The Daffodil Centre

The Australian Prevention Partnership Centre

Preventing liver cancer: Excess body weight, metabolic syndrome, metabolic-associated fatty liver disease and primary liver cancer

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A partnership between

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Excess body fatness, the metabolic syndrome and risk of liver disease and liver cancer

Introduction

Excess body weight is a leading cause of preventable death and disability in Australia and globally (1). More than one-third (39%) of the global adult population carries excess weight and higher in Australia, with 67% of Australian adults estimated to be overweight or obese, 36% and 31% respectively (2). Overweight and obesity, hereafter referred to under the umbrella term excess body weight, are known risk factors for many non-communicable conditions including metabolic associated fatty liver disease (MAFLD) and liver cancer.

MAFLD (formerly NAFLD, non-alcoholic fatty liver disease) is the most common chronic liver disease worldwide affecting 39% of the global population (3) and, according to recent estimates, approximately 37% of Australian adults (4). Previously the term NAFLD was used to describe the subset of patients who had fatty liver in the absence of other known causes (i.e., alcohol-related liver disease, viral hepatitis, and rare hereditary conditions) (5). However, the terminology was recently updated to MAFLD to reflect patient heterogeneity and allow for better treatment stratification (6).

MAFLD is diagnosed using positive criteria which are the presence of steatosis (fatty infiltration in >5% of hepatocytes) in addition to at least one of the following: excess body weight, type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation (7,8). While some patients with NAFLD are considered lean (body mass index (BMI) <25kgm^{-3}), the majority carry excess body weight (81%) (9), and a multinational cohort study involving Australian patients found this proportion was higher in a Caucasian population (86%) (10).

MAFLD can be categorised histologically into steatosis, steatohepatitis, fibrosis, and cirrhosis as shown in Figure 1 (5). Although the early stages of MAFLD are generally reversible, the end stages are not with higher rates of liver-related complications, mortality, and progression to primary liver cancer (11). Projections based on Australian modelling have predicted there will be a 25% increase in NAFLD cases from the current prevalence of 22% (12) and a 75% increase in NAFLD-related primary liver cancer deaths over 2019-30 (12). Using the broader definition of MAFLD is likely to increase this number as outlined in Figure 1 (3).

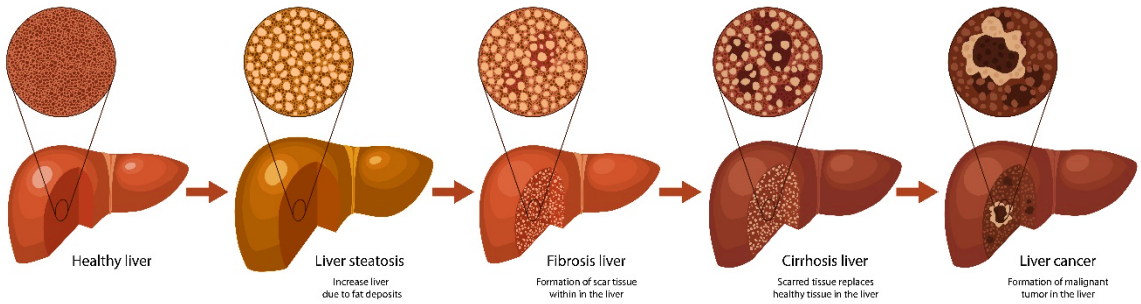

Figure 1 Stages of liver disease

Previously, the World Cancer Research Fund (WCRF) and International Agency for Research on Cancer (IARC) concluded there is convincing evidence that body fatness increases the risk liver cancer, and that the absence of body fatness protects against liver cancer (13,14). These reports by the WCRF and IARC were conducted in 2014 and 2016 respectively, and related only to risk of cancer, not the risk of NAFLD or MAFLD (13,14).

The objective of this report was to identity and review evidence from recently published systematic reviews, meta-analyses and pooled analyses, or studies of any type in the Australian context in relation to the association between excess body weight, the metabolic syndrome, and risk of NAFLD or MAFLD and primary liver cancer. The terms NAFLD and MAFLD are used as reported in original studies.

