The Daffodil Centre

The Australian Prevention Partnership Centre

Preventing liver cancer: Alcohol consumption, alcohol-related liver disease and primary liver cancer

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Alcohol consumption and risk of liver disease and liver cancer

Introduction

Alcohol use is common, and excessive alcohol consumption is a major contributor to the disease burden in Australia, and worldwide (1). Approximately eight in every ten Australian adults drink, with 6.3% consuming on average more than four drinks per day (2). More than 200 health conditions are linked to harmful alcohol use, and the casual relationship between liver disease and cancer is well established (3,4). Nearly half (48%) of all deaths from liver cirrhosis and 10% of all deaths from liver cancer are attributable to alcohol globally (5).

Alcohol-related liver disease (ARLD) is a common cause of liver cirrhosis and is associated with long-term heavy drinking (6). Alcohol can interfere with lipid metabolism to induce fat deposition in the liver, and this process is accelerated by excessive consumption (7). When fat cells comprise more than 5% of hepatocytes this is known as steatosis, or “fatty liver”. Steatosis may progress to steatohepatitis if liver tissue becomes inflamed, and on to fibrosis or cirrhosis if fat cells are replaced by scar tissue as outlined in Figure 2 (8). Although the early stages of liver disease are reversible, the end stages are not, and have higher rates of liver-related complications, mortality, and progression to primary liver cancer (8).

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer in Australia (9). In 85 to 90% of cases, HCC arises in the context of underlying liver cirrhosis (10). Currently, ARLD accounts for 25% of all decompensated liver cirrhosis cases in Australia with the remaining 29%, 23%, 13% and 10% due to chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, metabolic associated liver disease (MAFLD, formerly NAFLD, non-alcoholic fatty liver disease) and unknown causes (11).

While ARLD, HBV, HCV and NALFD are distinguished as separate aetiologies of liver cirrhosis and HCC, it is recognised in practice that patients may be comorbid (12). Alcohol consumption may exacerbate progression of chronic liver disease due to viral hepatitis (13) and following the shift in terminology from NAFLD to MAFLD, patients can be diagnosed as having fatty liver due to both metabolic and alcohol-related causes (14).

This report reviews evidence from international systematic reviews with meta-analyses, pooled analyses, and studies of any type in the Australian context regarding the association between alcohol consumption (any level) and risk of liver disease and primary liver cancer. We sought to identify studies which quantified the level of alcohol consumed by participants in grams per day (g/d) or equivalent and included studies involving participants with and without existing liver disease of any aetiology, not only ARLD.

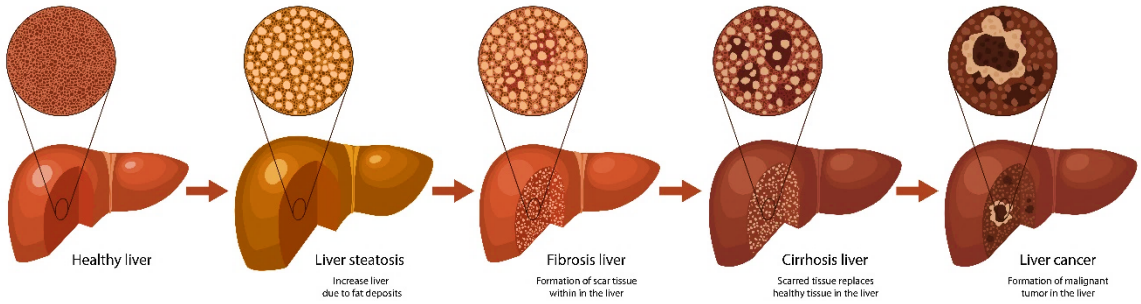

Figure 1 Stages of liver disease

Review questions and aims

Question 1: What is known about the association between alcohol consumption and risk of early-stage liver disease (i.e., steatosis or 'fatty liver' and steatohepatitis)?

Question 2: What is known about the association between alcohol consumption and risk of advanced liver fibrosis or cirrhosis?

Question 3: What is known about the association between alcohol consumption and risk of primary liver cancer?

This report presents the results and key findings for all questions. As a scoping review was conducted rather than a systematic review, this report does not provide a critical appraisal of the literature nor an assessment of the risk of bias. Rather, it provides summaries of the evidence and identifies areas where evidence was limited.

Methods

Search strategy

Electronic literature searches were performed from December 2011 to December 2021 to search national and international literature using key terms relating to "alcohol," "drinking" and "liver disease" or "liver cancer." Embase and MEDLINE databases were searched concurrently using the Ovid interface. In addition, the Cochrane Library of Systematic Reviews and the International Prospective Register of Systematic Reviews (PROSPERO) databases were searched. Reference lists of all included papers were scanned manually for other relevant studies. Complete details of the search provided in the Appendix Tables 1-3.

Eligibility criteria

The eligibility criteria and scope of the review were defined using the "Participant Concept Context" framework as described below. A detailed summary of the inclusion and exclusion criteria is provided in the Appendix Table 4.

Participants

To be included studies needed to involve participants who had consumed a quantifiable level of alcohol (g/d or equivalent, e.g., grams per week (g/w) whose stage of liver disease (normal liver, steatosis, steatohepatitis, fibrosis, cirrhosis, or liver cancer) was reported. Studies could involve participants from the general population and/or participants with existing liver disease of any aetiology including NAFLD, HBV- or HCV-related liver disease. The outcomes of HCC, primary liver cancer, and liver cancer were recorded as reported in the original study.

Studies reporting on descriptors such as "social" or "frequent" drinking or patients with alcohol-use disorder (AUD) were excluded as they did not clearly report the level of alcohol consumed. Studies involving participants who had undergone liver transplantations or bariatric surgery were excluded. Studies were excluded if they reported solely on other outcomes such as liver transplantation or rare primary liver cancers such as intrahepatic cholangiocarcinoma (ICC) or bile duct cancer.

Concept

Included studies needed to report on the relative risk of liver disease and/or liver cancer due to alcohol consumption using the comparator group of lifetime or current abstainers, non-drinkers and/or light drinkers,. Risk ratios (RR), odds ratios (OR) or hazard ratios (HR) and their corresponding 95% confidence intervals (CI) could be used to estimate the relative risk. The relative risk estimates were collected as reported in the original studies (e.g., drinks/day,

grams/day or grams/week), however for the purposes of comparison in this review have been categorised into similar groupings. Studies that did not estimate the relative risk or where the comparator/reference group was unclear were excluded.

Context

The searches were limited to human studies written in English. There were no specific exclusion criteria based on cultural/sub-cultural factors, geographic location, racial or gender-based interests or details about the setting; all international and national literature were considered relevant. The timeframe of the search is defined below.

Types of sources

Conference abstracts, letters, editorials, and narrative reviews were not included. Preliminary literature searches identified several existing systematic reviews with meta-analyses on the association between alcohol and the risk of liver disease (15,16) and liver cancer (17,18), As such, the literature search was conducted in two parts:

Part A: was restricted to review systematic reviews, meta-analyses, and pooled analyses published in the last decade (December 2011 to December 2021). We also searched the PROSPERO database for ongoing prospectively registered systematic reviews.

Part B: reviewed Australian literature of any study type published to December 2021. As literature in the Australian context is sparse, we also included Australian papers if qualitative rather than quantitative measures of alcohol intake were reported.

Study selection

Following the search, and exclusion of duplicates, all identified citations were collated and uploaded into Microsoft Excel. Titles and abstracts were screened by one reviewer (GC) for assessment against the inclusion criteria. Potentially relevant articles were retrieved in full and assessed in detail. Reasons for exclusion at full text were recorded and are reported in the Appendix Tables 5-6. Any difficulties in determining if a study should be included at each stage of the selection process were resolved through discussion with a senior researcher (EF). The results of the search and the study inclusion process are described in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) (19) and are presented in the results section Figures 1-3.

Data extraction

The following data were extracted: study information; setting; number of participants; exposure (quantity of alcohol consumption); reference group; outcomes and outcome measures; sub-group analyses (e.g., by gender or geographic location), quality assessment tool used; funding information, and author's key conclusions. A formal critical appraisal and risk of bias assessment were not performed, however the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) was used to identify key strengths and limitations of included studies (20). The AMSTAR-2 contains 16 domains and is not intended to generate an overall score but assists in the identification of high-quality systematic reviews as outlined in the Appendix Tables 7-9 (20).

Results

Search outcomes

Part A Search for systematic reviews, meta-analyses, and pooled analyses

The literature search identified 7,406 potentially relevant records as shown in Figure 2. After removing duplicates and studies that were not a systematic review, meta-analysis, or pooled analysis, 150 records were screened by their title and abstracts. Of these, 24 were retrieved and the full text read. Fifteen records were excluded, and an additional 3 identified by scanning reference lists were included to give a total of 12 studies included in Part A of the

review (15–17,21–29). Of the 12 studies, 11 were systematic reviews with meta-analyses, and one was a pooled analysis.

Previously, the World Cancer Research Fund (WCRF) concluded that there is convincing evidence that alcohol consumption increases the risk liver cancer. This report by the WCRF was conducted in 2014 in the form of a meta-analysis, and WCRF results are presented alongside relevant outcomes from studies identified in the literature search (18).

Ongoing systematic reviews with meta-analysis

Five systematic reviews are registered in PROSPERO, the international prospective register of systematic reviews, as of December 2021. All five studies aimed to investigate the association between light or moderate drinking and risk of NAFLD, as shown in Table 1.

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Part B Studies in the Australian context published at any time

The literature search identified 247 potentially relevant Australian records as shown in Figure 2. After removing duplicates, 163 records were screened by their titles and abstracts. Of these, 13 studies were retrieved, and the full text read, and an additional four were identified by scanning reference lists of included studies or by recommendation. In total, eight Australian studies were included (30–37). Of the eight Australian studies, none related to early-stage liver disease (steatosis/steatohepatitis), six related to advanced liver fibrosis or cirrhosis (30–35) and two related to primary liver cancer (36,37).

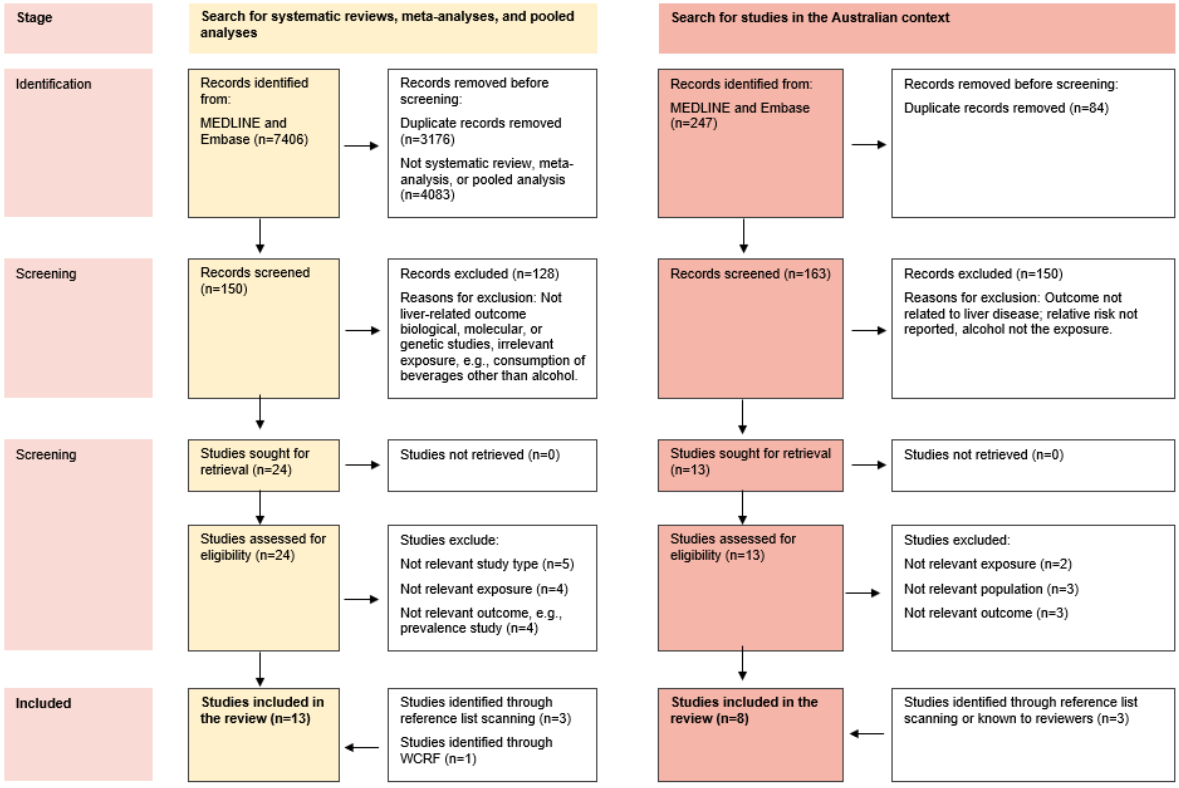

Figure 2 Search outcomes

Table 1 Characteristics of studies registered in PROSPERO.

Author (year registered)	Population	Exposure	Comparator	Outcome	PROSPERO ID	Status
Jarvis et al. (2019)	NAFLD	<57g/d men, <40g/d women	No alcohol consumption	NASH, fibrosis, HCC, cirrhosis or liver-related mortality	CRD42020168022	Completed
Niu et al. (2020)	NAFLD	<20g/d	Never consumed alcohol	Advanced liver fibrosis	CRD42020213845	Review ongoing
Van Parys et al. (2021)	NAFLD	NR	No alcohol consumption	NASH, liver fibrosis, cirrhosis, HCC, overall mortality	CRD42021246943	Review ongoing
Naasila et al. (2021)	General	Self-reported alcohol consumption	NR	CVD, T2DM, NAFLD, All-cause and cause-specific mortality	CRD42020151510	Review ongoing
Li et al. (2021)	General	<10g/d, 10-20g/d	Non-drinkers	NAFLD incidence or progression	CRD42021265050	Review ongoing

CVD; cardiovascular disease, g/d; grams per day, HCC; hepatocellular carcinoma, ID; identification number, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, NR; not reported, T2DM; type 2 diabetes mellitus.

