength of the association between the exposure and outcome of interest, or the relative risk estimate. There are several terms used to describe or interpret different relative risk estimates. Some commonly used descriptors are weak, small, moderate, medium, strong, or large [67, 69–72], however, the risk estimates associated with each term may differ or overlap (see Figure 2A–C). For example, according to Schoenbach and Rosamond 2000 [67], a moderate risk is equivalent to a relative risk of 1.8 to 3.0, while Craun and Calderon n.d., states that moderate to strong risk is equivalent to a relative risk greater than 1.5 [69, 70].

**Figure 2A.** Descriptions of magnitude of risk

|         |                             |
|---------|-----------------------------|
| 1.0     | No association (null value) |
| 1.1–1.3 | Weak                        |
| 1.4–1.7 | Modest                      |
| 1.8–3.0 | Moderate                    |
| 3–8     | Strong                      |

Source: Schoenbach and Rosamond 2000 [67]

**Figure 2B.** Descriptions of magnitude of risk

|                | Trivial | Small | Moderate | Large | Very Large | Nearly perfect | Perfect  |
|----------------|---------|-------|----------|-------|------------|----------------|----------|
| Correlation    | 0.0     | 0.1   | 0.3      | 0.5   | 0.7        | 0.9            | 1        |
| Diff. in means | 0.0     | 0.2   | 0.6      | 1.2   | 2.0        | 4.0            | infinite |
| Freq. diff.    | 0       | 10    | 30       | 50    | 70         | 90             | 100      |
| Rel. risk      | 1.0     | 1.2   | 1.9      | 3.0   | 5.7        | 19             | infinite |
| Odds ratio     | 1.0     | 1.5   | 3.5      | 9.0   | 32         | 360            | infinite |

Source: Hopkins 2002 [72]

**Figure 2C.** Descriptions of magnitude of risk

| Type of effect size estimate | Included indices                                                                                           | RMPE | Moderate effect | Strong effect |
|------------------------------|------------------------------------------------------------------------------------------------------------|------|-----------------|---------------|
| Group difference             | d, Δ, g                                                                                                    | 0.41 | 1.15            | 2.70          |
| Strength of association      | r, R, φ, p, partial r, β, rh, tau                                                                          | 0.2  | 0.5             | 0.8           |
| Squared association indices  | r <sup>2</sup> , R <sup>2</sup> , η <sup>2</sup> , adjusted R <sup>2</sup> , ω <sup>2</sup> ε <sup>2</sup> | 0.04 | 0.25            | 0.64          |
| Risk estimates               | RR, OR                                                                                                     | 2.0* | 3.0             | 4.0           |

Note. RMPE = recommended minimum effect size representing a “practically” significant effect for social science data. For effects with highly valid dependent measures (e.g., death) and using rigorous controlled outcomes trials, lower values may have practical value. RR = relative risk; OR = odds ratio.

\* These are not anchored to r and should be interpreted with caution.

Source: Ferguson 2016 [71]



## Appendix A

**Table A1.** 2023 Liver disease age-standardized incidence and mortality rates per 100,000 by World Bank Income levels

|                                |           | <b>Nonalcoholic fatty liver disease<br/>(including cirrhosis)</b> | <b>Cirrhosis due to alcohol</b> | <b>Cirrhosis other</b> | <b>Chronic hep B</b> | <b>Chronic hep C</b> | <b>Overall liver disease</b> |
|--------------------------------|-----------|-------------------------------------------------------------------|---------------------------------|------------------------|----------------------|----------------------|------------------------------|
| Global                         | Mortality | 0.99                                                              | 3.39                            | 1.80                   | 4.38                 | 3.72                 | 14.28                        |
|                                | Incidence | 582.67                                                            | 4.63                            | 4.23                   | 85.68                | 56.17                | 733.38                       |
| World Bank Low Income          | Mortality | 0.77                                                              | 3.81                            | 3.36                   | 10.48                | 8.89                 | 27.31                        |
|                                | Incidence | 568.45                                                            | 4.41                            | 6.45                   | 159.99               | 87.67                | 826.99                       |
| World Bank Lower Middle Income | Mortality | 0.71                                                              | 4.16                            | 2.39                   | 6.31                 | 4.94                 | 18.50                        |
|                                | Incidence | 590.57                                                            | 5.24                            | 5.16                   | 94.65                | 57.45                | 753.08                       |
| World Bank Upper Middle Income | Mortality | 0.97                                                              | 2.23                            | 1.26                   | 4.27                 | 2.79                 | 11.52                        |
|                                | Incidence | 661.70                                                            | 3.39                            | 3.07                   | 62.08                | 56.76                | 787.01                       |
| World Bank High Income         | Mortality | 1.38                                                              | 4.53                            | 1.46                   | 1.68                 | 3.29                 | 12.34                        |
|                                | Incidence | 441.87                                                            | 6.61                            | 3.23                   | 23.94                | 38.93                | 514.57                       |
| Low to High Ratio              | Mortality | 0.60                                                              | 0.80                            | 2.30                   | 6.20                 | 2.70                 | 2.20                         |
|                                | Incidence | 1.30                                                              | 0.70                            | 2.00                   | 6.70                 | 2.30                 | 1.60                         |

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**Table A2.** 2023 liver disease age-standardized incidence and mortality rates per 100,000 grouped by sex

|                                                        |       | Incidence rate | Mortality rate |
|--------------------------------------------------------|-------|----------------|----------------|
| Overall liver disease                                  | Women | 686.97         | 9.08           |
|                                                        | Men   | 777.52         | 19.80          |
| Nonalcoholic fatty liver disease (including cirrhosis) | Women | 552.93         | 0.97           |
|                                                        | Men   | 610.27         | 1.00           |
| Cirrhosis other                                        | Women | 4.83           | 1.76           |
|                                                        | Men   | 3.61           | 1.84           |
| Cirrhosis due to alcohol                               | Women | 2.36           | 1.45           |
|                                                        | Men   | 7.02           | 5.47           |
| Chronic hepatitis C (including cirrhosis)              | Women | 57.30          | 2.45           |
|                                                        | Men   | 55.15          | 5.06           |
| Chronic hepatitis B (including cirrhosis)              | Women | 69.55          | 2.45           |
|                                                        | Men   | 101.48         | 6.43           |