NAFLD	MAFLD
Steatosis (fatty infiltration in >5% of hepatocytes) AND	
No excessive alcohol consumption (>30grams per day (g/d) for men and >20g/d for women is generally considered the threshold for excessive drinking). **No other causes of hepatic steatosis** (e.g., viral hepatitis B and C, hemochromatosis, autoimmune disease, Wilsons' disease).	**At least one of the following criteria:** • Excess body weight (overweight/obesity) • Type 2 diabetes mellitus (T2DM) • Metabolic dysregulation **Metabolic dysregulation refers to at least two features of:** • Waist circumference ≥102/88 cm in Caucasian men and women (or ≥90/80 cm in Asian men and women), • Blood pressure ≥130/85 mmHg or specific drug treatment • Plasma triglycerides ≥150 mg/dl (≥1.70 mmol/L) or specific drug treatment • Plasma high density lipoprotein-cholesterol 2 mg/L • Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dl [5.6 to 6.9 mmol/L], or 2-hour post-load glucose levels 140 to 199 mg/dl [7.8 to 11.0 mmol] or HbA1c 5.7% to 6.4% [39 to 47 mmol/mol]) • Homeostasis model assessment of insulin resistance score ≥2.5 • Plasma high-sensitivity C-reactive protein level >2 mg/L

Box 1 Diagnostic criteria for NAFLD and MAFLD.

Source: Chalasani et al., 2018 (5) *and Eslam et al., 2020* (7,8)

Review questions and aims

Question 1: What is known about the association between excess body weight and risk of NAFLD, MAFLD and primary liver cancer?

Question 2: What is known about the association between metabolic syndrome and risk of NAFLD, MAFLD and primary liver cancer?

This report presents the results for both 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 2021 (updated May 2022) to search national and international literature for studies published in the last decade. For Question 1, we used key terms relating to “overweight,” “obesity,” “body mass index,” and “BMI,” and for Question 2 we conducted a separate search using terms relating to “metabolic syndrome.” Both searches were combined with key terms for “NAFLD,” “MAFLD,” “HCC,” and “liver cancer.” 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, 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. The search strategy was adapted for each information source, with complete details of the search provided in the Appendix Tables 2-4.

Eligibility criteria

The eligibility criteria and scope of the review were defined using the “Participant Concept Context” framework as described below. Detailed summaries of the inclusion and exclusion criteria are provided in the Appendix Table 1.

Participants

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

Concept

For Question 1, using the reference group of normal weight participants (BMI ≥ 18.5 to <25) or participants who were not overweight or obese (BMI <25), studies needed to report on incidence or mortality due to NAFLD, MAFLD or primary liver cancer with estimates of the relative risk in terms of risk ratios (RR), odds ratios (OR) or hazard ratios (HR) and their corresponding 95% confidence intervals (CI).

In line with the WCRF approach , we included only studies that involved participants where BMI was used as a marker for overweight and obesity (13). Although BMI is an imperfect measure of excess adiposity and does not distinguish between lean and fat mass, it enables us to draw conclusions across multiple varied studies.

For Question 2, using the reference group of participants without the metabolic syndrome, studies needed to report on the incidence or mortality due to NAFLD/MAFLD and/or primary liver cancer with RR, OR, or HR estimates corresponding 95% CI.

In keeping with the International Consensus Joint Interim Statement (which incorporates International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHALBI) criteria) (15) we included only studies that defined metabolic syndrome as a cluster of 3 or more metabolic risk factors. Studies that did not define metabolic syndrome, or only referred to individual components of metabolic syndrome were excluded.

Studies that did not estimate the relative risk, or where the reference group was unclear were excluded.

Context

Primary liver cancer refers to any malignant tumours that start in the liver. The most common type of primary liver cancer in adults in Australia is HCC. We sought to identify studies that reported on the outcome HCC. Studies which reported on rare primary liver cancers such as intrahepatic cholangiocarcinoma (ICC), angiosarcoma, or bile duct cancer were excluded. If the study did not specify which type of primary liver cancer was being reported on, the study was included using the classification as per the original study.

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 as we deemed all international and national literature to be relevant.

Types of sources

Conference abstracts, letters, editorials, and narrative reviews were not included. For each question, the literature search and review were conducted in two parts:

Part A: aimed to identify evidence from systematic reviews, meta-analyses, and pooled analyses published in the last decade (May 2012 to May 2022). The PROSPERO database was also searched for ongoing prospectively registered systematic reviews.

Part B: aimed to identify evidence from studies in the Australian context of any study type, published at any time (to May 2022).

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 6-8. 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) (16).

Data extraction

The following data: study information; setting; number of participants; participant group; exposure (BMI status or metabolic syndrome status); reference group; outcomes and outcome measures; funding information, and author's key conclusions were extracted. As this report is a scoping review 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. The AMSTAR-2 contains 16 domains and is not intended to generate an overall score but does assist in the identification of high-quality systematic reviews (17).