Association between alcohol consumption and risk of steatosis and steatohepatitis

Results from Part A: systematic reviews and meta-analyses

Study characteristics

Three systematic reviews with meta-analyses examined the association between alcohol consumption and risk of steatosis or steatohepatitis as shown in Table 2 (15,21,24). The most recent meta-analysis by Wongtrakul et al. (2021) involved only NAFLD patients and investigated risk of steatohepatitis following moderate alcohol consumption (<210g/w for men and <140g/w for women) (21). The second meta-analysis by Roerecke et al. (2016) investigated the risk of steatosis among participants with NALFD or ARLD who consumed <20g/day and excluded participants with HBV- or HCV-related liver disease (15). The third meta-analysis by Cao et al. (2016) involved participants with liver disease of any aetiology and investigated the risk of steatosis/steatohepatitis as a combined outcome among participants who consumed ≤40g/d or >40g/d (24). All three meta-analyses involved non-drinkers as the reference group participants (15,21,24).

Relevant outcomes are outlined in the text below and Table 3. While a formal critical appraisal of included studies was beyond the scope of this review, confidence in the overall findings of the systematic reviews with meta-analyses by Wongtrakul et al. and Roerecke et al. was rated 'moderate' and by Cao et al. 'low' using the AMSTAR-2 instrument (15,21,24).

Table 2 Characteristics of systematic reviews with meta-analyses which examined risk of steatosis or steatohepatitis

Author (year)	Literature search to:	# Studies included	Participants	Alcohol intake categories	Reference group	Outcome	AMSTAR-2
Wongtrakul et al. (2021) (21)	Oct 2020	6	NAFLD patients	<210g/w men, <140g/w women*	Non-drinkers	Steatohepatitis	Moderate
Roerecke et al. (2016) (15)	Dec 2015	18	Adults with or without existing liver disease	<20g/d	Non-drinkers	Steatosis	Moderate

Author (year)	Literature search to:	# Studies included	Participants	Alcohol intake categories	Reference group	Outcome	AMSTAR-2
Cao et al. (2016) (24)	NR	16	Adults with or without existing liver disease	≤40g/d >40g/d	Non-drinkers	Steatosis/Steato hepatitis	Low

Some variations were accepted, e.g., <200g/w and <40g/d. **Non-drinker referred to current (n=4) or lifetime abstainers (n=2 studies). Research quality was assessed using the AMSTAR-2 tool for critical appraisal of systematic reviews and the overall confidence of findings was rated as high, moderate, low or critically low (20). AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews, g/d; grams per day, g/w; grams per week, NAFLD; non-alcoholic fatty liver disease NR; not reported.* ***Type of included studies:* *Wongtrakul: All cross-sectional, Roerecke: 7 Cohort; 11 Cross-sectional, Cao: 1 Cohort; 15 Cross-sectional.* ***Location of included studies****: Wongtrakul: 2 US; 1 Australia; 1 Brazil; 1 Japan; 1 Malaysia; 1 Brazil, Roerecke (2016): 11 Japan; 3 China; 3 Europe; 1 US, Cao: 9 Japan; 2 US; 2 German; 2 South America; 1 Hong Kong.*

Relevant outcomes

Wongtrakul et al. found that moderate alcohol consumption (<210g/w for men and <140g/w for women) was associated with lower risk of steatohepatitis in NAFLD patients (OR=0.59 (0.45-0.78), p-value=0.0002, I^2=12%) (21). In their analysis, Wongtrakul et al. included studies with current (n=4) and lifetime (n=6) abstainers as the reference group participants (21).

Earlier meta-analyses by Roerecke et al. and Cao et al. found that alcohol consumption of <20g/d and ≤40g/d was associated with lowered risk of steatosis (RR=0.85 (0.75-0.96), I^2=86%) (15) and steatosis/steatohepatitis combined (OR=0.77 (0.70-0.86), I^2=79%) (24). It was unclear whether alcohol consumption of >40g/d was associated with increased risk of steatosis/steatohepatitis as the odds ratio estimate showed no association and was not statistically significant (OR=0.82 (0.59-1.12), I^2=0% as shown in Table 3 (24).

Sub-group analyses

It appeared that men and women were at similar risk of steatosis (RR=0.74 (0.66-0.78), I^2=0% versus RR=0.80 (0.68-0.95), I^2=82%) (15) and steatosis/steatohepatitis combined (RR=0.77 (0.66-0.91), I^2=90% versus RR=0.70 (0.63-0.78), I^2=0%) when drinking <20g/d and <40g/d respectively (24). The relative risk estimate was highest when sub-group analyses were restricted to men from studies conducted in non-Japanese countries (RR=1.68 (1.26-2.23), I^2=NR) (24).

In the meta-analysis by Roerecke et al., participants from studies conducted in Japan were at lower risk of steatosis compared to participants from studies located in non-Japanese countries (RR=0.75 (0.71-0.79), I^2=0% versus RR=1.05 (0.86-1.30), I^2=84%) (15). Similarly, in the meta-analysis by Cao et al. participants from studies located in Japan had lower risk of steatosis and steatohepatitis combined compared to those located in other countries (n=2 studies, both located in Germany) (RR=0.67 (0.58-0.77), I^2=62% versus RR=1.79 (1.06-3.00), I^2=94%) as shown in Table 3 (15).

Table 3 Relative risk of steatosis or steatohepatitis, results from meta-analyses

Author (year)	# Participants	# Cases	Group	Alcohol intake	Reference group	Relative risk (95% CI)	p-value	I^2 (%)	Outcome	Measure
Wongtrakul et al. (2021) (21)	1,314	806	NAFLD patients	<210g/women, <140g/women*	Non-drinker	0.59 (0.45-0.78)	0.0002	12	Steatohepatitis	OR
Roereckee et al. (2016) (15)	99,370	18,682	Overall	<20g/d	Non-drinker	0.85 (0.75-0.96)	NR	86	Steatosis	RR
		7,546	Men			0.80 (0.68-0.95)	NR	82		
		4,554	Women			0.74 (0.66-0.78)	NR	0		
		13,335	Japan			0.75 (0.71-0.79)	NR	0		
		5,346	Non-Japan			1.05 (0.86-1.30)	NR	84		
		6,949	Japan, Men			0.73 (0.68-0.78)	NR	0		
		3,714	Japan, Women			0.72 (0.62-0.83)	NR	0		
		597	Non-Japan, Men			1.68 (1.26-2.23)	NR	NR		
		840	Non-Japan, Women			0.80 (0.61-1.04)	NR	28		
Cao et al. (2016) (24)	31,942	NR	Overall	≤40g/d	Non-drinker	0.77 (0.70-0.86)	NR	79	Steatosis/steatohepatitis combined	OR
	19,858		Men			0.77 (0.66-0.91)	NR	90		
	5,955		Women			0.70 (0.63-0.78)	NR	0		
	5,468		Overall	>40g/d		0.82 (0.59-1.12)	NR	94		
	5,123		Japan			0.67 (0.58-0.77)	NR	NR		
	345		Germany			1.79 (1.06-3.00)	NR	70		

Data are also available for sub-group analyses by type of included study, i.e., cohort, cross-sectional as well as participant BMI <25 and BMI >25. CI; confidence interval, g/d; grams per day, g/w; grams per week, NAFLD; non-alcoholic fatty liver disease, NR; not reported, OR; odds ratio, RR; risk ratio.

Results from Part B: studies in the Australian context

No studies were identified that examined the association between alcohol consumption and risk of steatosis or steatohepatitis in the Australian context.

Association between alcohol consumption and risk of liver fibrosis and cirrhosis

Results from Part A: systematic reviews and meta-analyses

Study characteristics

Four systematic reviews with meta-analyses investigated the association between alcohol consumption and risk of advanced liver fibrosis or cirrhosis as shown in Table 4 (16,17,21,22).

Roerecke et al. (2019) examined the effect of drinking occasionally, and consuming 1, 2, 3-4, 5-6 and ≥ 7 drinks/day (where one drink was equivalent to 12g pure alcohol) compared to long-term abstinence on the risk liver cirrhosis incidence or mortality (16). This study involved participants with and without existing liver disease and the type of liver disease was not limited to patients with ARLD, as Roerecke et al. (2019) noted that, by definition, to include participants who were long-term abstainers their study had to involve participants without ARLD (16). Glyn-Owen (2021) et al. investigated the association between alcohol consumption and risk of advanced liver disease (cirrhosis and HCC combined) among participants with increasing body mass index (BMI; normal, overweight, obesity) (17).

Wijarnpreecha et al. (2021) and Wongtrakul et al. (2021) examined the association between moderate drinking (<210g/w for men and <140g/w for women) on risk of fibrosis among patients with NAFLD (21,22). The studies by Wijarnpreecha et al. and Wongtrakul et al. were of a small scale and used non-drinkers as the reference group which included both current or lifetime abstainers (21,22).

The overall confidence in findings was rated 'high' for the systematic review with meta-analysis by Glyn-Owen et al. (17) and 'moderate' for the remaining systematic reviews with meta-analyses as shown in Table 4 (16,21,22).

Table 4 Characteristics of systematic reviews and meta-analyses which examined risk of advanced fibrosis or cirrhosis

Author (year)	Literature search to:	# Studies included	Participants	Alcohol intake categories	Reference group	Outcome	AMSTAR-2
Wijarnpreecha et al. (2021) (22)	Feb 2019	6	NAFLD patients	<28g/d men, <14g/d women*	Non-drinkers	Fibrosis (F3-4)	Moderate
Wongtrakul et al. (2021) (21)	Oct 2020	8	NAFLD patients	<210g/w men, <140g/w women*	Non-drinkers**	Fibrosis (F3-4)	Moderate
Glyn-Owen et al. (2021) (17)	Jun 2020	9	Adults without existing liver disease	>112g/w	Light drinkers (0 to <112g/w)	Chronic liver disease***	High
Roereckе et al. (2019) (16)	Mar 2019	9	Adults with or without existing liver disease	Occasional, 1, 2, 3-4, 5-6 and ≥ 7 drinks/d Where 1 drink was equivalent to 12g ethanol	Long-term abstainers	Cirrhosis mortality	Moderate

Some variations were accepted e.g., <200g/w and <40g/d. **Non-drinker referred to current (n=3) or lifetime (n=5 studies) abstainers. ***Chronic liver disease referred to cirrhosis and HCC as a combined outcome. Research quality was assessed by the Research quality was assessed using the AMSTAR-2 tool for critical appraisal of systematic reviews and the overall confidence of findings was rated as high, moderate, low or critically low (20). AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews, AUD; alcohol-use disorder, g/day; grams per day, g/week; grams per week, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease NR; not reported.* ***Type of included studies:* *Wijarnpreecha: 6 Cross-sectional, Wongtrakul: All cross-sectional, Glyn-Owen: All were Cohort studies. Of the 9 included studies, 1 study had chronic liver disease only as the outcome, whilst 8 studies had chronic liver disease and HCC as the outcome, Roerecke (2019): 5 Cohort; 5 Case-control.* ***Location of included studies****: Wijarnpreecha: 3 US; 2 Australia; 1 Japan, Wongtrakul: 2 US; 2 Japan; 1 South Korea; 1 Sweden; 1 Australia; 1 Malaysia, Glyn-Owen: 7 Europe; 2 US. Roerecke (2019): 4 US; 3 Europe; 1 China.*

Relevant outcomes

Roerecke et al. (2019) found that there was a positive, dose-dependent relationship between increasing levels of alcohol intake and risk of liver cirrhosis (16). There was no "safe" level of drinking and those who consumed 1 drink per day were at increased risk of mortality due to cirrhosis compared to long-term abstainers (RR=1.40 (1.00-1.97), I^2=78%) (16). The relative risk of liver cirrhosis was greater in women compared to men and there was a 25-fold increased risk for women who consumed on average ≥7 drinks per day (RR=24.58 (14.77-40.90), I^2=98%) (16). Glyn-Owen et al. (2021) similarly found that there was increased risk among people who consumed above the recommended UK National Institute for Health and Care Excellence (NICE) guidelines (>112g/w) compared to those who consumed alcohol within the recommended guidelines (>0 to <112g/w) (RR=2.65 (2.48-2.84), I^2=NR) as shown in Table 5 (17).

In contrast, the meta-analyses by Wijampreecha et al. (2021) and Wongtrakul et al. (2021) found that, compared to non-drinkers, moderate drinkers (<210g/w for men and <140g/w for women) had a statistically significant lowered risk of fibrosis (OR=0.51 (0.35-0.75), p-value =0.0007 I^2=47%, and O= 0.59 (0.36-0.95), p-value=0.03, I^2=75%), respectively (21,22).