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**Table A3.** 2023 liver disease age-standardized incidence and mortality rates per 100,000 by WHO regions

|                              |           | Nonalcoholic fatty liver disease (including cirrhosis) | Cirrhosis due to alcohol | Cirrhosis other | Chronic hep B | Chronic hep C | Overall liver disease |
|------------------------------|-----------|--------------------------------------------------------|--------------------------|-----------------|---------------|---------------|-----------------------|
| Global                       | Mortality | 0.99                                                   | 3.39                     | 1.80            | 4.38          | 3.72          | 14.28                 |
|                              | Incidence | 582.67                                                 | 4.63                     | 4.23            | 85.68         | 56.17         | 733.38                |
| African Region               | Mortality | 1.04                                                   | 4.26                     | 3.30            | 10.27         | 8.10          | 26.97                 |
|                              | Incidence | 565.20                                                 | 5.29                     | 7.06            | 174.76        | 91.18         | 843.49                |
| Eastern Mediterranean Region | Mortality | 1.38                                                   | 1.13                     | 3.02            | 8.50          | 9.16          | 23.19                 |
|                              | Incidence | 897.65                                                 | 1.46                     | 6.31            | 80.70         | 65.51         | 1051.64               |
| European Region              | Mortality | 1.71                                                   | 5.78                     | 1.78            | 2.24          | 3.07          | 14.58                 |
|                              | Incidence | 500.50                                                 | 7.87                     | 4.05            | 30.34         | 45.50         | 588.26                |
| Region of the Americas       | Mortality | 2.13                                                   | 5.03                     | 1.83            | 1.51          | 4.80          | 15.30                 |
|                              | Incidence | 530.21                                                 | 7.50                     | 3.56            | 16.61         | 45.96         | 603.84                |
| South-East Asia Region       | Mortality | 0.50                                                   | 4.33                     | 1.94            | 4.74          | 3.10          | 14.60                 |
|                              | Incidence | 548.07                                                 | 5.30                     | 3.83            | 45.41         | 40.22         | 642.84                |
| Western Pacific Region       | Mortality | 0.41                                                   | 1.44                     | 1.02            | 4.62          | 2.38          | 9.87                  |
|                              | Incidence | 583.81                                                 | 2.41                     | 2.77            | 89.56         | 61.38         | 739.94                |

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**Table A4.** Descriptions of liver disease as defined by the GBD

|                                  | ICD 10 code | Definition                                               |
|----------------------------------|-------------|----------------------------------------------------------|
| Nonalcoholic fatty liver disease | K75.81      | Nonalcoholic steatohepatitis (NASH)                      |
| Liver cirrhosis due to alcohol   | K70         | Alcoholic liver disease                                  |
|                                  | K70.0       | Alcoholic fatty liver                                    |
|                                  | K70.1       | Alcoholic hepatitis                                      |
|                                  | K70.10      | Alcoholic hepatitis without ascites                      |
|                                  | K70.11      | Alcoholic hepatitis with ascites                         |
|                                  | K70.2       | Alcoholic fibrosis and sclerosis of liver                |
|                                  | K70.3       | Alcoholic cirrhosis of liver                             |
|                                  | K70.30      | Alcoholic cirrhosis of liver without ascites             |
|                                  | K70.31      | Alcoholic cirrhosis of liver with ascites                |
| Liver cirrhosis due to other     | B18.8       | Other chronic viral hepatitis                            |
|                                  | B18.9       | Chronic viral hepatitis unspecified                      |
|                                  | K71.7       | Toxic liver disease with fibrosis and cirrhosis of liver |
|                                  | K73         | Chronic hepatitis, not elsewhere classified              |
|                                  | K73.0       | Chronic persistent hepatitis, not elsewhere classified   |
|                                  | K73.1       | Chronic lobular hepatitis, not elsewhere classified      |
|                                  | K73.2       | Chronic active hepatitis, not elsewhere classified       |
|                                  | K73.8       | Other chronic hepatitis, not elsewhere classified        |
|                                  | K73.9       | Chronic hepatitis, unspecified                           |
|                                  | K75.2       | Nonspecific reactive hepatitis                           |
|                                  | K75.4       | Autoimmune hepatitis                                     |
|                                  | K75.8       | Other specified inflammatory liver diseases              |
|                                  | K75.89      | Other specified inflammatory liver diseases              |
|                                  | K75.9       | Inflammatory liver disease, unspecified                  |
|                                  | K76         | Other diseases of liver                                  |
|                                  | K76.1       | Chronic passive congestion of liver                      |
|                                  | K76.2       | Central hemorrhagic necrosis of liver                    |
|                                  | K76.4       | Peliosis hepatitis                                       |
|                                  | K76.5       | Hepatic veno-occlusive disease                           |
|                                  | K76.6       | Portal hypertension                                      |
|                                  | K76.7       | Hepatorenal syndrome                                     |
|                                  | K76.8       | Other specified diseases of liver                        |
|                                  | K76.81      | Hepatopulmonary syndrome                                 |
|                                  | K76.89      | Other specified diseases of liver                        |
|                                  | K76.9       | Liver disease, unspecified                               |
|                                  | K77.8       | Liver disorders in other diseases classified elsewhere   |
| Chronic hepatitis C              | B18.2       | Chronic viral hepatitis C                                |
| Chronic hepatitis B              | B18.0       | Chronic viral hepatitis B with delta-agent               |
|                                  | B18.1       | Chronic viral hepatitis B without delta-agent            |

Source: Sepanlou et al., 2020 [73]



## Appendix B

### SEARCH STRATEGIES

#### Systematic reviews/Meta analyses

##### *IARD Research Database*

1. IARD databases=Research; Text="meta analysis" AND ( "LD45" OR "liver disease" OR "liver cirrhosis" OR "hepatitis" OR steatosis OR steatohepatitis OR NASH OR NAFLD OR "fatty liver" OR MAFLD ); Languages=English; Publication Types=Research Paper, Review; Publish From=2000-01-01; Publish To=2024-12-31

► Search Date: 30 June 2023

##### *Pubmed Database*

1. Pubmed database=( "Liver diseases"[Mesh] OR "liver disease"[TIAB] OR "cirrhosis"[TIAB] OR "hepatitis"[TIAB] OR "steatosis"[TIAB] OR "hepatosteatois"[TIAB] OR "fatty liver"[TIAB] OR "NASH"[TIAB] OR "NAFLD"[TIAB] OR "MAFLD"[TIAB] ) AND ( "Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR "Alcoholic Beverages"[Mesh] OR drink\*[TIAB] ) AND ( "Meta-Analysis"[Publication Type] OR "meta analysis"[TIAB] )

► Search Date: 30 June 2023

#### Individual Studies

##### *IARD Research Database*

1. IARD databases=Research; Text=( "LD45" OR "liver disease" OR "liver cirrhosis" OR "hepatitis" OR steatosis OR steatohepatitis OR NASH OR NAFLD OR "fatty liver" OR MAFLD OR MASLD OR MetALD ) AND ( "prospective study" OR longitudinal\* OR prospectively OR ( "case control study" AND ( nested OR cohort OR prospective\* OR longitudinal\* ))) ; Publish From=2000-01-01; Publish To=2024-12-31; Date Added To=2023-06-30