Key findings

Search outcomes for Question 1: excess body weight

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

In total, 13,373 records were identified during the literature search for systematic reviews, meta-analyses and pooled analyses relating to excess body weight as outlined in **Error! Reference source not found.**. Following the removal of duplicates (n=8) and exclusion of studies that were not a systematic review or meta-analysis (n=12,819), 546 records were screened by their titles and abstracts, 27 articles read full text and 10 included in the review. One study was identified during reference list scans (18). Reasons for exclusion included not appropriate study type (e.g., case report), not relevant population (e.g., children), exposure (e.g., weight loss), or outcome (e.g., prevalence). Of the 10 included studies, nine were

systematic reviews with meta-analyses (19–27) and one was a pooled analysis (18). Four studies reported on the outcome of NAFLD (19–22), and six studies reported on the outcome of primary liver cancer (18,23–27). No studies reported on the outcome of MAFLD.

As stated in the introduction, there are two seminal reports relating to excess body weight and risk of liver cancer by the IARC and the WCRF (13,14). Data from these seminal reports were also extracted and are presented in the relevant outcomes for liver cancer (13,14).

Ongoing systematic reviews and meta-analysis

There were four studies registered in PROSPERO relating to excess body weight and risk of NAFLD, one relating to risk of ARLD, and two relating to risk of liver cancer. Additionally, there was one study registered which aimed to compare liver-related outcomes in patients diagnosed with MAFLD vs those diagnosed with NAFLD as shown in Table 1.

Part B Search for studies in the Australian context

Fifty-one records were identified during the literature search for Australian studies relating to excess body weight as outlined in Figure 2. One record was excluded as a duplicate and 50 screened by their titles and abstracts with five studies read full text. Three additional studies were identified in the literature review although two of these were excluded upon being read full text. Reasons for exclusion at full text included not relevant outcome (e.g., ALT levels (4,28,29), liver stiffness measure (30), or difference in mean BMI (31)). In total two studies in the Australian context were included (10,32). One reported on the outcome of NAFLD (32), one primary liver cancer (10) and no studies reported on the outcome of MAFLD.

Search outcomes for Question 2: metabolic syndrome

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

In total, 3,840 records were identified during the literature search for studies relating to the metabolic syndrome as outlined in Figure 3. Following the removal of duplicates (n=2) and exclusion of studies that were not a systematic review with meta-analysis, or pooled analyses (n=3,721), 117 records were screened by their titles and abstracts, nine articles read full text, one identified through reference lists and six included in the review. Reasons for exclusion at full text included: referred to components only of the metabolic syndrome, not relevant liver disease outcome (i.e., prevalence study), or did not report relative risk. Of the six included studies, one systematic review reported on the outcome of NAFLD (19) and five systematic reviews with meta-analyses reported on the outcome of liver cancer (33–37). No studies reported on the outcome of MAFLD.

Ongoing systematic reviews and meta-analysis

One systematic review with meta-analyses was registered by Lim et al. in 2021 to investigate the natural history of MAFLD, including prevalence, risk factors and outcomes (Table 1).

Part B Search for studies in the Australian context

One study relating to the metabolic syndrome and risk of NAFLD in the Australian context was identified (32) as outlined in Figure 3.