Table 5 Relative risk of advanced fibrosis or cirrhosis, from meta-analyses

Author (year)	# Participants	# Cases	Group	Alcohol intake	Reference group	Relative risk (95% CI)	p-value	I^2 (%)	Outcome	Measure
Wijarnpreecha et al. (2021) (22)	8,936	NR	NAFLD patients	<28g/d men, <14g/d women	Non-drinker	0.51 (0.35-0.75)	0.0007	45	Advanced fibrosis	OR
Wongtrakul et al. (2021) (21)	1,780	483	NAFLD patients	<210g/w men, <140g/w women*	Non-drinker	0.59 (0.36-0.95)	0.03	75	Advanced fibrosis	OR
Glyn-Owen et al. (2021) (17)	1,121,514	4,687	BMI 18.5 to <25	>112g/w	0 to <112g/w	2.65 (2.48-2.84)	NR	NR	Chronic liver disease*	RR
			BMI 25 to <30			3.32 (2.88-3.83)	NR	68		
			BMI 25 to <30			5.39 (4.62-6.29)	NR	77		
Roereck e et al. (2019) (16)	2,627,519	458	Overall	Occasional	Lifetime abstainer	1.11 (0.77-1.59)	NR	71	Cirrhosis	RR
		1,111		1 drink/d		1.40 (1.00-1.97)	NR	78		
		574		2 drinks/d		3.02 (1.95-4.70)	NR	92		
		203		3-4 drinks/d		3.27 (0.90-11.87)	NR	99		
		281		5-6 drinks/d		6.26 (2.38-16.50)	NR	97		
		276		≥7 drinks/d		10.70 (2.95-38.78)	NR	98		
	579,592	NR	Men	Occasional		1.23 (0.46-3.28)	NR	80		
		NR		1 drink/d		0.91 (0.31-2.64)	NR	87		
		NR		2 drinks/d		1.97 (0.89-4.37)	NR	91		
		NR		3-4 drinks/d		2.62 (0.42-16.21)	NR	99		
		NR		5-6 drinks/d		3.80 (0.85-17.02)	NR	98		
		NR		≥7 drinks/d		6.93 (1.07-44.99)	NR	99		
		NR	Women	Occasional		0.95 (0.77-1.16)	NR	14		
	2,049,680	NR		1 drink/d		1.64 (1.07-2.51)	NR	79		
		NR		2 drinks/d		4.33 (2.59-7.25)	NR	89		
		NR		3-4 drinks/d		3.87 (0.80-18.83)	NR	93		
		NR		5-6 drinks/d		12.44 (6.65-23.27)	NR	53		
		NR		≥7 drinks/d		24.58 (14.77-40.90)	NR	30		

**Some variations were accepted. **Chronic liver disease referred to cirrhosis and HCC as a combined outcome., BMI; body mass index, CI; confidence interval, drinks/d; drinks per day, g/d grams per day, g/w; grams per week, NAFLD; non-alcoholic fatty liver disease, NR; not reported, OR; odds ratio, RR; risk ratio*

Results from Part B: studies in the Australian context

Study characteristics

There were six studies identified in the review of Australian literature (30–35) as shown in Table 6. Of the six studies, two were published post-2011 (30,31), whilst the remaining four were published pre-2000 (32–35). There were mixed study designs including two cohort studies (30,31) and four case-control studies (32–35). Three studies involved patients with existing HBV- and/or HCV-related liver disease (31–33), one with NAFLD (30) and two with ARLD (34,35). Relevant outcomes are outlined in the text below and Table 7.

Table 6 Characteristics of studies in the Australian context which examined the risk of advanced fibrosis or cirrhosis.

Author (year)	Type of study	Location	Participants	Alcohol intake	Reference group	Liver disease stage
Mitchell et al. (2018) (30)	Cohort	WA	Patients with NAFLD undergoing liver biopsy with recorded weekly alcohol consumption history within the last 12 months	<70, and ≥70g/d	Lifetime abstainers	Fibrosis
Thurnheer et al. (2016) (31)	Cohort	VIC	Patients with HCV or HBV at tertiary hospital and outreach clinics	Any level	No alcohol	Fibrosis
Khan et al. (1998) (32)	Case-control	NSW	Patients with HCV whose consumption histories were recorded	<10, 10-40, 41-80, 81-120 and >120g/d	NR	Fibrosis
Ostapowicz et al. (1998) (33)	Case-control	VIC	Patients who had a liver biopsy and took part in an alcohol history questionnaire	Any level	No alcohol	Cirrhosis
Batey et al. (1992) (34)	Case-control	NSW	Men who had consumed alcohol recruited at Westmead and Royal Prince Alfred Hospitals	41-80 and ≥80g/d	0-40g/d	Cirrhosis
Norton et al. (1987) (35)	Case-control	NSW	Women who had consumed alcohol recruited at Westmead and Royal Prince Alfred Hospitals	21-40, 41-80 and ≥80g/d	0-40g/d	Cirrhosis

g/d; grams per day, HBV; hepatitis B virus, HCC; hepatocellular carcinoma, HCV; hepatitis C virus, NSW; New South Wales, NT; Northern Territory, NR; not reported, VIC; Victoria, WA; Western Australia

Relevant outcomes

There were mixed results from Australian studies regarding alcohol intake and risk of advanced fibrosis or cirrhosis. Thurnheer et al. (2016) found that patients with HBV who consumed any level of alcohol were at increased risk of fibrosis compared to those who did not drink (OR=2.84 (1.46-5.54), p-value<0.001), whereas there was no clear association for patients with HCV (OR=3.21 (0.37-29.64), p-value<0.001) (31). Mitchell et al. (2018) found that patients with NAFLD who consumed alcohol (either <70g/w or ≥70g/w) were at no greater risk of fibrosis compared to lifetime abstainers (30). In this study, consuming alcohol had a protective effect on risk of NAFLD-related fibrosis (OR=0.33 (0.15-0.71 for <70g/w and OR=0.10 (0.01-0.78) for ≥70g/w) (30). Case-control studies from pre-2011 showed that a large proportion of HCV patients with fibrosis stage 4 consumed more than 40g/d alcohol (32). Patients with HCV who consumed any level of alcohol were at increased risk of cirrhosis compared to those who did not drink (33). The odds ratios for cirrhosis among early case-control studies with hospital in-patients were high for both men and women as shown in Table 7 (34,35).

Table 7 Relative risk of advanced fibrosis or cirrhosis, results from studies in the Australian context

Author (year)	# Participants	# Cases	Group	Alcohol intake	Reference	Outcome	Relative risk (95% CI)	p-value	Measure
Mitchell et al. (2018) (30)	NR	NR	Patients with NALFD	<70g/w ≥70g/w	Lifetime abstainer	Fibrosis	0.33 (0.15-0.71) 0.10 (0.01-0.76)	NR	OR
Thurnheer et al. (2016) (31)	279 285	7 67	Patients with HBV Patients with HCV	Any level	No alcohol	Fibrosis (advanced)	2.84 (1.46-5.54) 3.21 (0.37-29.64)	<0.001	OR
Khan et al. (1998) (32)	186 78 43 69 35 23	NR	Patients with HCV	<10g/d 10-40g/d 41-80g/d 81-120g/d ≥120g/d unknown	NR	Fibrosis F4	0.23 0.15 0.11 0.16 0.23 0.39	NR	Proportion (%) *
Ostapowicz et al. (1998) (33)	234	50	Patients with HCV	Any level	No alcohol	Cirrhosis	1.16	<0.05	OR
Batey et al. (1992) (34)	158	43	Men	41-80g/d ≥80g/d	0-40g/d	Cirrhosis	9.00 (3.10-24.00) 22.00 (7.60-63.00)	NR	OR
Norton et al. (1987) (35)**	164	41	Women	21-40g/d 61-80g/d ≥80g/d	Men, 0-40g/d	Cirrhosis	0.07-61.52 4.70-4818.01 17.30-infinity	NR	OR

**Proportion (%) of patients with stage 4 fibrosis among those who consume each level of alcohol. Data are also available for the proportion of patients for fibrosis stage 0-3. **Estimates of the OR were reported as a 95% CI. CI; confidence interval, fibrosis F0-4; Fibrosis stage 0 to 4, g/d; grams per day, HBV; hepatitis B virus, HCV; hepatitis C virus, NAFLD; non-alcoholic fatty liver disease, NR; not reported, OR; odds ratio, RR; risk ratio.*

Association between alcohol consumption and risk of primary liver cancer

Results from part A: systematic reviews, meta-analyses, and pooled analyses

Study characteristics

The literature search of the seminal meta-analysis by the WCRF was last updated in 2013 (18). Over the last decade, an additional seven studies; six systematic reviews with meta-analyses and one pooled analysis of cohort studies, have been published (21,23,25–29) as shown in Table 8.

While a formal quality assessment of included studies was beyond the scope of this review, included studies were critically appraised using the AMSTAR-2 tool with all reviews included in this section rated ‘moderate’ as shown in Table 8 (21,23,25–29).

Table 8 Characteristics of systematic reviews with meta-analyses and pooled analyses relating to risk of liver cancer

Author (year)	Literature search to:	# Studies included	Participants	Alcohol intake categories	Reference group	Outcome	AMSTAR-2
WCRF (2018) (18)	Jun 2013	14	Adults with or without existing liver disease who consumed varying levels of alcohol	Per 10g increment alcohol	Various	Liver Cancer	NR
Wongtrakul et al. (2021) (21)	Oct 2020	2	NAFLD patients	<210g/w men, <140g/w women	Non-drinker	HCC	Moderate
Park et al. (2020) (23)	Jul 2019	36	Adults with or without existing liver disease who consumed varying levels of alcohol	≥25g/d men, ≥12.5g/d women	Never or light drinkers	Liver Cancer	Moderate
Petrick et al. (2018) (25)	NR	14	Adults with or without existing liver disease from the US-based Liver Cancer Pooling Project consortium	>0 to <0.5, 0.5 to <1,1 to <3, 3 to <5, 5 to <7, and ≥ 7 drinks/d Where 1 drink was equivalent to 14g	Non-drinker**	HCC	NR for pooled analysis
Chuang et al. (2015) (26)	May 2014	20	Adults with or without existing liver disease who consumed varying levels of alcohol.	12, 25, 50 and 75 g/d	Never drinkers	Liver Cancer	Moderate
Bagnardi et al. (2015) (27)	Sep 2012	36	Adults with various cancer types who were non-, light, moderate or heavy drinkers.	<12.5, >12.5 to ≤ 50g, and >50g/d	Non-drinkers	Liver Cancer	Moderate
Turati et al. (2014) (28)	Apr 2013	16	Adults with or without existing liver disease who consumed varying levels of alcohol	>0 to <37.5, and ≥37.5g/d	Non-drinkers	Liver Cancer	Moderate
Bagnardi et al. (2013) (29)	Dec 2010	38	Adults with varying cancer types who were modest alcohol drinkers	<12.5g/d	Non-drinkers	Liver Cancer	Moderate

Non-drinker referred to current (n=1) or lifetime (n=1 study) abstainers. **Data are also available using the reference group of light drinkers (0 to <0.5 drinks/d). Research quality was assessed using the AMSTAR-2 tool for critical appraisal of systematic reviews and the overall confidence of findings was rated as high, moderate, low or critically low (20). AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews, NR; not reported, **Type of studies included: Wongtrakul: 2 Cohort. Park: 22 Cohort; 6 Nested case-control, Petrick: All were cohort studies, Bagnardi (2015): 572 studies were included. Of these 36 related to liver cancer, 9 were cohort studies and 27 were case control studies. Chuang: 112 studies were included, of these 20 related to liver cancer, 7 were cohort studies and 13 were case control studies. Turati: 16 studies were included. Of these 10 were cohort studies, 1 gave results from a pooled analysis of 4 cohorts and 6 were case control studies. Bagnardi (2013): 247 studies were included of these 38 related to liver cancer. **Location**: Park: Petrick: All US, Bagnardi (2015): 18 Asia; 8 North America; 5 Europe; 1 Mixed, Chuang: NR. Turati: 15 Asia, 2 Europe, 1 US; 1 Hawaii. Bagnardi: 12 Asia, 5 Europe, 3 North America.*

Relevant outcomes

The WCRF found that there was increased risk of liver cancer per 10g/d increment of ethanol (RR=1.04 (1.02-1.06), I^2=64%) (18). The dose response relationship was derived from data in which the reference category used was “never” drinkers in five, “light” drinkers in one, and “non-” drinkers in nine studies out of the 14 primary cohort studies included in this meta-analysis (18). In support of findings by the WCRF, Petrick et al. (2018), Bagnardi et al. (2015), and Turati et al. (2014) showed that the risk of liver cancer becomes statistically significant above an average consumption of between 30-40g/d as shown in Table 9 (25,27,28).

The identified evidence did not find an association between light drinking and the risk of liver cancer in the general population shown in Table 9 (27–29). In patients with existing NAFLD,

those who consumed alcohol (<210g/w men and <140g/w women) were at nearly 4-fold increased risk of HCC compared to non-drinkers (HR=3.77 (1.19-8.15), I^2=0%) (21).