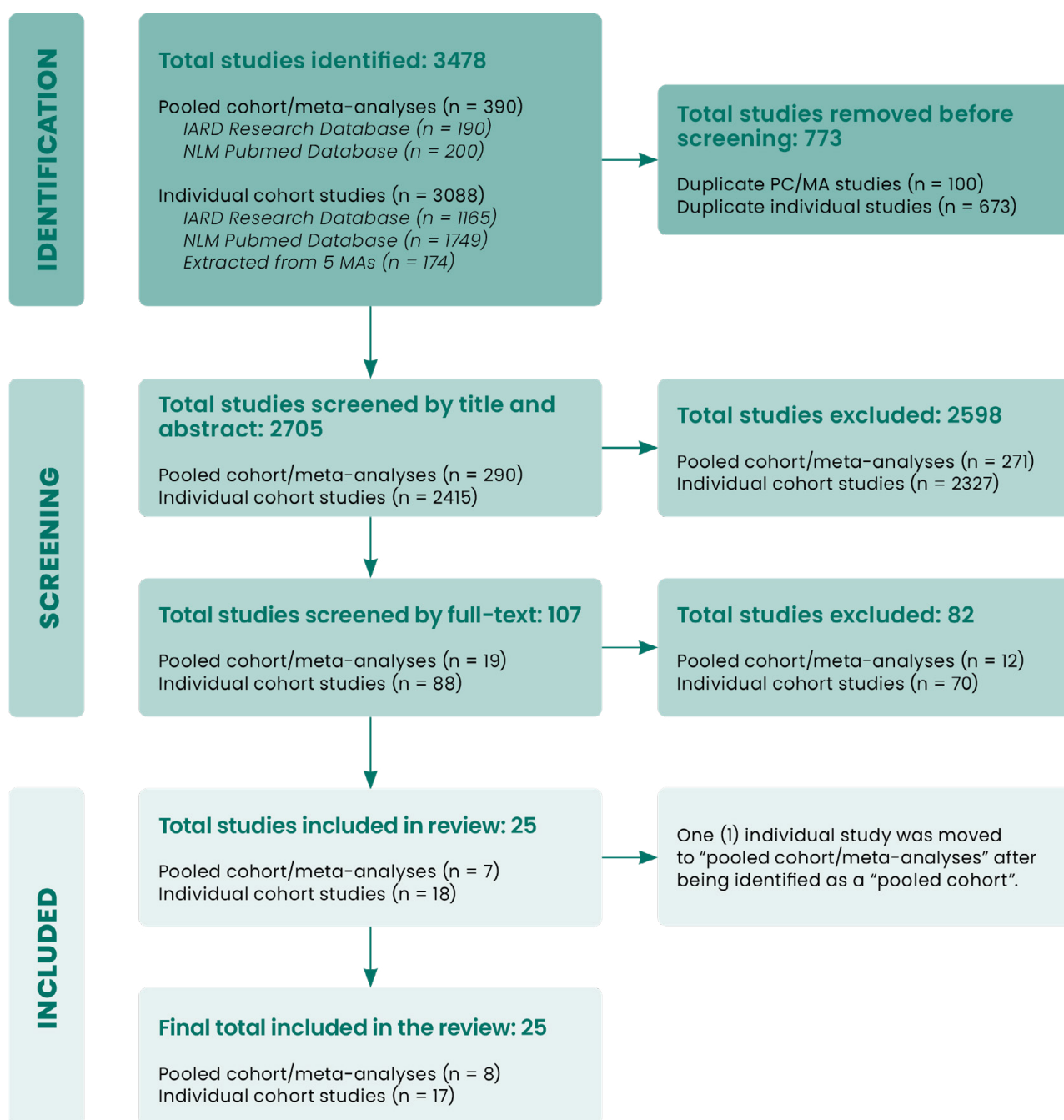
► Search Date: 30 September 2023

##### *Pubmed Database*

1. Pubmed: ( "Liver diseases"[Mesh] OR "liver disease"[TIAB] OR "cirrhosis"[TIAB] OR "hepatitis"[TIAB] OR "steatosis"[TIAB] OR "hepatosteatois"[TIAB] OR "fatty liver"[TIAB] OR "NASH"[TIAB] OR "NAFLD"[TIAB] OR "MAFLD"[TIAB] OR "MASLD"[TIAB] OR "MetALD"[TIAB] ) AND ( "Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh] OR "Alcoholic Beverages"[Mesh] OR drink\*[TIAB] ) AND ( "prospective studies"[MESH] OR "prospective study"[TIAB] OR longitudinal\*[TIAB] OR "longitudinal studies"[MESH] OR "follow-up studies"[MESH] OR cohort[TIAB] OR ( "case control studies" AND ( "nested"[TIAB] OR prospective\*[TIAB] OR longitudinal\*[TIAB] OR cohort[TIAB] ))) AND 1900/01/01:2023/06/30[EDAT] AND limited to English only and Pubdate from 2000

► Search Date: 30 September 2023

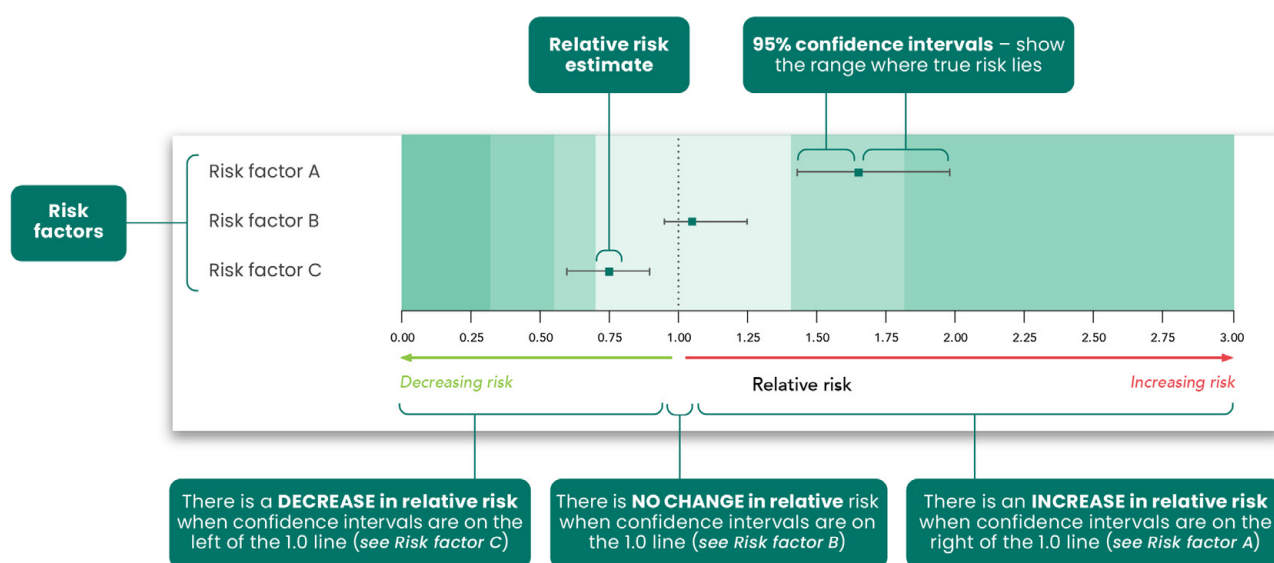
# **PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA)** **FLOW DIAGRAM OF STUDY SELECTION**