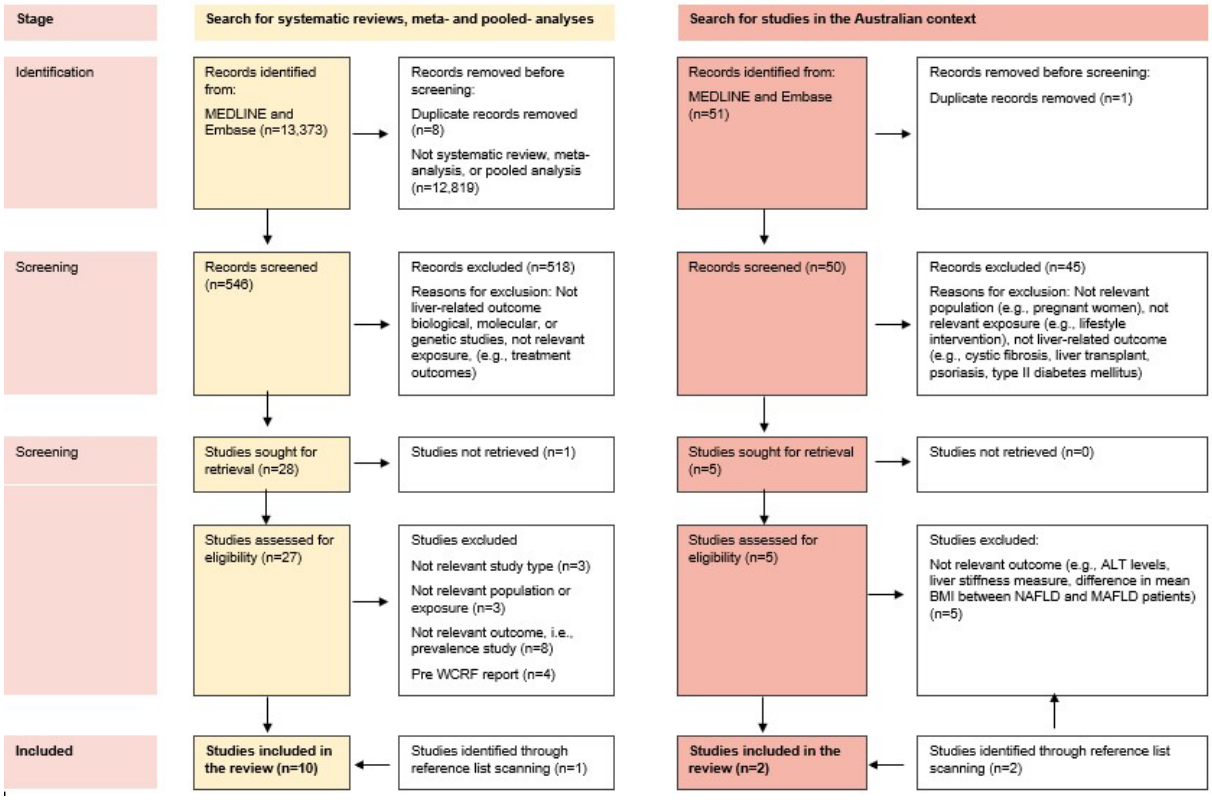

Figure 2 Search outcomes, excess body weight

NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic associated fatty liver disease, WCRF; World Cancer Research Fund.