Table 9 Relative risk of liver cancer, results from pooled and meta-analyses

Author (year)	# Participants	# Cases	Group	Alcohol intake	Reference group	Relative risk (95% CI)	p-value	I^2 (%)	Measure
WCRF (2018) (18)	NR	5,650	Overall	Per 10g increment	Various	1.04 (1.02-1.06)	NR	64	RR
Wongtrakul et al. (2021) (21)	489	213	NAFLD patients	<210g/w men, <140g/w women*	Non-drinker**	3.77 (1.75-8.15)	0.0007	0	HR
Park et al. (2020) (23)	NR	4,899	Overall	≥25g/d men, ≥12.5g/d women	Never or light drinker	1.42 (1.19-1.69)	NR	61	OR
Petrick et al. (2018) (25)	NR	443	Overall	>0 to <7 g/d	Non-drinker	0.77 (0.67-0.89)	NR	NR	HR
		73		7 to <14 g/d		0.57 (0.44-0.73)			
		148		14 to <42 g/d		0.71 (0.58-0.87)			
		67		42 to <70 g/d		1.04 (0.79-1.36)			
		28		70 to <98 g/d		1.00 (0.68-1.49)			
		62		≥98 g/d		1.87 (1.41-2.47)			
Chuang et al. (2015) (26)	NR	NR	Overall	12g/d	Never drinker	1.08 (1.04-1.11)	NR	NR	RR
				25g/d		1.19 (1.12-1.27)			
				50g/d		1.54 (1.36-1.74)			
				75g/d		2.14 (1.74-2.62)			
				100g/d		3.21 (2.34-4.40)			
				125g/d		5.20 (3.25-8.29)			
Bagnardi et al. (2015) (27)	12,695	NR	Overall	≤12.5g/d	Non-drinker	1.00 (0.85-1.18)	NR	NR	RR
				>12.5 to ≤ 50g/d		1.08 (0.97-1.20)			
				>50g/d		2.07 (1.66-2.58)			
Turati et al. (2014) (28)	10,000		Overall	<37.5g/d	Non-drinker	0.91 (0.81-1.02)	NR	66	RR
				≥37.5g/d		1.16 (1.01-1.34)	NR	61	
Bagnardi et al. (2013) (29)	4,626		Overall	≤12.5g/d	Non-drinker	1.03 (0.90-1.17)	NR	>50	RR

**Some variations were accepted. **Non-drinker referred to current (n=1) or lifetime (n=1 study) abstainers. CI; confidence interval, g/d; grams per day, HR; hazard ratio, NR; not reported, OR; odds ratio, RR; risk ratio, WCRF; World Cancer Research Fund.*

Sub-group analyses

Women were reportedly at greater risk of liver cancer compared to men when consuming large amounts of alcohol (25–27). Bagnardi et al. (2015) found that among people who consumed >50g/day, women were more than two times as likely as men to develop liver cancer (RR=3.89 (1.60-9.48), I^2=10.0% for women versus RR=1.59 (1.21-2.09), I^2=69% for men) (Appendix Table 10).

Geographical location of the populations studied did not generally impact on key findings of the meta-analyses. Only one study by Bagnardi et al. (2015) suggested that participants from studies based in North America had a higher risk of liver cancer compared to those in Europe and Asia when consuming >50g/day of alcohol (RR=3.40 (2.54-4.55, I^2=0%; RR=2.00 (1.07-3.74), I^2=85%; and RR=1.59 (1.27-2.00), I^2=69%; for North America, Europe and Asia, respectively) (Appendix Table 10).

Participants with excess body weight and who had high alcohol consumption were at higher risk of liver cancer compared to those with excess body weight who did not drink. Petrick et al. (2015) found that people who were overweight (BMI 25 to <30 kgm^{-2}) and heavy drinkers (consumed >5 drinks/day) were at increased risk of liver cancer (RR=1.60 (1.13-2.25)), as for people who were obese (BMI ≥30 kgm^{-2}) (RR=1.45 (1.12-1.87)) (Appendix Table 10).

Results from Part B: studies in the Australian context

Study Characteristics

Two studies in the Australian context were identified as shown in Table 10. Sarich et al. (2021) examined the association between alcohol and risk of several cancer types in an Australian cohort of 226,162 participants aged 45 years and over (36). Huang et al. (2018) retrospectively examined risk factors for the late diagnosis of HCC among a cohort of 270 patients with HCC in Western Australia (37).

Relevant outcomes

Sarich et al. found that compared to light drinking (≥10 to ≤35g/w), consuming 0 to <10g/w and >280g/w (equivalent to an average of 0 to <1g and >40g/d) were associated with a statistically significant increased risk of liver cancer (HR=1.93 (1.08-3.47) and HR=3.02 (1.49–6.13), respectively) (36). However, drinking between >35 to ≤70 g/w, >70 to ≤140 g/w, and >140 to ≤280 g/w showed no significant association with risk of liver cancer (HR=1.09 (0.54–2.17), 1.48 (0.76–2.86), and 1.19 (0.57–2.50), respectively) (36). Sarich et al. found that per every 70g (equivalent to 10g/d increment) increase in weekly alcohol consumption the relative risk of liver cancer was HR=1.22 (1.04-1.44), p-value(trend)=0.01) as shown in Table 11 (36).

Similarly, Huang et al. (2018) found that current heavy drinkers were at increased risk of HCC compared to non-drinkers (OR=7.60 (2.85-20.30), p-value<0.001) (37). There was no statistically significant association evident for current drinkers (OR=1.86 (0.86-4.03), p-value=0.118) (37). Ex-drinkers demonstrated lowered risk compared to non-drinkers however the result was not statistically significant (OR=0.49 (0.18-1.38), p-value=0.117) as shown in Table 11 (37).

Table 10 Characteristics of studies in the Australian context which examined the risk of liver cancer.

Author (year)	Type of study	Location	Participants and study period	Alcohol intake	Reference group	Outcome
Sarich et al. (2021)	Cohort	NSW	Australian adults aged 45 years and older.	0 to <10, >35 to ≤70, >70 to ≤140 >140 to ≤280, and >280 g/w	≥10 to ≤35g/w	Liver Cancer
Huang et al. (2018)	Cohort	WA	Patients diagnosed with HCC	Current heavy drinker, current drinker, ex-drinker	Non-drinker	HCC

g/w; grams/week, NSW; New South Wales, NR; not reported, WA; Western Australia

Table 11 Relative risk of liver cancer, results from studies in the Australian context

Author (year)	# Participants	# Cases	Group	Alcohol intake	Reference	Relative risk (95% CI)	p-value	Measure
Sarich et al. (2021)	226,162	158	Adults 45 years and older	0 to <10 g/w	≥10 to ≤35 g/w	1.93 (1.08-3.47)	NR	HR
				>35 to ≤70 g/w		1.09 (0.54-2.17)		
				>70 to ≤140 g/w		1.48 (0.76-2.86)		
				>140 to ≤280 g/w		1.19 (0.57-2.50)		
				>280 g/w		3.02 (1.49-6.13)		
		93		Per 70g/w increase	No change in weekly alcohol consumption	1.22 (1.04-1.44)	0.01	HR
Huang et al. (2018)	270	NR	Patients diagnosed with HCC	Current heavy drinker	Non-drinker	7.60 (2.85-20.30)	<0.001	OR
				Current drinker		1.86 (0.86-4.03)	0.118	
				Ex-drinker		0.49 (0.18-1.38)	0.117	

CI; confidence interval, drinks/w; drinks/week, HCC; hepatocellular carcinoma, HR; hazard ratio, NR; not reported, OR; odds ratio

Discussion

Brief overview of findings

This review identified international meta- and pooled- analyses (23,25–29) as well as one large-scale Australian cohort study (36) which found that heavy drinking (>40g/d or equivalent) increases risk of liver cancer, supporting the WCRF report findings (18). It was unclear whether light or moderate drinking (≤40g/d) increased risk of liver cancer as results from studies relating to light drinking were either not statistically significant (29) or showed no association (26–29,36). There was evidence that alcohol consumption increases the risk of liver cirrhosis in a dose-dependent manner (16). There was some evidence that light (<20g/d) and moderate drinking (<40g/d) may have a protective effect on the relative risk of steatosis and steatohepatitis (15,21,24). The included meta-analyses were conducted on a large scale, involving participants from a wide range of geographical locations and various ethnicities. Results by population subgroups illustrated that participants involved in Japanese studies who were light or moderate drinkers were at lower risk of steatosis and steatohepatitis compared participants in non-Japanese countries (15,24).

There is no internationally recognised definition of a “standard drink” or “safe” level of alcohol consumption. Until these definitions are standardised, reporting, and drawing conclusions in this field will remain difficult. As a result, there was high heterogeneity (I^2>50%) noted in the included meta-analyses. This was partially attributed to the large variations in definition of “light,” “moderate” and “heavy” drinking, as well as the variations in study design, inclusion and exclusion criteria, and choice of reference group participants for the included primary studies. Some of the included meta-analyses did not distinguish between non-drinkers and never drinkers (21,22,25,27–29) so the reference group participants may include former drinkers, potentially biasing results to the “sick-quitter” effect (38). Other meta-analyses, such as by Park et al., Roerecke et al., and Glyn-Owen et al., and the large Australian cohort study by Sarich et al. involved long-term abstainers or light drinkers as the reference group which reduces the risk of bias in their findings (16,17,23,36).

Several meta-analyses were predominately comprised of cross-sectional studies (15,21,22,24). Cross-sectional studies do not always well characterise changes in levels of alcohol consumption throughout the lifetime and may be biased by reverse causality (i.e.,

those with liver damage could newly abstain to alcohol) as well as inaccurate participant recall. A recent systematic review by Jarvis et al., (2022; published post our literature search to December 2021) investigated the impact of moderate alcohol consumption (<40g/d) on risk of NAFLD, and was restricted to only include longitudinal cohort studies (39). The authors found clear evidence that any level of alcohol consumption was associated with worsening NAFLD, which contrasts from the results of meta-analyses relating to NAFLD patients included in this review (21,22), emphasising that results from meta-analyses of cross-sectional studies should be interpreted cautiously (39).

Strengths and limitations of the review

A strength of this scoping review is the comprehensive nature of the search across international and Australian literature, and appraisal using the AMSTAR-2 checklist. We included relevant studies of any type published at any time in the Australian context. However, as this report was a scoping and not systematic review, no formal risk of bias assessment was performed. We restricted included international studies to those published in the last decade and in English.

Additionally, we reviewed studies which quantified alcohol consumption in g/d or equivalent and reported relative risk in terms of groupings (>40g/d or <40g/d) in line with the Australian guidelines to reduce the risk of alcohol-related harm (40). While this allowed us to categorise and compare findings, it should be acknowledged that, for example, drinking on average <280g/w is not the same as drinking on average <40g/d, as some people may consume 280g over just one or two days whilst others may spread their alcohol consumption over each day of the week. Better understanding of relative risk from patterns of drinking may help to explain geographical differences in relative risk of liver disease and primary liver cancer and may enable targeted population-based interventions that reach individuals most at risk.

Implications and future directions

Future scoping reviews could be broadened to investigate the role of drinking frequency (i.e., number of days drinking each week), patterns of drinking (e.g., heavy episodic “binge” drinking versus regular alcohol consumption, drinking with meals versus without meals) and type of alcohol consumed (i.e., beer, wine, spirits, sake).

Additionally, future scoping reviews could be broadened to include participants with alcohol-use disorder (AUD). AUD is diagnosed using the AUDIT-C checklist which provides an integrated score out on how often people drink, how many drinks people consume on a typical day, and how often people binge drink (41). As the checklist does not refer to the quantity of alcohol consumed in g/d, studies relating to AUD were not eligible for inclusion in this report. Evidence from at least two systematic reviews with meta-analyses indicated that patients with AUD have more than 3-fold increased relative risk of HCV-related liver disease progression and 14.8-fold increased relative risk of liver cirrhosis-related mortality (42,43).

It is crucial that population-based interventions continue to target excessive alcohol consumption using a comprehensive, multicomponent systems approach (44). Evidence identified in this report shows it is important to monitor even low levels of alcohol consumption which have the potential to cause harm, particularly in patients with existing liver disease (39).

Conclusion

This report identified evidence that heavy alcohol consumption (>40g/d) increases the risk of liver disease and primary liver cancer, but findings relating to light or moderate alcohol consumption (0 to ≤40g/d) are less clear.

Literature in this field is highly heterogenous. There is no internationally recognised definition of a “standard drink” or “safe” level of alcohol consumption and there was inconsistency in the reference groups used between studies which limits the ability to generalise conclusions.

As alcohol use remains common, a detailed understanding of the level and frequency of consumption alongside other risk factors will improve our understanding of the causes of liver disease. It is important that efforts continue to understand the impact of preventable risk factors such as alcohol consumption so that action can be taken to reduce the future burden of liver disease and primary liver cancer in Australia.

Progression from ARLD to liver fibrosis, cirrhosis, primary liver cancer and mortality

Introduction

Alcohol-related liver disease (ARLD) affects nearly all (90-100%) people who are chronic heavy drinkers (2). In Australia, 6.3% of adults (8.7% of men and 2.5% of women) report consuming on average more than four standard drinks per day (1), putting them at high risk of developing ARLD and other alcohol-related conditions over their lifetime (3).

Although the early stages of ARLD (steatosis, steatohepatitis) are relatively common, a subset of patients develop advanced liver disease, primary liver cancer and death (4). A recent review of the natural history of ARLD that 10-30% of patients with alcohol-related steatosis or “fatty liver” progress to steatohepatitis, 8-20% of patients with alcohol-related steatohepatitis progress to cirrhosis, and that approximately 2% of patients with alcohol-related cirrhosis progress to hepatocellular carcinoma (HCC) as shown in Figure 3 (2).

Hepatocellular carcinoma is the most common form of primary liver cancer in Australia (5) and in most cases HCC arises as a result of underlying liver cirrhosis (6). Currently, ARLD accounts for 25% of all decompensated liver cirrhosis cases in Australia with the remaining 29%, 23%, 13% and 10% due to chronic hepatitis B virus (HBV), hepatitis C virus (HCV), metabolic associated liver disease (MAFLD, formerly NAFLD, non-alcoholic fatty liver disease) and unknown causes (7). Projections based on Australian modelling have predicted that that up to 7.2% of all alcohol-related liver cancers could be avoided over a 25-year period (2013-2037) if alcohol consumption in Australia stopped and up to 6.7% could be avoided if alcohol consumption was reduced (8).

The purpose of this scoping report was to identify if there was any additional evidence available from systematic reviews with meta-analyses, pooled analyses, and modelling studies published in the last decade, or studies of any type in the Australian context regarding progression rates of ARLD.