## Appendix C

**Figure C1.** Understanding and interpreting forest plots.



**Table C2.** Descriptions of meta-analysis and pooled cohort studies that compare alcohol consumption and risk of liver disease

| Author, year<br>(alphabet-sized) | Study design | Search year                              | Age<br>(range or median) | Sample size<br>(analyzed sample size) | Country/ies or region                                | Study population or study inclusions†                                                                                                                                                                                                                                                                                                                                                                                                            | Sex                 | Outcome<br>(as defined by study) | Reference group<br>(as defined by study) | Alcohol exposure<br>(as defined by study) | Measure-ment type | Risk estimate<br>(95% CI)‡ | Confounders<br>(alphabet-sized)                                                                                                                |  |
|----------------------------------|--------------|------------------------------------------|--------------------------|---------------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------------------------|------------------------------------------|-------------------------------------------|-------------------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Incidence                        |              |                                          |                          |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                     |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
| Becker et al., 2002              | PC           | 1976, 1977, 1983, 1984, 1985, 1986, 1991 | 21–93                    | 16,295                                | Denmark                                              | Pooled data from the Copenhagen City Heart Study, Copenhagen Male Study, and Copenhagen County Centre of Preventive Medicine (eight cohorts) of men and women from urban and suburban Copenhagen                                                                                                                                                                                                                                                 | men                 | alcohol-induced cirrhosis        | 1–7 drinks/week                          | < 1 drink/week                            | RR                | 7.76 (3.35–8.00)           | age, BMI, educational level, percentage wine of total alcohol intake, and smoking habits                                                       |  |
|                                  |              |                                          |                          | 8–21 drinks/week                      |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 2.34 (1.18–4.62)    |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
|                                  |              |                                          |                          | 22–35 drinks/week                     |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 10.40 (5.40–19.90)  |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
|                                  |              |                                          |                          | > 35 drinks/week                      |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 20.40 (10.80–38.80) |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
|                                  |              |                                          |                          | < 1 drink/week                        |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1.32 (0.51–3.38)    |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
|                                  |              |                                          |                          | 1–7 drinks/week                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1.19 (0.54–2.59)    |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
|                                  |              |                                          |                          | 8–21 drinks/week                      |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 5.33 (2.63–10.80)   |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
|                                  |              |                                          |                          | 22–35 drinks/week                     |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 10.80 (4.28–27.1)   |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
| 14,335                           | women        | > 35 drinks/week                         | 14.10 (4.45–44.60)       |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                     |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
| Cao et al., 2016                 | MA           | 2008–2015                                | 18+                      | 76,608                                | Argentina, Brazil, Germany, Hong Kong, Japan, and US | 1. cross-sectional, case-control, cohort study or randomized controlled trial study designs<br>2. reporting association between alcohol consumption and risk of fatty liver disease with non-drinkers as referent group<br>3. report odds ratios with 95% confidence intervals or original data<br>4. diagnose populations with fatty liver disease (hepatic steatosis) or steatohepatitis through the imaging, laboratory tests or liver biopsy | combined            | fatty liver disease              | 0 g/day (nondrinkers)                    | 0–40 g/day (light to moderate drinking)   | OR                | 0.77 (0.69–0.86)           | age, BMI, dyslipidemia, glycated hemoglobin, hypertension, metabolic syndrome, physical activity, sex, smoking status, and waist circumference |  |
|                                  |              |                                          |                          |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | men                 |                                  |                                          | 0–40 g/day (light to moderate drinking)   |                   | 0.77 (0.66–0.91)           |                                                                                                                                                |  |
|                                  |              |                                          |                          |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | women               |                                  |                                          | 0–40 g/day (light to moderate drinking)   |                   | 0.70 (0.63–0.78)           |                                                                                                                                                |  |
|                                  |              |                                          |                          |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | combined            |                                  |                                          | > 40 g/day (heavy alcohol consumption)    |                   | 0.67 (0.58–0.77)           |                                                                                                                                                |  |
|                                  |              |                                          |                          |                                       | Japan                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | men                 |                                  |                                          | > 40 g/day (heavy alcohol consumption)    |                   | 0.66 (0.57–0.77)           |                                                                                                                                                |  |
|                                  |              |                                          |                          |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  | women               |                                  |                                          | > 40 g/day (heavy alcohol consumption)    |                   | 0.87 (0.55–1.36)           |                                                                                                                                                |  |
|                                  |              |                                          |                          |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                     |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |
|                                  |              |                                          |                          |                                       |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                     |                                  |                                          |                                           |                   |                            |                                                                                                                                                |  |

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**Table C2.** Descriptions of meta-analysis and pooled cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                         |    |           |              |           |                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |          |                       |                                      |                                     |    |                  |                                                                                                                        |
|-------------------------|----|-----------|--------------|-----------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------------|--------------------------------------|-------------------------------------|----|------------------|------------------------------------------------------------------------------------------------------------------------|
| Glyn-Owen et al., 2021  | MA | 1946–2020 | 14+          | 1,121,514 | Denmark, Finland, Sweden, UK, and US                                        | 1. cohort studies of adults without pre-existing liver disease, where data were collected on BMI and a quantifiable measure of alcohol consumption.<br>2. incident morbidity or mortality due to chronic liver disease (with cirrhosis or HCC as a minimum requirement).<br>3. liver disease diagnosed using any one of the following: appropriate diagnostic imaging, histology, cancer registry, ICD code, or clinician's diagnosis                                                                                                                                                                               | combined | chronic liver disease | ≤ 112 g/week (alcohol within limits) | > 112 g/week (alcohol above limits) | RR | 2.65 (2.48–2.84) | "Study (as random effect) and sample size (as offset) were entered in to the model to adjust for confounding effects." |
| Hutchinson et al., 2005 | MA | 1989–2004 | 31–61 (mean) | 15,187    | Australia, Brazil, France, Germany, Italy, Japan, Spain, Sweden, UK, and US | 1. study members had chronic HCV, confirmed by a positive serum result on first-, second-, or third-generation ELISA and verified with recombinant immunoblot assay or PCR.<br>2. outcomes included histopathologic cirrhosis (graded by established scoring systems), decompensated cirrhosis (clinically defined by bleeding esophageal varices, ascites, hepatic encephalopathy, or hyperbilirubinemia), or advanced fibrosis (bridging fibrosis with many septa and cirrhosis).<br>3. provided sufficient data to estimate the RR or OR of outcomes and their variance for high versus low alcohol consumption. | combined | liver disease         | < 210 g/week                         | 210–560 g/week                      | RR | 2.14 (1.61–2.85) | age, duration of infection, HIV status, route of infection, sex.                                                       |
|                         |    |           |              |           |                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |          | < 210 g/week          | 210–260 g/week                       | 2.38 (1.61–3.52)                    |    |                  |                                                                                                                        |
|                         |    |           |              |           |                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |          | < 280 g/week          | 280–504 g/week                       | 2.07 (1.30–3.30)                    |    |                  |                                                                                                                        |
|                         |    |           |              |           |                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |          | < 560 g/week          | > 560 g/week                         | 1.94 (1.26–2.99)                    |    |                  |                                                                                                                        |