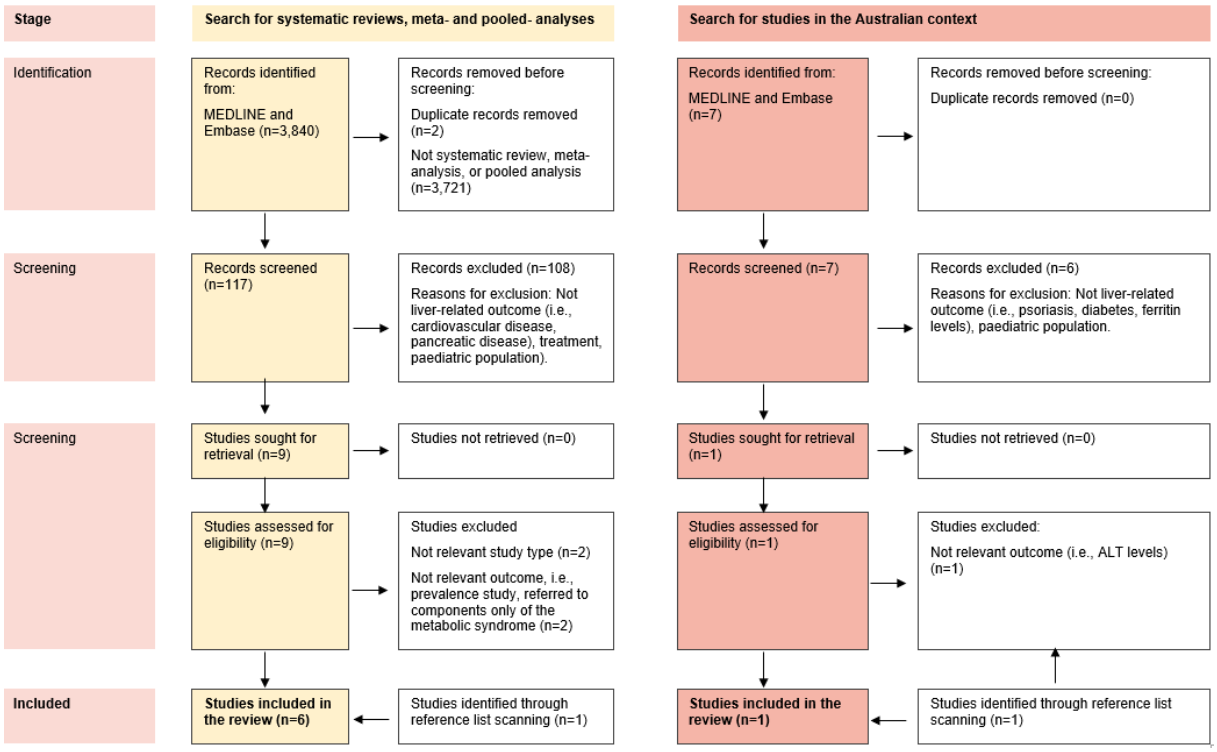

Figure 3 Search outcomes for studies, metabolic syndrome

ALT; alanine aminotransferase

Table 1 Characteristics of studies registered in PROSPERO

Author (year registered)	Population	Exposure	Comparator	Outcome	PROSPERO ID	Status
Bhadoria et al. (2022)	ARLD	BMI	BMI	Morbidity Mortality	CRD42022300673	Review ongoing
Xuan et al. (2021)	NAFLD	Obese	Not obese	Cirrhosis, HCC	CRD42021277038	Review ongoing
Prasoona et al. (2021)	General	MetS	No MetS	Liver Cancer	CRD42021230899	Review ongoing
Huang et al. (2021)	NAFLD	BMI	BMI	Mortality	CRD42021286309	Review ongoing
Kim et al. (2020)	General	BMI	BMI	NAFLD; HCC	CRD42020209826	Review ongoing
Wang et al. (2015)	General	Obese	Normal weight	NAFLD	CRD42015024356	Review ongoing

BMI; body mass index, ARLD; alcohol-related liver disease, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic associated fatty liver disease, MetS; metabolic syndrome

Association between excess body weight and risk of NAFLD

Results from Part A: systematic reviews and meta-analyses

Study characteristics

No studies were identified that reported on the association between overweight and risk of NAFLD. Four systematic reviews with meta-analyses reported on the association between obesity and risk of NAFLD as shown in Table 2 (19–22) with relevant outcomes outlined in Table 5. While a formal critical appraisal of included studies was beyond the scope of this review, the quality of the meta-analyses by Jarvis et al. (2020) and Li et al. (2016) were rated "excellent," Sookoian et al. (2018) "good," and Lu et al. (2018) "moderate" using the AMSTAR-2 tool for critical appraisal of systematic reviews as shown in Table 2 (19–22).

Relevant outcomes

The most recent meta-analysis by Jarvis et al. (2020) found that there was a positive association between obesity (BMI >30) and risk of advanced NAFLD incidence (HR 1.20 (1.12-1.28), p-value<0.001, I^2=87%), however there was no statistically significant association for risk of advanced NAFLD mortality (HR 1.15 (0.97-1.36), p-value=0.11, I^2=71%) as shown in Table 5 (19). Lu et al. (2018) similarly found a statistically significant association between obesity and risk of NASH (OR 1.73 (1.15-1.28), I^2=11%) and pooled NAFLD-related fibrosis stage >2 (OR 3.22 (2.33-4.87), I^2=0%) (20). However the result was not statistically significant for advanced fibrosis stage F3-4 (OR 1.49 (0.93-2.39), I^2=43%) (20).

Sookoian et al. (2018) found that lean NAFLD patients (BMI <25) had a lower risk of NASH compared to those with excess body weight (BMI >25) (OR 0.58 (0.35-0.98), p-value 0.040, I^2=67) (21).

Li et al. (2016) found there was a positive association between obesity (BMI ≥30) and risk of NAFLD where normal weight (BMI ≥18.5 to <25) participants constituted the reference group (RR 3.58 (2.48-5.03), p-value <0.001, I^2=95%) (22). This positive relationship was evident in sub-group analyses by gender, ethnicity, and study type (prospective or retrospective cohort) in the study by Li et al. (2016) as shown in Table 3 (22).

It should be noted that five studies used "not obese" (BMI <25) as the reference group, rather than normal weight (BMI 18.5 to <25.0) (19–21,24,27). This may potentially skew the results toward higher risk estimates (19–21,24,27).

Table 2 Characteristics of systematic reviews with meta-analyses which examined the association between BMI and risk of NAFLD

Author (year)	Literature search to:	# Studies included	Participants	BMI (kg/m ^{2}) categories	Reference group BMI	Outcome	AMSTAR-2 score
Jarvis et al. (2020) (19)	Jan 2020	22	Patients with and without existing NAFLD	>30	NR	Advanced NAFLD	14
Lu et al. (2018) (20)	Jul 2017	13	Patients with NAFLD	≥25 Asian ≥30 non-Asian	<25 Asian <30 non-Asian	NAFL, F0-4, F3-4	11
Sookoian et al. (2018) (21)	Jul 2017	8	Patients with NAFLD	≤25	>25	NASH	13
Li et al. (2016) (22)	Oct 2015	21	Patients with and without existing NAFLD	≥30, dose-response per 1 unit increase	≥18.5 to <25	NAFLD	14