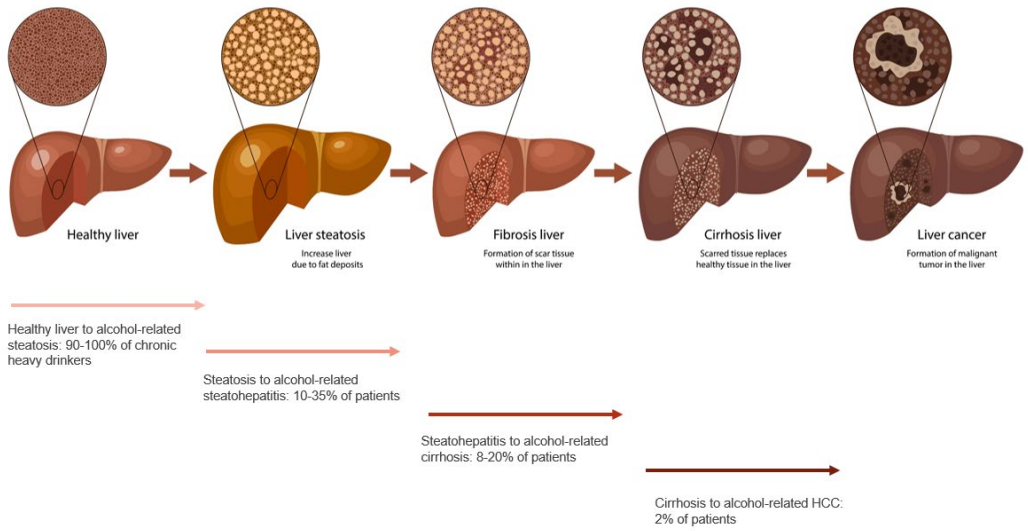

Figure 3 Stages of ARLD

Review question

Question 1: What is known about the progression from ARLD to liver fibrosis, cirrhosis, primary liver cancer and mortality?

Methods

Search strategy

Electronic literature searches were performed in April 2022 to search national and international literature for studies published in the last decade (April 2012 to April 2022). Key terms relating to liver disease, steatosis, steatohepatitis, alcohol-related liver disease, ARLD, fibrosis, cirrhosis, liver cancer, hepatocellular carcinoma and HCC were combined with terms relating to progression, risk, natural history, epidemiology, and burden as outlined in Table 12-13 of the Appendix.

Embase and MEDLINE databases were searched concurrently using the Ovid interface. In addition, the Cochrane Library of Systematic Reviews, the ANZCTR online registry of clinical trials being undertaken in Australia, New Zealand and elsewhere, the International Prospective Register of Systematic Reviews (PROSPERO), and the International Agency for Research on Cancer (IARC) databases were searched (Appendix Table 14). Reference lists of all included papers were scanned manually for other relevant studies. The search strategy was adapted for each information source.

Eligibility criteria

The eligibility criteria and scope of the review were defined using the "Participant Concept Context" framework (9). Detailed summaries of the inclusion and exclusion criteria are provided in the Appendix Table 11.

Participants

Studies could involve adult participants (>18 years) from the general population and/or participants with existing ARLD. Studies reporting on liver function biomarkers such as alanine aminotransferase (AMT) or aspartate transaminase (ART) were excluded. Studies reporting on genetic polymorphisms such as PNPLA3 or rs738409 were excluded. Studies with a paediatric or adolescent population were excluded.

Concept

To be included, studies needed to report progression, transition, incidence, or mortality rates and their 95% confidence intervals (CI). These could be transition probabilities from modelling studies, annual progression rates, or incident rates per person-years (PYs). The data were collected as reported in the original study and, for the purposes of this review, were converted to progression rates per 100 PYs where possible. Studies which reported on only other outcomes such as liver transplantation or rare primary liver cancers such as intrahepatic cholangiocarcinoma (ICC) or bile duct cancer were excluded.

Context

The searches were limited to human studies written in English. There were no specific exclusion criteria based on cultural/sub-cultural factors, geographic location, racial or gender as we deemed all international and national literature to be relevant.

Types of sources

Conference abstracts, letters, editorials, and narrative reviews were not included. Preliminary searches identified one systematic review with meta-analysis (10). However, there were few studies in the Australian context. As such the literature search was conducted in 2 parts:

Part A: reviewed only systematic reviews, meta-analyses, pooled analyses, and modelling studies published in the last decade (April 2012 to April 2022). Additionally, the PROSPERO database was searched for ongoing prospectively registered systematic reviews.

Part B: reviewed Australian literature published to April 2022. As literature in the Australian context is sparse, we included Australian papers of any study type.

Study selection

Following the search, all identified citations were collated and duplicates removed. Titles and abstracts were screened by one reviewer (GC) for assessment against the inclusion criteria. Potentially relevant articles were retrieved in full and assessed in detail. Reasons for exclusion at full text were recorded and are reported in the Appendix Tables 15-16. Any difficulties in determining if a study should be included at each stage of the selection process was resolved through discussion with a senior researcher (EF). Results of the search and inclusion process are described in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) (11).

Data extraction

The following data: study information; setting; number of participants; participant group; initial disease stage(s); outcome(s) and outcome measure(s); funding information, and author's key conclusions were extracted. A formal critical appraisal and risk of bias assessment were not performed, however the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) was used to identify key strengths and limitations of included studies (20). The AMSTAR-2 contains 16 domains and is not intended to generate an overall score but assists in the identification of high-quality systematic reviews as outlined in the Appendix Tables 17-19 (20).

Key findings

Search outcomes

Part A Search for systematic reviews, meta-analyses, pooled analyses, and modelling studies

The literature search for Part A identified 7,885 potentially relevant records as shown in Figure 4. After removing duplicates and studies that were not a systematic review, meta-analysis, pooled analysis, or modelling study, 632 records were screened by their title and abstracts. Of these, eight were deemed relevant and were retrieved and read full text. Four records were included, and no additional studies identified by scanning reference lists. Reasons for exclusion at full-text included not specifically related to ARLD i.e., reported on the progression rates of liver diseases including NAFLD (13) and HCV (14).

Of these four included studies, one was a systematic review with meta-analysis (10) and three were modelling studies (15–17). No pooled analyses were eligible for inclusion. Confidence in the overall findings of the systematic review with meta-analysis was rated 'high' using the AMSTAR-2 tool as shown in Table 12.

Ongoing systematic reviews with meta-analyses

One systematic review with meta-analysis was registered by Niu et al. in 2021 as shown in Table 13. Niu et al. proposed to investigate the global prevalence, incidence, and outcomes of ARLD in the general population. The review status was ongoing as of April 2022.

Part B Search for studies in the Australian context

The literature search for Part B identified 71 potentially relevant records as shown in Figure 4. No duplicates were identified and so 71 records were screened by their title and abstracts. Of these, five were deemed relevant and were retrieved and read full text. One study by Liang et al. (18) was included, as well as an additional study known to the reviewers (19) giving a total of two Australian studies in the review. Reasons for exclusion at full text included that the outcomes were not specific to ARLD, or not relevant to the Australian context.

Table 12 Characteristics of systematic reviews with meta-analyses, and modelling studies

Author (year)	Type of study	Study period/ Literature search to:	# Studies included	Participants	Stage(s) of ARLD	Measure	Outcome(s)	AMSTAR-2
Julien et al. (2020) (15)	Markov model - US	2005 to 2018 with predictions to 2040	NR	US general population	ARLD	Age-standardized rate per 100,000 PYs	Mortality, DC, HCC	NR
Delacôte et al. (2020) (16)	Markov model – France	Jan 1982 to Dec 1997	NR	Chronic heavy drinkers (>50g/day)	Normal, steatosis F0-2, F3-4, steatohepatitis F0-2, F3-4	Instantaneous hazard rate (%)	Steatosis F0-2, F3-4, Steatohepatitis F0-2, F3-4, liver complications (DC and HCC combined),	NR
Ioannou et al. (2020) (17)	Cox proportional hazards model	2012 to 2018	NR	Patients with ARLD cirrhosis	Cirrhosis	Annual incidence rate (%)	HCC	NR
Parker et al. (2019) (10)	Meta-analysis	May 2018	37	Participants with and without existing ARLD	Normal, steatosis, steatohepatitis, cirrhosis	Annual progression rate	Cirrhosis, Mortality (all-cause, liver-related, non-liver related)	High

AMSTAR-2; A measurement tool for the Identification of high-quality systematic reviews, ARLD; alcohol-related liver disease, DC; decompensated cirrhosis, F0-4; fibrosis stage 0 to 4; HCC; hepatocellular carcinoma, NR; not reported, US; United States.

Table 13 Characteristics of systematic reviews registered in PROSPERO

Author (year registered)	Title	Population	Outcome	Measure	PROSPERO ID	Status
Niu et al. (2021)	Global prevalence, incidence and outcomes of alcohol related liver disease: a systematic review and meta-analysis	General population	Prevalence, incidence and complications of ARLD	NR	CRD42021286192	Review ongoing

As of April 2022. ARLD; alcohol-related liver disease, NR; not reported.

Table 14 Characteristics of studies in the Australian context

Author (year)	Type of study	Location	Study period	Participants	Stage(s) of ARLD	Measure	Outcome(s)
Vaz et al. (2021)	Cohort retrospective	VIC	2010 to 2019	Patients with ARLD	Alcoholic hepatitis	Proportion (%)	In-hospital, 30-day, 90-day and 12-month mortality
Liang et al. (2011)	Cross-sectional	Australia-wide	1993 to 2005	Whole population	Not specified	Age-standardized rate	Mortality due to ARLD

ARLD; alcohol-related liver disease. VIC; Victoria

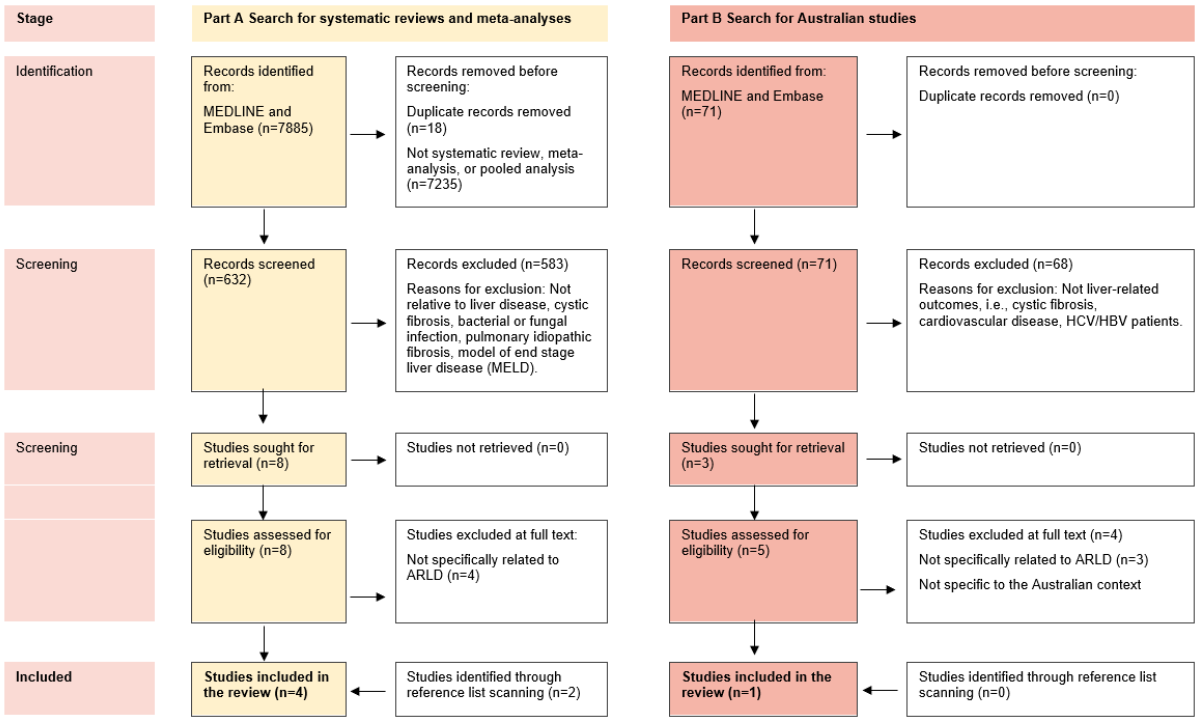

Figure 4 Search outcomes

The following sections outline results by liver disease outcome (i.e., progression to fibrosis, progression to cirrhosis, progression to HCC and progression to mortality). As some studies reported on more than one outcome, they are referred to more than once within the review.

Progression to fibrosis in patients with ARLD

Results from Part A: systematic reviews, meta-analyses, and modelling studies

Study characteristics

No systematic reviews with meta-analyses were identified that related to progression to fibrosis in patients with ARLD. One Markov modelling study by Delacôte et al. reported on model-fitted rates of progression to fibrosis in patients with ARLD (16). The study involved 2,334 chronic heavy drinkers (consumed on average >50g/day) who had undergone histological assessment (16). Delacôte et al. categorised patients into five groups based on their liver disease histology at baseline: normal liver, steatosis F0-2, steatosis F3-4, steatohepatitis F0-2 and steatohepatitis F3-4. Instantaneous transition hazard rates to steatosis F0-2, steatohepatitis F3-4 and steatohepatitis were calculated in a first group of 1,599 patients and then validated against a second group of 735 patients (2,334 participants in total) and are reported in Table 15 (16).

Relevant outcomes

As outlined in Table 15, the highest progression rate was observed in patients with baseline steatohepatitis F0-2 to F3-4 at 14.0% (95% CI 13.9-14.1%). The instantaneous hazard rate of transition from normal liver to steatosis F0-2 was 9.2% (95% CI 9.2-9.3%) and the hazard rate of transition from steatosis F0-2 to steatosis F3-4 was 3.0% (95% CI 2.7-3.3%) (16).