*Continued on next page*

**Table C2.** Descriptions of meta-analysis and pooled cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     |             |            |                     |                                                                                                                                                                                                      |
|-------------------|-----------------------|---------------------|-----------|-----------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|-------------|------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rehm et al., 2010 | MA                    | 1980–2008           | n/a       | 1,477,887 | China, Denmark, Italy, Japan, and US | 1. case-control or cohort design.<br>2. reported hazard ratios, relative risks, or odds ratios with 95% confidence intervals, or provided sufficient information to calculate them.<br>3. outcome was liver cirrhosis morbidity and/or mortality, assessed clinically or via death certificates.<br>4. reported three or more categories of alcohol consumption, including abstinence as one category. | men                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | liver cirrhosis     | lifetime abstainers | 0–12 g/day  | RR         | 0.30<br>(0.10–0.90) | If a study only reported RRs relative to current abstinence, the RR and its 95% CI were adjusted to lifetime abstinence; adjustments were extracted from the study but not described by the authors. |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 12–24 g/day |            | 0.30<br>(0.20–0.40) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 24–36 g/day |            | 0.70<br>(0.50–1.00) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 36–48 g/day |            | 2.00<br>(1.50–2.70) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 48–60 g/day |            | 2.30<br>(1.70–3.20) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        | women                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                     |                     | ≥ 60 g/day  |            | 5.00<br>(3.90–6.40) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 0–12 g/day  |            | 0.40<br>(0.10–1.20) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 12–24 g/day |            | 1.00<br>(0.50–1.90) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 24–36 g/day |            | 2.40<br>(1.80–3.20) |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     | 36–48 g/day |            | 1.90<br>(1.40–2.60) |                                                                                                                                                                                                      |
|                   | 48–60 g/day           | 5.90<br>(3.70–9.30) |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     |             |            |                     |                                                                                                                                                                                                      |
|                   | ≥ 60 g/day            | 6.10<br>(4.60–8.00) |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                     |                     |             |            |                     |                                                                                                                                                                                                      |
|                   | Roerecke et al., 2016 | MA                  | 2005–2015 | 18+       | 99,370                               | China, Finland, Germany, Japan, Spain, and US                                                                                                                                                                                                                                                                                                                                                          | 1. reporting original, adjusted population-based data (cross-sectional or cohort design).<br>2. outcome is hepatic steatosis using non-invasive methods, including ultrasound, computed tomography, magnetic resonance imaging, or proton magnetic resonance spectroscopy.<br>3. results reported in categories of alcohol consumption relative to non-drinkers, with:<br>– At least one category reporting alcohol intake between 0–20g/day (0–40g/day in sensitivity analyses) for categorical meta-analyses.<br>– At least three drinking groups based on average intake ing/day for dose-response meta-analyses. | combined            | hepatic steatosis   | nondrinkers | < 20 g/day | RR                  | 1.05<br>(0.86–1.30)                                                                                                                                                                                  |
| men               |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 1.68<br>(1.26–2.23) |                     |             |            |                     |                                                                                                                                                                                                      |
| women             |                       |                     |           |           |                                      |                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.80<br>(0.61–1.04) |                     |             |            |                     |                                                                                                                                                                                                      |
| Japan             |                       |                     |           |           |                                      | combined                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.75<br>(0.71–0.79) |                     |             |            |                     |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      | men                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.73<br>(0.68–0.78) |                     |             |            |                     |                                                                                                                                                                                                      |
|                   |                       |                     |           |           |                                      | women                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.72<br>(0.62–0.83) |                     |             |            |                     |                                                                                                                                                                                                      |

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**Table C2.** Descriptions of meta-analysis and pooled cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        |              |    |                               |                                                                                                                                                                                                              |
|--------------------|----|------------|-----|-----------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------------|----------------------------------------|--------------|----|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zhang et al., 2022 | MA | up to 2022 | 18+ | 1,005,339 | China, Denmark, UK, and US       | 1. cohort studies (prospective or retrospective).<br>2. participants aged ≥ 18 years, without alcohol-related liver disease (ALD) at baseline.<br>3. outcome was newly diagnosed ALD (including alcohol-related liver injury, simple steatosis, alcoholic hepatitis, steatohepatitis, fibrosis, or cirrhosis).<br>4. original data reporting risk and protective factors for incident ALD.                                                      | combined | alcohol-related liver disease | < 280 g/week (low alcohol consumption) | ≥ 280 g/week | RR | 4.96 (2.71–9.07) <sup>†</sup> | "The data we extracted are the raw un-adjusted ones because the adjusted data from included articles are not suitable for direct combining considering the different adjustment strategies for confounders." |
| Mortality          |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        |              |    |                               |                                                                                                                                                                                                              |
| Rehm et al., 2010  | MA | 1980–2008  | n/a | 1,477,887 | China, Denmark, Italy, Japan, US | 1. The study had a case-control or cohort design.<br>2. The study reported hazard ratios, relative risks, or odds ratios with 95% confidence intervals, or provided sufficient information to calculate them.<br>3. The outcome was liver cirrhosis morbidity and/ or mortality, assessed clinically or via death certificates.<br>4. The study reported three or more categories of alcohol consumption, including abstinence as one category. | men      | liver cirrhosis               | lifetime abstainers                    | 0–12 g/day   | RR | 1.00 (0.60–1.60)              | If a study only reported RRs relative to current abstinence, the RR and its 95% CI were adjusted to lifetime abstinence; adjustments were extracted from the study but not described by the authors.         |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 12–24 g/day  |    | 1.60 (1.40–2.00)              |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 24–36 g/day  |    | 2.80 (2.30–3.40)              |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 36–48 g/day  |    | 5.60 (4.50–7.00)              |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 48–60 g/day  |    | 7.00 (5.80–8.50)              |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | ≥ 60 g/day   |    | 14.00 (11.70–16.70)           |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 | women    |                               |                                        | 0–12 g/day   |    | 1.90 (1.10–3.10)              |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 12–24 g/day  |    | 5.60 (4.50–6.90)              |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 24–36 g/day  |    | 7.70 (6.30–9.50)              |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 36–48 g/day  |    | 10.10 (7.50–13.50)            |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | 48–60 g/day  |    | 14.70 (11.00–19.60)           |                                                                                                                                                                                                              |
|                    |    |            |     |           |                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |          |                               |                                        | ≥ 60 g/day   |    | 22.70 (17.20–30.10)           |                                                                                                                                                                                                              |

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**Table C2.** Descriptions of meta-analysis and pooled cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    |                |                       |                                                                                                                                                                              |
|-----------------------|----|------------|-----|-----------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|----------------------|----|----------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Roerecke et al., 2019 | MA | up to 2019 | n/a | 2,629,272 | China, Denmark, Italy, UK, US | 1. cohort and case-control studies examining sex-specific association between average alcohol consumption and liver cirrhosis.<br>2. analyses were adjusted for age at baseline.<br>3. data for at least 2 quantitatively defined categories of average alcohol consumption in relation to nondrinkers, or data for former drinkers in relation to long-term abstainers were reported.<br>4. more than 50 cases of liver cirrhosis occurred. | combined | liver cirrhosis | long-term abstainers | RR | Occasional     | 1.11<br>(0.77–1.59)   | age, aspirin use, BMI/waist circumference, coronary disease, diet, diabetes, education, HCV, hypertension, marital status, race, region of residence, sex, SES, and smoking. |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 1 drink/day    | 1.40<br>(1.00–1.97)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 2 drinks/day   | 3.02<br>(1.95–4.70)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 3–4 drinks/day | 3.27<br>(0.90–11.87)  |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 5–6 drinks/day | 6.26<br>(2.38–16.50)  |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | ≥ 7 drinks/day | 10.70<br>(2.95–38.78) |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              | men      |                 |                      |    | Occasional     | 1.23<br>(0.46–3.28)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 1 drink/day    | 0.91<br>(0.31–2.64)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 2 drinks/day   | 1.97<br>(0.89–4.37)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 3–4 drinks/day | 2.62<br>(0.42–16.21)  |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 5–6 drinks/day | 3.80<br>(0.85–17.02)  |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | ≥ 7 drinks/day | 6.93<br>(1.07–44.99)  |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              | women    |                 |                      |    | Occasional     | 0.88<br>(0.77–1.00)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 1 drink/day    | 1.33<br>(1.19–1.48)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 2 drinks/day   | 3.59<br>(2.58–4.99)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 3–4 drinks/day | 2.00<br>(0.99–4.03)   |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | 5–6 drinks/day | 8.73<br>(2.69–25.76)  |                                                                                                                                                                              |
|                       |    |            |     |           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |                 |                      |    | ≥ 7 drinks/day | 15.20<br>(5.81–39.76) |                                                                                                                                                                              |

\* MA = meta-analysis; PC = pooled cohort

† For meta-analyses, the study inclusion criteria were described instead of the study population.