Research quality was assessed by the AMSTAR-2 tool for critical appraisal of systematic reviews and the score ranged from 0 to 16 points. AMSTAR-2; a measurement tool to assess systematic reviews, BMI; body mass index, F0-4; fibrosis stage 0-4, F3-4; NA; not applicable, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, NR; not reported. ***Type of included study:*** *Jarvis: All cohort studies, Lu: 12 Cross-sectional; 1 Cohort. Sookoian: NR. Li: All Cohort.* ***Location:*** *Jarvis: 9 Europe; 5 North America; 2 Asia. Lu: 12 Asia; 1 Europe. Sookoian: Italy; India; Hong Kong; Argentina; Greece. Li: 17 Asia; 3 Europe; 1 US.*

Table 3 Relative risk of NAFLD stratified by BMI and sub-group analyses where available.

Author (year)	# Participants	# Cases	Group	BMI (kg/m ^{3}) categories	Relative risk (95% CI)	p-value	I^2 (%)	Outcome	Measure
Jarvis et al. (2020)	19,300,000	49,541	General	>30	1.20 (1.12-1.28)	<0.01	87	Advanced NAFLD	HR
					1.07 (1.02-1.14)	0.01	85	Incidence	
					1.15 (0.97-1.36)	0.11	71	Mortality	
Lu et al. (2018)	11,043	1,256	NAFLD	≥25 Asian ≥30 non-Asian	1.45 (0.84-2.51)	NR	57	NASH	OR
					1.73 (1.15-2.61)	NR	11	NASH*	
					3.22 (2.13-4.87)	NR	0	F0-4	
					1.49 (0.93-2.39)	NR	43	F3-4	
Sookoian et al. (2017)	2,702	NR	NAFLD	≤25	0.58 (0.35-0.98)	0.040	67	NASH	OR
Li et al. (2016)	381,655	NR	General	≥30	3.58 (2.48-5.03)	<0.001	95	NAFLD	RR
			Men	≥30	4.09 (3.65-4.58)	<0.001	0		
			Women	≥30	4.78 (3.05-7.47)	<0.001	76		
			Caucasian	≥30	2.67 (1.58-4.52)	<0.001	10		
			Asian	≥30	3.74 (2.51-5.55)	<0.001	96		
			Prospective	≥30	2.82 (2.11-3.76)	<0.001	71		
			Retrospective	≥30	4.93 (3.12-7.78)	<0.001	91		

**Sensitivity analysis excluding one study by Alam et al. (2014) which was identified as a source of heterogeneity. **data are also available for a dose-response meta-analyses per 1 unit increase in BMI. BMI; body mass index, NAFLD; non-alcoholic fatty liver disease NASH; non-alcoholic steatohepatitis, NR; not reported, OR; odds ratio, F0-4; fibrosis 0-4, F3-4; fibrosis 3-4, HBV; hepatitis B virus; HCC; hepatocellular carcinoma, HCV; hepatitis C virus, HR; hazard ratio.*

Results from Part B: studies in the Australian context

One Australian study were identified during the literature search (32). Roberts et al. (2021) in a prospective cohort study with 704 participants from regional Victoria found that overweight (BMI 25 to <30) and obesity (BMI >30) increased the relative risk of NAFLD prevalence (RR 12.0 (4.6-33.0) and RR 32.0 (12.0-86.0) for overweight and obesity, respectively).

Association between excess body weight and risk of primary liver cancer

Results from Part A: systematic reviews and meta-analyses

Study characteristics

Since the release of the WCRF report and IARC handbook, an additional five systematic reviews with meta-analyses and one pooled analysis have been published which report on the association between excess body weight and risk of liver cancer as shown in Table 4 with relevant outcomes outlined in Table 5 (18,23–27). While a formal quality assessment was beyond the scope of this review, the included meta-analyses were rated “good” using the AMSTAR-2 tool as shown in Table 4 (18,23–27).

Relevant outcomes

The WCRF (2018) found that the relative risk of liver cancer per every 5 kg/m^2 increment increase in BMI was 1.30 (1.16-1.46), I^2=78% with no evidence of publication bias (Egger’s test, p=0.27) (13). When stratified by outcome, the relative risk was 1.43 (1.19-1.70), I^2=84%) for incidence and 1.13 (1.00-1.28), I^2=43% for mortality (13). The IARC (2016) report supported these results and found that compared with normal weight, the relative risk of liver cancer was approximately 1.5 times greater for patients who were overweight and about 1.8 times greater for those who were obese (14).