Results from Part B: studies in the Australian context

No studies in the Australian context were identified that related to ARLD and progression to fibrosis.

Table 15 Instantaneous transition hazard rates to fibrosis

Author (year)	# Participants	# Cases	Initial ARLD stage	Progression to	Transition hazard rate (95% CI)
Delacôte et al. (2020) (16)	2,334	NR	Normal liver	Steatosis F0-2	9.2% (9.2-9.3%)
		NR	Steatosis F0-2	Steatosis F3-4	3.0% (2.7-3.3%)
		NR	Steatohepatitis F0-2	Steatohepatitis F3-4	14.0% (13.9-14.1%)
		NR	Steatosis	Steatohepatitis	2.0% (1.8-2.2%)

ARLD; alcohol-related liver disease, CI; confidence interval, F0-4; fibrosis stage 0 to 4, NR; not reported.

Progression to cirrhosis in patients with ARLD

Results from Part A: systematic reviews, meta-analyses, and modelling studies

Study characteristics

One systematic review with meta-analysis by Parker et al. reviewed available evidence from observational cohort studies and reported on rates of progression to cirrhosis in patients with ARLD (10). One Markov modelling study by Delacôte et al. estimated transition rates to cirrhosis in patients with ARLD (16).

Relevant outcomes

As outlined in Table 16 the annual progression rate to cirrhosis in the meta-analysis by Parker et al. was highest in patients with alcohol-related steatohepatitis at 10.0% (95% CI 6.0-17.0%), I^2=75% (10). The rate of progression to cirrhosis among patients with normal liver histology, steatosis and fibrosis was 1.0% (95% CI 0.0-8.0%), I^2=42%, 3.0% (95% CI 2.0-4.0%), I^2=0%, and 8.0% (95% CI 3.0-19.0%), I^2=66% respectively (10). This result is supported by findings from the modelling study by Delacôte et al. which found that patients with alcohol-related steatohepatitis F3-4 had higher rates of progression to liver-related complications (including cirrhosis) compared to patients with alcohol-related steatosis F3-4 (instantaneous hazard rate 8.1% (95% CI 8.4-8.5%) versus 4.3% (95% CI 3.9-4.8% respectively) (16).

Results from Part B: Studies in the Australian context

No studies in the Australian context were identified that related to ARLD and progression to cirrhosis.

Table 16 Annual transition or progression rate to cirrhosis

Author (year)	# Participants	# Cases	Initial ARLD stage	Progression to:	Transition hazard rate (95% CI)	I^2 (%)
Delacôte et al. (2020) (16)	2,334	NR	Steatosis F3-4	Overall	4.3% (3.9-4.8%)	NR
			Steatohepatitis F3-4	Liver complications*	8.4% (8.4-8.5%)	NR
Parker et al. (2019) (10)	233	1	Normal liver	Cirrhosis	1.00% (0.00-8.00%)	42
	613	15	Steatosis	Cirrhosis	3.00% (2.00-4.00%)	0
	471	44	Steatohepatitis	Cirrhosis	10.00% (6.00-17.00%)	75
	353	21	Fibrosis	Cirrhosis	8.00% (3.00-19.00%)	66

*The study by Delacôte et al. was a modelling study and reported on the annual transition probability (%). The study by Parker et al. was a meta-analysis of observational studies and reported on the annual progression rate (%). *Liver complications were defined as the presence of HCC or decompensations (defined as bilirubin >50um/l, gastrointestinal hemorrhage, or ascites). ARLD; alcohol-related liver disease, CC; compensated cirrhosis, CI; confidence interval, DC; decompensated cirrhosis, F0-4; fibrosis stage 0 to 4, NR; not reported.*

Progression to HCC in patients with ARLD

Results from Part A: systematic reviews, meta-analyses, and modelling studies

Study characteristics

No relevant systematic reviews with meta-analyses were identified that related to ARLD and progression to HCC. Two modelling studies were identified. The study by Julien et al. reported on a model-calibrated progression rate to HCC among patients with ARLD using published estimates from cohort studies (15). The study by Ioannou et al. reported on the annual incidence rate of HCC among patients with alcohol-related cirrhosis who were followed-up from 2012 to 2018 (17).

Relevant outcomes

As outlined in **Error! Reference source not found.**, Julien et al. estimated that 1.7% (95% CI 1.2-2.2%) of patients with alcohol-related cirrhosis will develop HCC annually (15). Ioannou et al. similarly found that annual incidence rate of HCC was 1.4% among patients with alcohol-related cirrhosis (17).

Results from Part B: studies in the Australian context

No studies in the Australian context were identified that related to ARLD and progression to HCC.

Table 17 Annual transition or incidence rate of HCC

Author (year)	# Participants	# Cases	Initial ARLD stage	Progression to:	Annual incidence rate (95% CI)	I^2 (%)
Julien et al. (2020) (15)	NR	NR	Cirrhosis	HCC	1.7% (1.2-2.2%)	NR
Ioannou et al. (2020) (17)	16,175	871	Cirrhosis	HCC	1.4%	NR

The study by Julien et al., reported on the state transition probability to HCC whilst the study by Ioannou et al., reported on the annual incidence rate of HCC. ARLD; alcohol-related liver disease, CI; confidence interval, HCC; hepatocellular carcinoma, F0-4; fibrosis stage 0 to 4, NR; not reported.

Progression to mortality in patients with ARLD

Results from Part A: systematic reviews, meta-analyses, and modelling studies

Study characteristics

One systematic review with meta-analysis by Parker et al. and one Markov modelling study by Julien et al. reported on the rate of progression to mortality (all-cause, liver-related and non-liver related) among patients with ARLD (10,15).

Relevant outcomes

As outlined in Table 18, Parker et al. found that the rate of liver-related mortality was highest for participants with steatohepatitis at 7.00% (95% CI 3.00-14.00%), I^2=0% whereas for all other stages of ARLD the annual progression to non-liver related mortality was higher (10). Julien et al. found that there was a high probability of transition to mortality (39%) among patients with HCC, compared to those with alcohol-related cirrhosis (2%) (15).

Table 18 Annual transition or progression rate to mortality

Author (year)	# Participants	# Cases	Initial ARLD stage	Type of mortality	Progression rate (95% CI)	I^2 (%)
Julien et al. (2020) (15)	NR	NR	Cirrhosis	Liver-related	2% (1.0-2.0%)	NR
			HCC		39% (NR)	NR
Parker et al. (2019) (10)	1,091	58	Steatosis	All-cause	3.0% (4.0-7.0%)	14
	732	108	Steatohepatitis		11.0% (6.0-19.0%)	83
	930	74	Cirrhosis		8.0% (5.0-13.0%)	69
	893	8	Steatosis	Liver-related	1.0% (1.0-2.0%)	0
	133	7	Steatohepatitis		7.0% (3.0-14.0%)	0
	552	32	Cirrhosis		6.0% (3.0-10.0%)	46
	893	38	Steatosis	Non- liver related	4.0% (3.0-6.0%)	0
	133	5	Steatohepatitis		4.0% (2.0-9.0%)	0
	552	13	Cirrhosis		2.0% (1.0-4.0%)	0

The study by Julien et al., was a modelling study and reported on the state transition probability of mortality (15). *The study by Parker et al., was a meta-analysis of observational studies and reported on the annual mortality rate* (10). *ARLD; alcohol-related liver disease, CI; confidence interval, HCC; hepatocellular carcinoma, F0-4; fibrosis stage 0 to 4, NR; not reported.*

Results from Part B: studies in the Australian context

Study characteristics

Two Australian studies was identified that reported on rates of progression to mortality among patients with ARLD (18,19). Vaz et al. (2021) conducted a retrospective study of consecutive patients admitted with alcoholic hepatitis to a major liver centre in Victoria between 2010 to 2019 and estimated in-hospital, 30-day, 90-day and 12-month mortality rates (19). Liang et al. (2011) conducted a cross-sectional Australian population-wide study using International Classification of Disease codes and data from the Australian Bureau of Statistics to estimate the number of patients who died from ARLD each year over the period 1993 to 2005 (18).

Relevant outcomes

The in-hospital, 30-day, 90-day and 12-month mortality rates for Australian patients with alcoholic hepatitis were estimated at 7.9%, 8.7%, 14.3% and 27.1% respectively in the cohort study by Vaz et al. (19). The standardised rate of mortality attributable to ARLD for Australian men decreased from 7.9 (95% CI 7.2-8.6) to 7.2 (95% CI 6.6-7.8) over the period 1993 to 2005. For women, the rate of mortality due to ARLD decreased from 2.3 (95% CI 1.9-2.7) to 2.2 (95% CI 1.8-2.5) according to estimates by Liang et al. (18).

Discussion

Brief overview of findings

This scoping review identified a small body of evidence relating to rates of progression of ARLD. One systematic review with meta-analysis estimated annual progression rates to cirrhosis and mortality based on evidence from cohort studies (10). Three modelling studies reported on annual progression or state transition probabilities through ARLD (15–17). There were two Australian studies identified and these reported mortality rates (18,19).

Notably, the highest rates of progression to cirrhosis were observed among patients with alcohol-related steatohepatitis (10,15). Patients with alcohol-related steatohepatitis also had higher rates of liver-related and all-cause mortality compared to patients with alcohol-related cirrhosis (10). It is plausible that the high rates of cirrhosis and mortality among patients with alcohol-related steatohepatitis may be due to discrepancies in the primary data sources used (10), which has been corroborated by hepatologists. The authors noted that higher rates of mortality were only observed among hospitalised patients with steatohepatitis whilst mixed

cohorts of inpatients and outpatients with alcohol-related steatohepatitis showed a similar pattern of mortality to those with alcohol-related steatosis (10). The authors also noted there was a high degree of heterogeneity which made meta-regression difficult and consequently calculations of annual progression rates were based on average values (10). The authors reported that heterogeneity was due to a variety of factors including the type of cohort studies included, variations in study population, variations in the method of diagnosis ARLD and patterns of drinking behaviors (10). Only studies involving patients who had undergone liver biopsy were included in the meta-analysis, which may have introduced selection bias as it is possible that patients with worse liver disease prognosis are more likely to undergo liver biopsy (10). Due to its invasive nature, very few population-based studies capture liver biopsy results.

Evidence in the Australian context was limited. The cohort study conducted in 2021 by Vaz et al. involved only patients with alcoholic hepatitis, and therefore comprised a limited sub-group of patients with ARLD. The cross-sectional population-wide analysis of trends in mortality attributable to ARLD is of limited relevance to current work given the older data (sourced from 1993 to 2005) and changes to hospital classification codes for ARLD since this period (18).

Strengths and limitations of the review

A strength of this scoping review is the comprehensive nature of the search across international and national literature and appraisal using the AMSTAR-2 checklist. We included studies of any type published at any time in the Australian context. However, as this report was a scoping and not systematic review, no formal risk of bias assessment was performed. We restricted included international studies to those published in the last decade and in English.

Implications and future directions

Future scoping reviews should seek to identify what evidence is available from high-quality longitudinal cohort studies. In particular, it will be important to identify how rates of progression through ARLD differ depending on patient characteristics such as age, gender, ethnicity, and geographical location. There is scope for further research in the Australian context to clarify the natural history of ARLD in Australia.

Conclusion

This scoping report identified and reviewed evidence from one recently published systematic reviews with meta-analysis, three modelling analyses, and two studies in the Australian context in relation to rates of disease progression in ARLD.

This review indicated that patients with alcohol-related steatohepatitis may have higher rates of progression to mortality (both all-cause and liver-related) and cirrhosis compared to patients with alcohol-related cirrhosis. It should be noted that the one included meta-analysis may be limited by a degree of selection bias as it only reviewed only population-based cohort studies where ARLD was diagnosed by liver biopsy (patients who have a repeat biopsy may do so because of suspected worsening in their liver disease, and therefore be predisposed to higher rates of disease progression).

As alcohol use remains common, and a significant proportion (6.3%) of the Australian population are heavy drinkers, it is necessary to understand progression rates of ARLD. It is important that efforts continue to understand the impact of preventable risk factors for primary liver cancer so that action can be taken to reduce the future burden in Australia.

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Definitions and terminology

Alcohol-related liver disease (ARLD) encompasses the entire spectrum of fatty liver disease in individuals who are chronic heavy drinkers with the exclusion of other causes such as viral hepatitis and hereditary disorders.

Compensated cirrhosis refers to the build-up of scar tissue in the liver. Compensated cirrhosis is the asymptomatic stage of cirrhosis, also known as fibrosis (F4).

Decompensated cirrhosis refers to the build-up of scar tissue in the liver. Decompensated cirrhosis patients have at least one complication including ascites, jaundice, variceal haemorrhage, or hepatic encephalopathy.

Body mass index for adults, the World Health Organization (WHO) defines a BMI (in kg/m 2) of: ≥ 18.5 to <25 as normal weight; ≥ 25 to <30 as overweight, and ≥ 30 as obese. Certain populations, for example, people of Asian descent may have a modified BMI index: ≥ 18.5 to <23 as normal weight; ≥ 23 to <27.5 as overweight, and ≥ 27.5 as obese. There are age-standardised reference sheets which can be used for children, however, as the report focuses on the adult population, they are not discussed here.