‡ Risk estimates are unadjusted estimates

**Table C3.** Descriptions of individual cohort studies that compare alcohol consumption and risk of liver disease

| Author, year        | Study design | Follow-up year (average or median) | Age (range or median) | Sample size (analyzed sample size) | Country/Region | Study population description (as stated in the study)                                                                                                                                                                                                               | Sex              | Outcome (as defined by study) | Reference group (as defined by study) | Alcohol exposure (as defined by study) | Measure-ment type | Risk estimate (95% CI) <sup>‡</sup>   | Confounders                                                                                                                                                                                                                       |
|---------------------|--------------|------------------------------------|-----------------------|------------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------------------|---------------------------------------|----------------------------------------|-------------------|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Incidence           |              |                                    |                       |                                    |                |                                                                                                                                                                                                                                                                     |                  |                               |                                       |                                        |                   |                                       |                                                                                                                                                                                                                                   |
| Carter et al., 2019 | P-C          | n/a                                | 20+                   | 91,552                             | Denmark        | Residents of Copenhagen of white, Danish descent were recruited from national registers. Participants with liver disease were excluded at baseline.                                                                                                                 | combined         | liver disease                 | 0 units/week                          | 1–14 units/week                        | OR                | 0.84 (0.62–1.13)                      | age, education, income, physical activity, pre-existing conditions, sex, smoking                                                                                                                                                  |
|                     |              |                                    |                       |                                    |                |                                                                                                                                                                                                                                                                     |                  |                               |                                       | > 15 units/week                        |                   | 1.58 (1.16–2.14)                      |                                                                                                                                                                                                                                   |
| Chang et al., 2020  | P-C          | 4.1                                | 18+                   | 190,048                            | South Korea    | Healthy, educated, Korean men and women with comprehensive exam history at Kangbuk Samsung Hospital Total Healthcare Center in Seoul or Suwon, South Korea. Participants with history of cirrhosis, fibrosis, NAFLD, high alcohol intake, Hep B or C were excluded. | men (combined)   | hepatic steatosis             | nondrinkers (0 g/day)                 | light drinkers (1 g/day–9.9 g/day)     | HR                | 0.93 (0.90–0.95)                      | age, BMI, center, education level, history of diabetes, history of hypertension, medication for diabetes, medication for dyslipidemia, medication for hypertension, regular exercise, sex, smoking status, year of screening exam |
|                     |              |                                    |                       |                                    |                |                                                                                                                                                                                                                                                                     | women (combined) |                               |                                       | moderate drinkers (10 g/day–30 g/day)  |                   | 0.90 (0.87–0.92)                      |                                                                                                                                                                                                                                   |
|                     |              |                                    |                       |                                    |                |                                                                                                                                                                                                                                                                     |                  |                               |                                       | light drinkers (1 g/day–9.9 g/day)     |                   | 0.93 (0.90–0.95)                      |                                                                                                                                                                                                                                   |
|                     |              |                                    |                       |                                    |                |                                                                                                                                                                                                                                                                     |                  |                               |                                       |                                        |                   | moderate drinkers (10 g/day–20 g/day) |                                                                                                                                                                                                                                   |

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**Table C3.** Descriptions of individual cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         |                               |    |                      |                                                                           |
|------------------------|-------|------|-------------------|-----------------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------------------|-----------------------------------------|-------------------------------|----|----------------------|---------------------------------------------------------------------------|
| Hagstrom et al., 2018  | P-C   | 37.8 | 18-20             | 43,269                            | Sweden | Swedish men who were included in a nationwide population-based study when compulsorily enlisted for conscription. Participants without severe disabilities or disease excluded.                                                                                                         | men | severe liver disease | 0 g/day                                 | 1-5 g/day                     | HR | 1.39<br>(0.74-2.59)  | BMI, cardiovascular fitness, cognitive ability, smoking, use of narcotics |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 6-10 g/day                    |    | 1.50<br>(0.79-2.87)  |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 11-15 g/day                   |    | 1.33<br>(0.67-2.65)  |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 16-20 g/day                   |    | 1.58<br>(0.77-3.24)  |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 21-25 g/day                   |    | 2.03<br>(0.98-4.23)  |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 26-30 g/day                   |    | 1.95<br>(0.87-4.35)  |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 31-40 g/day                   |    | 2.32<br>(1.06-5.05)  |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 41-50 g/day                   |    | 2.99<br>(1.28-7.00)  |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 51-60 g/day                   |    | 4.83<br>(2.07-11.29) |                                                                           |
|                        |       |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | > 60 g/day                    |    | 3.66<br>(1.65 -8.11) |                                                                           |
| Hashimoto et al., 2015 | P-C   | 10.0 | mean<br>40.9-44.7 | 3,447                             | Japan  | Citizens of local communities and their spouses who were registered for the health checkup program at Murakami Memorial Hospitals in Gifu, Japan and received the health checkup programs repeatedly over a decade. Participants with Hep B or C, or history of liver disease excluded. | men | fatty liver          | none or minimal drinker (< 40.0 g/week) | light drinker (40-140 g/week) | HR | 0.72<br>(0.60-0.86)  | age, BMI, physical activity, smoking                                      |
|                        |       |      |                   | moderate drinker (140-280 g/week) |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 0.69<br>(0.57-0.84)           |    |                      |                                                                           |
|                        |       |      |                   | heavy drinker (> 280 g/week)      |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 0.80<br>(0.57-1.00)           |    |                      |                                                                           |
|                        |       |      |                   | light drinker (40-140 g/week)     |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 0.86<br>(0.52-1.42)           |    |                      |                                                                           |
|                        |       |      |                   | moderate drinker (140-280 g/week) |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 1.23<br>(0.62-2.41)           |    |                      |                                                                           |
|                        |       |      |                   | heavy drinker (> 280 g/week)      |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         | 1.12<br>(0.35-3.55)           |    |                      |                                                                           |
| 1,990                  | women |      |                   |                                   |        |                                                                                                                                                                                                                                                                                         |     |                      |                                         |                               |    |                      |                                                                           |