More recent meta- and pooled analyses by Sohn et al. (2021), Yang et al. (2020), Gupta et al. (2018), and Campbell et al. (2016) have similarly found a statistically significant positive association between excess body weight and primary liver cancer (18,23–27). The relative risk of liver cancer incidence ranged from 1.16 (1.09-1.23) to 1.31 (1.11-2.77) among patients who were overweight and ranged from 1.83 (1.60-2.09) to 2.32 (1.95-2.77) among those who were obese as shown in Table 8Table 5 (18,25,27). Gupta et al. (2018) found there was a statistically significant positive association between obesity (BMI ≥30) and risk of liver cancer mortality (HR 1.96 (1.17-5.05), p-value=0.002, I^2=0%) (26). However, while there was a positive trend, the association between overweight (BMI 25 to <30) and liver cancer mortality was not statistically significant (HR 1.08 (0.97-1.21), p-value=0.15, I^2=37%) (26). Chen et al. (2021) examined the risk of HCC incidence among patients with existing NAFLD and found that excess body weight had a positive association (HR 1.31 (1.00-1.71), I^2=0%) (23). Campbell et al. (2016) in a pooled analysis of 14 cohort studies involving patients with and without existing liver disease found that per every 5 increment increase in BMI, the relative risk of HCC was 1.41 (1.32-1.51) (18), supporting results of the WCRF report as shown in Table 5.

Table 4 Characteristics of systematic reviews, meta- and pooled- analyses which examined the association between BMI and risk of liver cancer

Author (year)	Literature search to:	# Studies included	Participants	BMI (kg/m ^{2}) categories	Reference group BMI	Outcome	AMSTAR-2 score
IARC (2018) (14)	Jul 2016	20	Patients with and without existing liver disease	≥25 to <30 ≥30	≥18.5 to <25	Liver Cancer	NA
WCRF (2018) (13)	Jun 2013	12	Patients without existing liver disease	Per 5 units	NA	Liver Cancer	NA
Sohn et al. (2021) (24)	Nov 2018	28	Patients with and without existing liver disease (including HCV/HBV)	Overall ≥25 ≥30 ≥35	<25	Liver Cancer	13
Chen et al. (2021) (23)	Apr 2021	4	Patients with NAFLD	≥25	NR	HCC	12
Yang et al. (2019) (25)	Sep 2018	37	Patients with and without existing liver disease (including HBV, HCV, cirrhosis)	≥25 to <30 ≥30	≥18.5 to <25	Liver Cancer	12
Gupta et al. (2018) (26)	Mar 2016	9	Patients with and without existing liver disease	≥25 to <30 ≥30	≥18.5 to <25	Liver Cancer	12
Yao et al. (2017) (27)	May 2017	17	Patients with and without existing liver disease	≥25 to <30 ≥30	<25	Liver Cancer	13
Campbell et al. (2016) (18)	NR	14	Patients with and without existing liver disease	<18.5 ≥25 to <30 ≥30	≥18.5 to <25	HCC	NR for pooled analysis

Research quality was assessed by the AMSTAR-2 tool for critical appraisal of systematic reviews and the score ranged from 0 to 16 point. AMSTAR-2; a measurement tool to assess systematic reviews, BMI; body mass index, NA; not applicable, NAFLD; non-alcoholic fatty liver disease, NR; not reported, HBV; hepatitis B virus; HCC; hepatocellular carcinoma, HCV; hepatitis C virus, IARC; International Agency for Research on Cancer, WCRF; World Cancer Research Fund. ***Type of included study: Sohn:*** *All cohort. Chen All cohort. Yang: 34 Cohort; 3 Nested case-control. Gupta: All cohort including 3 pooled studies. Yao: 13 Cohort; 4-Case-control. WCRF: All cohort, Campbell; All cohort.* ***Location: Sohn*** *13 Asia; 10 Europe; 5 US. Chen; 2 Japan; 1 US; 1 Italy. Yang: 19 Asia; 6 US; 12 Europe. Gupta: 5 North America and Europe (including 2 pooled studies from Scotland and Switzerland); 4 Asia-Pacific (including 1 pooled study). Yao: 7 Asian; 5; US/Canada; 5 Europe, WCRF: NR, Campbell; all US.*

Sub-group analyses

Sex

When stratified by sex, the WCRF report showed that men and women had nearly identical risk of liver cancer per 5 kg/m^2 increments increase in BMI (RR 1.21 (1.02-1.44), I^2=84% and RR 1.21 (1.10-1.33), I^2=11% respectively) (13). However, more recent analyses by Yang et al., Yao et al., and Campbell et al. indicate that men who have excess body weight are at higher risk compared to women (18,25,27). The relative risk men for who were overweight ranged from 1.18 (1.05-1.33) to 1.18 (1.01-1.30) and for women who were overweight ranged from 1.08 (0.96-1.22) to 1.17 (0.85-1.60) (18,25,27). The relative risk of primary liver cancer for men who were obese ranged from 1.89 (1.60-2.22) to 2.36 (1.91-2.92) and for women who were obese ranged from 1.56 (1.37-1.78) to 2.17 (1.59-2.95) as shown in Table 5 (18,25,27).