Fibrosis refers to the formation of scar tissue in the liver. It can be classified into fibrosis stage F0, F1, F2, F3 and F4 each with increasing severity. F0 means there is no fibrosis, F1 portal fibrosis without septa, F2 portal fibrosis, F3 numerous septa without cirrhosis, F4 cirrhosis. Hepatic steatosis refers to fatty infiltration in more than 5% of hepatocytes

Non-alcoholic fatty liver disease (NAFLD) encompasses the entire spectrum of fatty liver disease in individuals without other causes such as significant alcohol consumption, chronic viral hepatitis, hereditary disorders, or use of steatogenic medications. NAFLD can be categorised histologically into NAFL or NASH.

Non-alcoholic fatty liver (NAFL) refers to the presence of hepatic steatosis without evidence of hepatocellular injury in the form of ballooning of the hepatocytes or evidence of fibrosis

Non-alcoholic steatohepatitis (NASH) refers to the presence of hepatic steatosis with evidence of inflammation and hepatocellular injury in the form of ballooning of the hepatocytes, with or without fibrosis.

Metabolic syndrome refers to a cluster of 3 or more metabolic risk factors including but not limited to elevated waist circumference, elevated triglycerides, abnormal high density and low-density cholesterol, hypertension, and elevated fasting blood glucose.

Metabolic-associated fatty liver disease (MAFLD) is the presence of hepatic steatosis in combination with one or more of the following overweight/obesity (defined as BMI ≥ 25 kg/m^2 in Caucasians or BMI ≥ 23 kg/m^2 in Asian participants, T2DM; or two or more markers of metabolic dysregulation including (a) waist circumference ≥ 102/88 cm in Caucasian men and women (or ≥ 90/80 cm in Asian men and women), (b) blood pressure ≥ 130/85 mmHg or on anti-hypertensive treatment, (c) plasma triglycerides ≥ 1.70 mmol/L or on lipid lowering treatment, (d) plasma HDL-c < 1.0 mmol/L for men and < 1.3 mmol/L for women on lipid lowering treatment, (e) prediabetes (i.e. fasting glucose levels 5.6 to 6.9 mmol/L, or 2-h post-load glucose levels 7.8 to 11.0 mmol or HbA1c 5.7% to 6.4%) (39–46 mmol/mol), (f) homeostasis model assessment of insulin resistance score ≥ 2.5, or (g) plasma high-sensitivity C-reactive protein level > 2 mg/L.

Standard drinks were reported differently among studies included in this review but were generally defined as containing between 10-15g pure alcohol (18). The Australian guidelines define one standard drink as containing 10g of alcohol (40).

Appendix

Appendix Table 1 Database search for Part A

#	Search for systematic reviews, meta-analyses, and pooled analyses	# Results
1	(liver disease* or liver fibrosis or fibrotic liver or steatosis* or steatohepatitis or fatty liver or cirrhosis or cirrhot* or hepatit* or hepatocellullar or HCC or liver cancer).tw.	1116271
2	(alcohol* adj4 (consum* or intake or use*)).tw.	283424
3	(ethanol adj4 (consum* or intake or use*)).tw.	30878
4	(drink* adj4 (light or heavy or moderate or harmful or excess*)).tw.	36069
5	non drink*.tw.	4606
6	nondrink*.tw.	3430
7	2 or 3 or 4 or 5 or 6	322072
8	1 and 7	26178
9	limit 8 to (english language and humans and yr="2011 -Current")	13235
10	limit 9 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	9100
11	limit 10 to medline	3271
12	10 not 11	5829
13	9 not 12	7406
14	limit 13 to yr="2011 - 2017"	4209
15	13 not 14	3197
16	remove duplicates from 14	2280
17	remove duplicates from 15	1952
18	16 or 17	4232

Database(s): Embase Classic+Embase 1947 to 2021 December, Ovid MEDLINE® ALL 1946 to December 2021

Appendix Table 2 Database search for Part B

#	Search for studies in the Australian context	# Results
1	(liver disease* or liver fibrosis or fibrotic liver or steatosis* or steatohepatitis or fatty liver or cirrhosis or cirrhot* or hepatit* or hepatocellullar or HCC or liver cancer).tw.	1121878
2	(alcohol* adj4 (consum* or intake or use*)).tw.	285233
3	(ethanol adj4 (consum* or intake or use*)).tw.	30967
4	(drink* adj4 (light or heavy or moderate or harmful or excess*)).tw.	36254
5	non drink*.tw.	4633
6	nondrink*.tw.	3449
7	2 or 3 or 4 or 5 or 6	324025
8	1 and 7	26343
9	(australia or australian).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, sy]	498827
10	8 and 9	307
11	remove duplicates from 10	223
12	limit 11 to (english language and humans)	198

Database(s): Embase Classic+Embase 1947 to 2021 December, Ovid MEDLINE(R) ALL 1946 to December 2021

Appendix Table 3 Cochrane and PROSPERO database search

Database	Search terms	# Results
Cochrane Database of Systematic Reviews	Alcohol AND liver disease in Title Abstract Keyword – (Word variations have been searched)	36
PROSPERO database for registered prospective systematic reviews	(Liver disease* or liver fibrosis or fibrotic liver or steatosis* or steatohepatitis or fatty liver or cirrhosis or cirrhot* or hepatit or hepatocellular or HCC or liver cancer) AND (alcohol* adj (consum* or intake) or Alcohol adj* (light or moderate or heavy or harmful or excess*) or non-drink*)	182

PROSPERO; The International Prospective Register of Systematic Reviews

Appendix Table 4 Study selection criteria

Selection criteria	Inclusion	Exclusion
Publication type	Original research articles	Conference abstracts, letters, editorials, narrative reviews, posters, academic theses
Study design	Part A: Systematic reviews with meta-analyses, randomized-controlled trials, pooled analyses Part B: any study design	Part A: Cohort studies, case control studies, case report or case series. Part B: no exclusion criteria*
Population	People who consume a quantified level of alcohol and whose stage of liver pathology (normal, steatosis, steatohepatitis, fibrosis, cirrhosis, or cancer) is reported in the original study.	Studies involving participants who were undergoing or had undergone liver transplant or bariatric surgery, genetic studies.
Intervention	Any level of alcohol consumption (none, light, moderate or heavy drinkers) reported in grams or drinks per day or week.	Level of alcohol consumed is unclear (e.g., alcohol use disorder, alcoholism)
Comparator	Non-drinkers or light drinkers	Comparator is unclear
Outcome	Incidence, morbidity, or mortality due to liver disease (any stage) or liver cancer (HCC)	Rare liver cancers (ICC), liver transplantation.
Outcome measures	Hazard ratios; risk ratios; odds ratios and their 95% confidence intervals, or information allowing for their calculation.	Studies that did not report any odds ratios, risk ratios, or hazard ratios for the outcome of interest.
Language	English	Not in English
Publication period	Part A: Systematic reviews and meta-analyses undertaken in the past 10 years (December 2011-December 2021) Part B Australian studies published at any time	Part A: Prior to December 2011 Part B: No exclusion criteria

**For Australian studies, the scope of the review was expanded to include all research articles including cohort studies, case-control studies published at any time. HCC; hepatocellular carcinoma, ICC; intrahepatic cholangiocarcinoma.*

Appendix Table 5 Studies excluded at full text from Part A, with reason for exclusion

Author (date)	Title	Reason excluded
Lyu et al. (2016)	Analysis of risk factors associated with the development of hepatocellular carcinoma in chronic HBV-infected Chinese: A meta-analysis.	Not relevant exposure – did not quantify level of alcohol intake
Llamosas-Falcon et al. (2021)	The relationship between different dimensions of alcohol use and the burden of disease-an update.	Not relevant exposure – did not quantify level of alcohol intake
He et al. (2021)	Relationship between alcohol consumption and the risks of liver cancer, esophageal cancer, and gastric cancer in China: Meta-analysis based on case-control studies.	Not relevant outcome – combined estimates of the risk of various cancers

Llamosas-falcon et al. (2020)	Alcohol use disorders and the risk of progression of liver disease in people with hepatitis C virus infection - a systematic review.	Not relevant exposure – did not quantify level of alcohol intake
Askgaard et al. (2019)	Opportunities to Prevent Alcoholic Liver Cirrhosis in High-Risk Populations: A Systematic Review With Meta-Analysis.	Not relevant outcome – looked at prevention measures
Parker et al. (2020)	The natural history of alcohol-related liver disease.	Not relevant exposure – did not quantify level of alcohol intake
Trembling et al. (2017)	Risk of chronic liver disease in post-menopausal women due to body mass index, alcohol and their interaction: a prospective nested cohort study within the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).	Not relevant study type – cohort study
Jones et al. (2015)	Relationship between alcohol-attributable disease and socioeconomic status, and the role of alcohol consumption in this relationship: a systematic review and meta-analysis.	Not relevant exposure – did not quantify level of alcohol intake
Sookian et al. (2014)	Modest alcohol consumption decreases the risk of nonalcoholic fatty liver disease: A meta-analysis of 43 175 individuals.	Not relevant study type – letter to the editor
Holmes et al. (2012)	The temporal relationship between per capita alcohol consumption and harm: A systematic review of time lag specifications in aggregate time series analyses.	Not relevant outcome – time lag analysis
Li et al. (2019)	Alcohol and HBV synergistically promote hepatic steatosis.	Not relevant study type – animal study
Sookoian et al. (2014)	Modest alcohol consumption decreases the risk of non-alcoholic fatty liver disease: a meta-analysis of 43 175 individuals.	Not relevant study type – full article not published
Shimazu et al. (2012)	Alcohol drinking and primary liver cancer: a pooled analysis of four Japanese cohort studies.	Not relevant study type – published prior to December 2011
Llamosas-Falcon et al. (2020)	Impact of alcohol on the progression of HCV-related liver disease: A systematic review and meta-analysis.	Not relevant population – HCV

HBV; hepatitis B virus, HCV; hepatitis C virus

Appendix Table 6 Studies excluded at full text from Part B, with reason for exclusion

Author (year)	Title	Reason excluded
Najman et al. (2007)	Increasing socioeconomic inequalities in male cirrhosis of the liver mortality: Australia 1981 - 2002.	The exposure was manual versus non-manual labourers, not alcohol intake
Kerr et al. (2000)	Beverage-specific alcohol consumption and cirrhosis mortality in a group of English-speaking beer-drinking countries.	Did not provide Australian-specific data
Einsiedel et al. (2013)	Non-communicable diseases, infection and survival in a retrospective cohort of Indigenous and non-Indigenous adults in central Australia.	Not relevant population - Patients admitted with a blood stream infection
Treacy et al. (2021)	The associations of factors with previous alcohol use in the Northern Territory compared to other states - an observational study.	Not relevant exposure - alcohol use is not the independent variable
Jiang et al. (2014)	Alcohol consumption and liver disease in Australia: Atime series analysis of the period 1935-2006.	Time-series analysis - does not provide relative risk
Vaz et al. (2021)	Determinants of Short- and Long-Term Outcomes of an Australian Cohort of Patients Admitted with Alcoholic Hepatitis.	Did not report on level of alcohol consumption.
Alavi et al. (2019)	Declining hepatitis C virus-related liver disease burden in the direct-acting antiviral therapy era in New South Wales, Australia.	Not relevant outcome – incidence rate ratio for liver-related mortality
Brotodihardjo et al. (1994)	Hepatocellular carcinoma in western Sydney: Aetiology, changes in incidence, and opportunities for better outcomes.	Not relevant outcome - outcome was difference in history of excessive alcohol intake as a risk factor in people who were Australian-born versus overseas-born

Appendix Table 7 Domains of AMSTAR-2 instrument

AMSTAR-2 Domains	
1	Did the research questions and inclusion criteria for the review include the components of PICO?
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3	Did the review authors explain their selection of the study designs for inclusion in the review?
4*	Did the review authors use a comprehensive literature search strategy?
5	Did the review authors perform study selection in duplicate?
6	Did the review authors perform data extraction in duplicate?
7	Did the review authors provide a list of excluded studies and justify the exclusions?
8	Did the review authors describe the included studies in adequate detail?
9*	Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?
10	Did the review authors report on the sources of funding for the studies included in the review?
11*	If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12	If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?
13*	Did the review authors account for risk of bias in primary studies when interpreting/discussing the results of the review?
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Domains marked with an asterisk (*) were considered critical domains which could critically affect the validity of a review and its conclusions. AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews

Appendix Table 8 Rating overall confidence in results using AMSTAR-2

Rating	Description
High	No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate	More than one non-critical weakness: the systematic review has more than one weakness by no critical flaws. It may provide an accurate summary of the results of the available studies that were provided in the review.
Low	One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that addresses the question of interest.
Critically low	More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews

Appendix Table 9 Assessment of included systematic reviews using AMSTAR-2

Author (date)	1	2	3	4*	5	6	7	8	9*	10	11*	12	13*	14	15*	16	Rating:
Wijarnpreecha et al. (2021)	y	n	y	y	y	y	n	y	y	n	y	y	y	y	y	n	Moderate
Wongtrakul et al. (2021)	y	n	y	y	y	n	n	y	y	n	y	y	y	y	y	y	Moderate
Glyn-Owen et al. (2021)	y	y	y	y	y	y	n	y	y	y	y	y	y	y	y	y	High
Park et al. (2020)	y	n	y	y	y	y	n	y	y	n	y	y	y	y	y	y	Moderate

Roerecke et al. (2019)	y	n	y	y	y	y	n	y	y	n	y	y	y	y	y	y	Moderate
Roerecke et al. (2016)	y	n	n	y	y	n	n	y	y	n	y	y	y	y	y	y	Moderate
Cao et al. (2016)	y	n	y	y	y	y	n	y	y	n	y	n	n	n	y	y	Low
Bagnardi et al. (2015)	y	n	y	y	y	y	n	n	y	n	y	y	y	y	y	y	Moderate
Chuang et al. (2015)	y	n	n	y	n	n	n	y	y	n	y	y	y	y	y	y	Moderate
Turati et al. (2014)	y	n	y	y	y	y	n	n	y	n	y	y	y	y	y	y	Moderate
Bagnardi et al. (2013)	y	n	y	y	y	y	n	n	y	n	y	y	y	y	y	y	Moderate