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**Table C3.** Descriptions of individual cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                |                                           |    |                  |                                                                                                                |
|---------------------------|-----|-----|-----------|-----------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------------------------------------------------|----------------|-------------------------------------------|----|------------------|----------------------------------------------------------------------------------------------------------------|
| Liu et al., 2009          | P-C | 6.1 | mean 56.0 | 1,290,413 | England, Scotland | Middle-aged women of marginally higher socioeconomic status who were recruited through the United Kingdom National Health Service Breast Screening Service. Participants with liver cirrhosis, cancer, hepatitis, or gallbladder disease excluded.                                                                                                     | women    | liver cirrhosis                                      | 1-2 units/week | 0 units/week (never or former drinker)    | RR | 1.23 (0.74-2.06) | age, BMI, region of recruitment, SES, smoking                                                                  |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | 3-6 units/week                            |    | 1.73 (1.04-2.86) |                                                                                                                |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | 7-14 units/week                           |    | 1.92 (1.15-3.21) |                                                                                                                |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | ≥ 15 units/week                           |    | 5.38 (3.02-9.58) |                                                                                                                |
| Peeraphatdit et al., 2020 | R-C | 5.8 | mean 55.8 | 18,506    | U.S.              | Primarily white participants enrolled in the Mayo Clinic Biobank. Participants with fatty liver disease, cirrhosis, hepatitis B or C, or autoimmune hepatitis excluded.                                                                                                                                                                                | combined | hepatic steatosis                                    | nondrinkers    | low to moderate drinkers (0-2 drinks/day) | HR | 1.09 (0.90-1.33) | age, BMI, cardiac event at baseline, diabetes, dyslipidemia, hypertension, race/ethnicity, sex, smoking status |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | heavy drinkers (> 2 drinks/day)           |    | 2.19 (1.54-3.06) |                                                                                                                |
| Sogabe et al., 2023       | P-C | n/a | mean 51.6 | 1,192     | Japan             | Patients recruited from Shikoku Central Hospital of the Mutual Aid Association of Public School Teachers, who underwent abdominal ultrasonography and laboratory examination more than twice during regular health checkups in Shikokuchuo, Japan. Participants with previous liver surgery, hospital treatment, previous liver disease were excluded. | men      | metabolic dysfunction-associated fatty liver disease | nondrinkers    | 0.1-69.9 g/week                           | OR | 0.76 (0.53-1.08) | current smoking status, eating before going to bed, regular exercise, the custom of eating breakfast           |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | 70-139.9 g/week                           |    | 1.15 (0.84-1.58) |                                                                                                                |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | 140-279.9 g/week                          |    | 0.87 (0.65-1.15) |                                                                                                                |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | ≥ 280 g/week                              |    | 1.60 (0.85-2.99) |                                                                                                                |
|                           |     |     | mean 49.8 | 1,566     |                   |                                                                                                                                                                                                                                                                                                                                                        | women    |                                                      |                | 0.1-69.9 g/week                           |    | 1.14 (0.79-1.65) |                                                                                                                |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | 70-139.9 g/week                           |    | 1.16 (0.70-1.94) |                                                                                                                |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | 140-279.9 g/week                          |    | 1.35 (0.74-2.45) |                                                                                                                |
|                           |     |     |           |           |                   |                                                                                                                                                                                                                                                                                                                                                        |          |                                                      |                | ≥ 280 g/week                              |    |                  |                                                                                                                |

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**Table C3.** Descriptions of individual cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                       |     |     |           |                            |       |                                                                                                                                                                        |                            |                     |                                |                                                    |    |                  |                                                                                 |
|-----------------------|-----|-----|-----------|----------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------|--------------------------------|----------------------------------------------------|----|------------------|---------------------------------------------------------------------------------|
| Sugiyama et al., 2021 | R-C | 6.0 | 10+       | 17,289                     | Japan | Residents who received ultrasonography at health checkups in Hiroshima or Iwate Prefecture, Japan. Participants with fatty liver, hepatitis B or C were excluded.      | men (combined)             | fatty liver disease | nondrinkers (< 30.0 g/day)     | moderate drinker (30–60 g/day)                     | OR | 1.00 (0.90–1.10) | age, BMI, diabetes, sex                                                         |
|                       |     |     |           | heavy drinker (≥ 60 g/day) |       |                                                                                                                                                                        | 1.20 (1.00–1.40)           |                     |                                |                                                    |    |                  |                                                                                 |
|                       |     |     | 13,773    | women (combined)           |       |                                                                                                                                                                        | nondrinkers (< 20.0 g/day) |                     | moderate drinker (20–40 g/day) | 1.00 (0.90–1.10)                                   |    |                  |                                                                                 |
|                       |     |     |           |                            |       |                                                                                                                                                                        | heavy drinker (≥ 40 g/day) |                     | 1.20 (1.00–1.40)               |                                                    |    |                  |                                                                                 |
| Yamada et al., 2010   | R-C | 5.0 | mean 49.8 | 5,444                      | Japan | Participants undergoing medical checkups at Okazaki City Medical Association, Public Health Center. Participants with hepatic diseases, virus, or fatty liver disease. | men                        | fatty liver disease | nondrinkers                    | occasional drinkers                                | OR | 0.95 (0.77–1.17) | age, BMI, elevated blood pressure, fasting blood glucose, hypertension, smoking |
|                       |     |     |           |                            |       |                                                                                                                                                                        |                            |                     |                                | daily moderate drinkers (23.0 g/day)               |    | 0.72 (0.58–0.89) |                                                                                 |
|                       |     |     |           |                            |       |                                                                                                                                                                        |                            |                     |                                | daily heavy drinkers (46 and 69 g/day, > 69 g/day) |    | 0.65 (0.50–0.85) |                                                                                 |
|                       |     |     | mean 50.4 | 4,980                      |       |                                                                                                                                                                        | women                      |                     |                                | occasional drinkers                                |    | 0.81 (0.63–1.04) |                                                                                 |
|                       |     |     |           |                            |       |                                                                                                                                                                        |                            |                     |                                | daily moderate drinkers (23.0 g/day)               |    | 0.71 (0.44–1.16) |                                                                                 |
|                       |     |     |           |                            |       |                                                                                                                                                                        |                            |                     |                                | daily heavy drinkers (46 and 69 g/day, > 69 g/day) |    | 0.74 (0.25–2.17) |                                                                                 |

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**Table C3.** Descriptions of individual cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

| Mortality         |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    |                                |    |                       |                                                                                                                                                                                                                     |
|-------------------|-----|------|-------|---------|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------------|--------------------|--------------------------------|----|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fan et al., 2022  | P-C | 13.1 | 40-79 | 81,694  | U.S.     | Participants (about 65% Black) were enrolled from community health centers or through mailed invitations across 12 southeastern U.S. states (Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia). | men      | liver disease                   | nondrinkers        | former drinkers                | HR | 1.37<br>(0.70-2.69)   | age, BMI, daily intake of total energy, education, healthy eating index 10, insurance coverage, physical activity, race, recruitment source, sex, smoking status, socioeconomic index                               |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | moderate drinkers (≤ 28 g/day) |    | 1.61<br>(0.84-3.10)   |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | heavy drinkers (> 28 g/day)    |    | 2.77<br>(1.42-5.40)   |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              | women    |                                 |                    | former drinkers                |    | 1.11<br>(0.67-1.83)   |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | moderate drinkers (≤ 14 g/day) |    | 1.06<br>(0.63-1.76)   |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | heavy drinkers (> 14 g/day)    |    | 2.09<br>(1.20-3.64)   |                                                                                                                                                                                                                     |
| Hart et al., 2008 | P-C | 29.0 | 21-65 | 6,000   | Scotland | Relatively healthy men from 27 work-places in Glasgow, Clydebank and Grangemouth in Scotland, relatively healthy and able to work.                                                                                                                                                           | men      | liver disease                   | none               | 1-7 units/week                 | HR | 1.06<br>(0.18-6.37)   | angina, BMI, bronchitis, car use, cholesterol, deprivation category, education, father's social class, forced expiratory volume in 1 second (fev1), ischaemia on electrocardiogram, siblings, smoking, social class |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | 8-14 units/week                |    | 1.72<br>(0.34-8.56)   |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | 15-21 units/week               |    | 7.28<br>(1.86-28.50)  |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | 22-34 units/week               |    | 7.44<br>(1.88-29.40)  |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | ≥ 35 units/week                |    | 15.50<br>(4.13-58.60) |                                                                                                                                                                                                                     |
| Patra et al.,     | P-C | 7.0  | 18+   | 231,666 | U.S.     | Civillian and noninstitutionalized individuals who participated in the NHIS.                                                                                                                                                                                                                 | combined | chronic liver disease cirrhosis | lifetime abstainer | Former                         | HR | 0.90<br>(0.43-1.89)   | age at baseline, education, excluded 2 years of follow-up, race/ethnicity, sex, smoking status                                                                                                                      |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | Up to 20 g/day                 |    | 0.49<br>(0.26-0.94)   |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | > 20-40 g/day                  |    | 1.44<br>(0.47-4.44)   |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | > 40-60 g/day                  |    | 6.17<br>(2.32-16.44)  |                                                                                                                                                                                                                     |
|                   |     |      |       |         |          |                                                                                                                                                                                                                                                                                              |          |                                 |                    | > 60 g/day                     |    | 4.46<br>(1.23-15.83)  |                                                                                                                                                                                                                     |

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**Table C3.** Descriptions of individual cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                       |                       |                             |    |                      |                                                                                                                               |
|-----------------------|-----|------|-------|-----------------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-----------------------|-----------------------|-----------------------------|----|----------------------|-------------------------------------------------------------------------------------------------------------------------------|
| Persson et al., 2013  | P-C | 7.0  | 50-71 | 494,743                     | U.S.        | Majority white members of the American Association of Retired Persons residing in 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia and Detroit, Michigan) in the US. Participants with cancer excluded.                                                                                                                                                                  | combined               | liver disease         | < 1 drink/day         | none                        | HR | 1.88<br>(1.55-2.28)  | age, BMI, diabetes, education, race, sex, smoking                                                                             |
|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                       |                       | 1-3 drinks/day              |    | 2.03<br>(1.63-2.52)  |                                                                                                                               |
|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                       |                       | > 3 drinks/day              |    | 5.84<br>(4.81-7.10)  |                                                                                                                               |
| Schwartz et al., 2013 | P-C | n/a  | 50-69 | 27,086                      | Finland     | Men living in southwestern Finland recruited into a prevention trial. Participants with cirrhosis excluded.                                                                                                                                                                                                                                                                                                                                                | men                    | liver disease         | < 5.33 g/day          | 5.33-20.44 g/day            | HR | 2.06<br>(1.22-3.50)  | age, BMI, diabetes, education, smoking, study arm                                                                             |
|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                       |                       | > 20.44 g/day               |    | 6.68<br>(4.16-10.71) |                                                                                                                               |
| Setiawan et al., 2016 | P-C | 19.6 | 45-75 | 18,485                      | U.S.        | US-born Hispanic men and women recruited from DMV, voter registration, and health care financing admisnitation in California (mostly Los Angeles County). Participants with cancer, except non-melanoma skin cancer excluded.<br><br>Foreign born Hispanic men and women living in the US for 15+ years, majority from Mexico (~70%), and the remainder from Central or South America. Participants with cancer, except non-melanoma skin cancer excluded. | combined               | chronic liver disease | nondrinkers (0 g/day) | < 2 drinks/day (< 24 g/day) | HR | 0.66<br>(0.47-0.94)  | age at cohort entry, BMI, cigarette, diabetes, dietary factors, education, level of education, sex, smoking vigorous activity |
|                       |     |      |       | ≥ 2 drinks/day (≥ 24g/day)  |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                       |                       | 2.23<br>(1.52-3.29)         |    |                      |                                                                                                                               |
|                       |     |      |       | < 2 drinks/day (< 24 g/day) |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                       |                       | 1.07<br>(0.68-1.70)         |    |                      |                                                                                                                               |
|                       |     |      |       | ≥ 2 drinks/day (≥ 24 g/day) |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                        |                       |                       | 2.74<br>(1.53-4.91)         |    |                      |                                                                                                                               |
| Sinn et al., 2021     | P-C | n/a  | 40-84 | 150,667                     | South Korea | Patients without chronic viral hepatitis in the NHIS-NSC who underwent at least 1 health screening examination during the study period.                                                                                                                                                                                                                                                                                                                    | men (combined)         | liver disease         | none                  | Light (< 20 g/day)          | HR | 1.03<br>(0.82-1.29)  | antiviral treatment, BMI, charlson comorbidity index, income percentile, residential area, sex, smoking status                |
|                       |     |      |       | women (combined)            |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Moderate (20-60 g/day) |                       |                       | 1.78<br>(1.42-2.23)         |    |                      |                                                                                                                               |
|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Heavy (≥ 60 g/day)     |                       |                       | 3.33<br>(2.34-4.75)         |    |                      |                                                                                                                               |
|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Light (< 10 g/day)     |                       |                       | 1.03<br>(0.82-1.29)         |    |                      |                                                                                                                               |
|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Moderate (10-40 g/day) |                       |                       | 1.78<br>(1.42-2.23)         |    |                      |                                                                                                                               |
|                       |     |      |       |                             |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Heavy (≥ 40 a/day)     |                       |                       | 3.33<br>(2.34-4.75)         |    |                      |                                                                                                                               |

*Continued on next page*

**Table C3.** Descriptions of individual cohort studies that compare alcohol consumption and risk of liver disease (*continued*)

|                      |     |      |       |         |       |                                                                                                                                                                                                                                                                              |     |                 |             |                |    |                     |                               |
|----------------------|-----|------|-------|---------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----------------|-------------|----------------|----|---------------------|-------------------------------|
| Yang et al.,<br>2012 | P-C | 15.0 | 40–79 | 218,189 | China | Nationally representative population of middle-aged men, recruited from 45 areas (23 urban and 22 rural) randomly selected from China's National Disease Surveillance Points for clinical survey. Men with previous disease or death within the first 3 years were excluded. | men | liver cirrhosis | nondrinkers | < 140 g/week   | HR | 1.12<br>(0.76–1.64) | age, area, education, smoking |
|                      |     |      |       |         |       |                                                                                                                                                                                                                                                                              |     |                 |             | 140–279 g/week |    | 0.84<br>(0.59–1.21) |                               |
|                      |     |      |       |         |       |                                                                                                                                                                                                                                                                              |     |                 |             | 280–419 g/week |    | 1.16<br>(0.85–1.56) |                               |
|                      |     |      |       |         |       |                                                                                                                                                                                                                                                                              |     |                 |             | 420–699 g/week |    | 1.22<br>(0.83–1.79) |                               |
|                      |     |      |       |         |       |                                                                                                                                                                                                                                                                              |     |                 |             | ≥ 700 g/week   |    | 1.74<br>(1.22–2.48) |                               |

\* R-C = retrospective cohort; P-C = prospective cohort

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