**Critical domains that seriously impact on the validity of findings. AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews, Y; yes, N; no, P; partial yes*

Appendix Table 10 Relative risk of liver cancer, results from systematic reviews and meta-analyses

Author (year)	# Participants	# Cases	Group	Alcohol intake	Reference group	Relative risk (95% CI)	p-value	I^2 (%)	Measure
WCRF (2018)	NR	4,132	Men	Per 10g increment	No change in alcohol consumption	1.03 (1.01-1.05)	NR	51%	RR
		637	Women			1.19 (1.04-1.35)	NR	12%	
		4,720	Asia			1.04 (1.02-1.07)	NR	63%	
		930	North America and Europe			1.08 (1.00-1.16)	NR	74%	
Petrick et al. (2018)	NR	161	BMI 18.5 to <25	0 to <3 drinks/d	Non-drinker	0.56 (0.43-0.73)	NR	NR	HR
		287		3 to <5 drinks/d		1.11 (0.68-1.83)	NR		
		216		≥5 drinks/d		1.09 (0.64-1.87)	NR		
		19	BMI 25 to <30	0 to 3 drinks/d		0.76 (0.62-0.94)	NR		
		22		3 to <5 drinks/d		0.85 (0.54-1.34)	NR		
		26		≥5 drinks/d		1.60 (1.13-2.25)	NR		
		16	BMI ≥30	0 to 3 drinks/d		0.85 (0.60-1.07)	NR		
		45		3 to <5 drinks/d		1.32 (1.13-2.25)	NR		
		29		≥5 drinks/d		1.45 (1.12-1.87)	NR		
Bagnardi et al. (2015)	12,695	NR	Men	≤12.5g/d	Non-drinker	1.05 (0.84-1.32)	NR	53	RR
				>12.5 to ≤ 50g/d		1.08 (0.88-1.32)	NR	57	
				>50g/d		1.59 (1.21-2.09)	NR	69	
			Women	≤12.5g/d		0.81 (0.59-1.12)	NR	26	
				>12.5 to ≤ 50g/d		1.24 (0.88-1.75)	NR	39	
				>50g/d		3.89 (1.6-9.48)	NR	10	
			Europe	≤12.5g/d		0.92 (0.58-1.46)	NR	31	
				>12.5 to ≤ 50g/d		0.83 (0.7-0.97)	NR	0	
				>50g/d		2.00 (1.07-3.74)	NR	85	
			North America	≤12.5g/d		1.24 (0.73-2.10)	NR	0	
				>12.5 to ≤ 50g/d		1.23 (0.97-1.56)	NR	33	
				>50g/d		3.40 (2.54-4.55)	NR	0	
			Asia	≤12.5g/d		1.02 (0.83-1.26	NR	58	
				>12.5 to ≤ 50g/d		1.14 (0.97-1.33)	NR	9	
				>50g/d		1.59 (1.27-2.00)	NR	69	
Chuang et al. (2015)	NR	NR	Men	25g/d	Never drinker	1.21 (1.10-1.32)	NR	NR	RR
				50g/d		1.48 (1.25-1.74)	NR		
				75g/d		1.83 (1.45-2.30)	NR		
				100g/d		2.29 (1.68-3.11)	NR		
				125g/d		2.89 (1.93-4.33)	NR		
			Women	25g/d		1.27 (1.05-1.53)	NR		
				50g/d		2.08 (1.22-3.55)	NR		
				75g/d		4.68 (1.51-14.5)	NR		
				100g/d		14.4 (2.01-10.34)	NR		
	10,000	NR	Men	<37.5g/d	Non-drinker	0.9 (0.76-1.07)	NR	73	RR

Turati et al. (2014)				≥37.5g/d		1.14 (0.96-1.34)	NR	60	
			Women	<37.5g/d		0.89 (0.71-1.12)	NR	1	
				≥37.5g/d		NR	NR	NR	
			Asia	<37.5g/d		0.97 (0.86-1.08)	NR	60	
				≥37.5g/d		1.17 (1.00-1.37)	NR	67	
			Not Asia	<37.5g/d		0.66 (0.52-0.84)	NR	26	
				≥37.5g/d		1.13 (0.75-1.71)	NR	0	
Bagnardi et al. (2013)	4,626	NR	Men	≤12.5g/d	Non-drinker	0.99 (0.89-1.10)	NR	NR	RR
			Women	≤12.5g/d		1.00 (0.64-1.57)	NR		
			Europe	≤12.5g/d		1.10 (0.77-1.58)	NR	NR	
			North America	≤12.5g/d		0.92 (0.56-1.51)	NR	NR	
			Asia	≤12.5g/d		1.02 (0.89-1.17)	NR	NR	

BMI; body mass index, CI; confidence interval, g/d; grams per day, HR; hazard ratio, NR; not reported, OR; odds ratio, RR; risk ratio, WCRF; World Cancer Research Fund.

Appendix Table 11 Study selection criteria

Selection criteria	Inclusion	Exclusion
Publication type	Original research articles	Conference abstracts, letters, editorials, narrative reviews, posters, academic theses
Study design	Systematic reviews with meta-analyses, randomized controlled trials (RCTs), models or modelling studies and pooled analyses	Cohort studies, case control studies, case report or case series.*
Population	Participants with or without existing liver disease. Stage of liver disease (normal, ARLD fibrosis, cirrhosis, or primary liver cancer) had to be reported. Studies could involve people from the general population and/or participants with existing liver disease of ARLD etiology.	Participants who had undergone liver transplantations were excluded. Studies reporting on liver function biomarkers such as alanine aminotransferase (AMT) or aspartate transaminase (ART) were excluded. Studies reporting on genetic polymorphisms such as PNPLA3 or rs738409 were excluded. Studies involving participants with liver diseases of other aetiologies (i.e., NAFLD/MAFLD, HBV- or HCV-related were excluded.
Intervention	NA	NA
Comparator	NA	NA
Outcome	Incidence, morbidity, or mortality due to liver disease (any stage) or liver cancer (HCC)	Rare liver cancers (ICC) liver transplantation.
Outcome measures	**For the review on progression**: state transition probabilities, incidence, or mortality rates and their 95% confidence interval. Can be annual progression rate, or incident rates per person-years	Studies that did not report any progression, transition, incidence, or mortality rates.
Language	English	Not in English
Publication period	Systematic reviews and meta-analyses undertaken in the past 10 years (April 2012-April 2022).	Prior to April 2022*

**For Australian studies, the scope of the review was expanded to include all research articles including cohort studies, case-controls published at any time. ARLD; alcohol-related liver disease, HBV; hepatitis B virus, HCC; hepatocellular carcinoma, HCV; hepatitis C virus, ICC; intrahepatic cholangiocarcinoma, NA; not applicable, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic associated fatty liver disease*

Appendix Table 12 Database search for Part A

#	Searches	# Results
1	(liver disease* or steatosis or steatohepatitis or alcohol-related liver disease or alcoholic fatty liver disease or ARLD or ALD or alcoholic steatohepatitis or steatohepatitis or fibrosis or fibrotic liver or cirrhosis or cirrhotic liver or hepatocellullar or HCC or liver cancer).ti.	436829
2	(incidence or mortality or morbidity or burden or epidemiology or natural history or progression or association or risk*).ti.	2935240
3	1 and 2	34099
4	limit 3 to english language	34099
5	Limit 4 to human	32138
6	Limit 5 to yr="2012-Current"	237377

#	Searches	# Results
7	Limit 6 to conference abstracts	12517
8	6 not 7	7885
9	(systematic review or meta-analysis or meta-analytic or pooled analysis or randomised control* trial or RCT or model or models or modelling or modeling).ti	2099379
10	8 and 9	650
11	Remove duplicates from 10	632

Database(s): Embase Classic+Embase 1947 to April 2022, Ovid MEDLINE® ALL 1946 to March 2022

Appendix Table 13 Database search for Part B

#	Searches	# Results
1	(liver disease* or steatosis or steatohepatitis or alcohol-related liver disease or alcoholic fatty liver disease or ARLD or ALD or alcoholic steatohepatitis or steatohepatitis or fibrosis or fibrotic liver or cirrhosis or cirrhotic liver or hepatocellullar or HCC or liver cancer).ti.	436618
2	(incidence or mortality or morbidity or burden or epidemiology or natural history or progression or association or risk*).ti.	2933745
3	1 and 2	3408
4	limit 3 to english language	32118
5	Limit 4 to human	27355
6	Limit 5 to conference abstracts	16138
7	5 not 6	11217
8	(Australia or Australian).tw.	373298
9	7 and 8	71
10	Remove duplicates from 9	71

Database(s): Embase Classic+Embase 1947 to April 2022, Ovid MEDLINE® ALL 1946 to April 2022

Appendix Table 14 Cochrane, PROSPERO and clinical trial registry search terms

Database	Search terms	# Results
Cochrane Database of Systematic Reviews	(“liver disease*” or steatosis or steatohepatitis or “alcoholic liver disease” or “alcohol-related liver disease” or ARLD or ALD or “alcoholic steatohepatitis” ASH or “alcoholic cirrhosis” or fibrosis or “fibrotic liver” or cirrhosis or “cirrhotic liver” or hepatocellular or HCC or liver cancer) AND (incidence or mortality or morbidity or burden or epidemiology or “natural history” or progression or association or risk*) in Title Abstract Keyword – with Cochrane Library publication ate between Mar 2012 and Mar 2022 restricted to Gastroenterology and Hepatology.	195
PROSPERO database for registered prospective systematic reviews	Alcohol-related liver disease	27
Australian New Zealand Clinical Trials Registry	liver disease*” or steatosis or steatohepatitis or “alcoholic liver disease” or “alcohol-related liver disease” or ARLD or ALD or “alcoholic steatohepatitis” ASH or “alcoholic cirrhosis” or fibrosis or “fibrotic liver” or cirrhosis or “cirrhotic liver” or hepatocellular or HCC or liver cancer Key terms searched individually in observational studies	0

ALD; alcoholic liver disease, ARLD; alcohol-related liver disease, ASH; alcoholic steatohepatitis, PROSPERO; The International Prospective Register of Systematic Reviews

Appendix Table 15 Studies excluded at full text for Part A, with reason for exclusion

Author (date)	Title	Reason excluded
Jarvis et al. (2022)	Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis.	Exclude - does not report progression rates for ARLD, this study is about NAFLD
Llamosas-Falcon et al. (2020)	Alcohol use disorders and the risk of progression of liver disease in people with hepatitis C virus infection - a systematic review.	Exclude - does not report progression rates for ARLD, this study is about HCV
Liu et al. (2021)	Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: A modelling study.	Exclude – does not relate to ARLD, this study is about liver cancer more generally
Stine et al. (2018)	Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases.	Exclude - does not report progression rates for ARLD, this study is about NASH

ARLD; alcohol-related liver disease, HCV; hepatitis C virus, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis

Appendix Table 16 Studies excluded at full text for Part B, with reason for exclusion

Author (year)	Title	Reason excluded
Rutherford et al. (2021)	Comparison of liver cancer incidence and survival by subtypes across seven high-income countries.	Not specific to ARLD – this paper was about liver cancer generally and the histological subtypes HCC, ICC, and unspecified.
Maher et al. (2021)	Community screening identifies undiagnosed chronic liver disease in high-risk populations.	Not specific to ARLD – relates to viral hepatitis.
Liu et al. (2021)	Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: A modelling study.	Not specific to the Australian context – no estimates for Australia
Majumda et al. (2017)	Declining mortality in critically ill patients with cirrhosis in Australia and New Zealand between 2000 and 2015.	Not specific to ARLD – reports overall cirrhosis mortality rates.

ARLD; alcohol-related liver disease, HCC; hepatocellular carcinoma, ICC; intrahepatic cholangiocarcinoma

Appendix Table 17 Domains of AMSTAR-2 instrument

AMSTAR-2 Domains	
1	*Did the research questions and inclusion criteria for the review include the components of PICO?*
2	*Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*
3	*Did the review authors explain their selection of the study designs for inclusion in the review?*
4*	*Did the review authors use a comprehensive literature search strategy?*
5	*Did the review authors perform study selection in duplicate?*
6	*Did the review authors perform data extraction in duplicate?*
7	*Did the review authors provide a list of excluded studies and justify the exclusions?*
8	*Did the review authors describe the included studies in adequate detail?*
9*	*Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?*
10	*Did the review authors report on the sources of funding for the studies included in the review?*
11*	*If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?*
12	*If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?*
13*	*Did the review authors account for risk of bias in primary studies when interpreting/discussing the results of the review?*
14	*Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?*
15	*If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*
16	*Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?*

Domains marked with an asterisk (*) were considered critical domains which could critically affect the validity of a review and its conclusions. AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews

Appendix Table 18 Rating overall confidence in results using AMSTAR-2

Rating	Description
High	No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate	More than one non-critical weakness: the systematic review has more than one weakness by no critical flaws. It may provide an accurate summary of the results of the available studies that were provided in the review.
Low	One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that addresses the question of interest.
Critically low	More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews

Appendix Table 19 AMSTAR-2 tool for the identification of high-quality systematic reviews

Author (date)	1	2	3	4*	5	6	7	8	9*	10	11*	12	13*	14	15*	16	Rating:
Parker et al. (2019)	y	y	y	y	n	n	n	y	y	n	y	y	y	y	y	y	High

**Critical domains that seriously impact on the validity of findings. AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews, Y; yes, N; no, P; partial yes*