Geographic Location

The WCRF report found that there was a weaker association between BMI and risk of liver cancer in Asian studies compared to in European or non-Asian studies (RR 1.18 (1.04-1.34), I^2=60% for Asian studies vs. RR 1.59 (1.35-1.87), I^2=42% for non-Asian studies) (13). This was supported in subsequent meta-analyses by Sohn et al., Yang et al., and Yao et al. (24,25,27). The relative risk of primary liver cancer ranged from 1.10 (1.00-1.22) to 1.36 (1.02-1.82) among overweight participants in Asian countries and 1.21 (1.11-1.33) to 1.98 (1.71-2.29) among overweight participants in non-Asian countries (25,27,24). The relative risk of primary liver cancer ranged from 1.44 (1.24-1.67) to 1.85 (1.50-2.27) among obese participants in Asian countries and 1.95 (1.64-2.31) to 3.08 (1.21-7.86) among obese participants from non-Asian countries (24,25,27) as shown in Table 5.

Results from Part B: studies in the Australian context

One multinational cohort study involving Australian patients (n=52) was identified in the literature search (10). Younes et al. (2022) found that patients who carried excess body weight (BMI ≥25 for Caucasian persons and ≥23 for Asian persons) compared to those who did not had an increased trend in the relative risk of HCC however, when adjusted for age, the result was not significant (adjusted HR 1.90 (0.46-0.8.10), p-value=0.37) (10).

Table 5 Relative risk of liver cancer stratified by BMI and sub-group analyses where available

Author (year)	# Participants	# Cases	Group	BMI (kg/m^2) categories	Relative risk (95% CI)	p-value	I^2 (%)	Outcome	Measure
WCRF (2018) (13)	NR	14,311	General	Per 5 unit	1.30 (1.16-1.46)	NR	78	Incidence	RR
			Men	Per 5 unit	1.21 (1.02-1.44)	NR	84		
			Women	Per 5 unit	1.21 (1.10-1.33)	NR	11		
			Europe	Per 5 unit	1.59 (1.35-1.87)	NR	42		
			Asia	Per 5 unit	1.18 (1.04-1.34)	NR	60		
Sohn et al. (2021) (24)	8,135,906	NR	General	Overall	1.69 (1.50-1.91)	<0.001	56	Incidence	HR
				>25	1.36 (1.02-1.81)	0.040	56		
				>30	1.77 (1.56-2.01)	<0.001	51		
				>35	3.08 (1.21-7.86)	0.02	0		
			Not Asia	Overall	2.00 (1.73-2.31)	<0.001	32		
				>25	1.98 (1.71-2.29)	<0.001	36		
				>30	3.08 (1.21-7.86)	0.02	0		
			Asia	Overall	1.42 (1.23-1.63)	<0.001	37		
				>30	1.36 (1.02-1.82)	0.040	56		
				>35	1.44 (1.24-1.67)	<0.001	13		
Chen et al. (2021) (23)	297,956	NR	NAFLD	>25	1.31 (1.00-1.71)	NR	0	Incidence	HR
Yang et al. (2019) (25)	12,892,304	NR	General	≥25 to <30	1.16 (1.09-1.23)	NR	53	Incidence	RR
				≥30	1.84 (1.64-2.06)	NR	74		
			Men	≥25 to <30	1.18 (1.05-1.33)	NR	61		
				≥30	1.89 (1.60-2.22)	NR	67		
			Women	≥25 to <30	1.08 (0.96-1.22)	NR	0		
				≥30	1.61 (1.41-1.83)	NR	0		
			Not Asia	≥25 to <30	1.27 (1.14-1.42)	NR	59		
				≥30	1.96 (1.71-2.24)	NR	61		
			Asia	≥25 to <30	1.11 (1.01-1.23)	NR	56		
				≥30	1.85 (1.50-2.27)	NR	75		
Gupta et al. (2018) (26)	1,599,453	5,705	General	≥25 to <30	1.08 (0.97-1.21)	0.15	37	Mortality	HR
			General	≥30	1.96 (1.17-5.05)	<0.002	0		
			Men	≥30	2.50 (2.02-3.09)	<0.01	NR		
			Women	≥30	1.45 (1.08-1.97)	<0.01	NR		
			Not Asia	≥30	2.10 (1.77-2.48)	0.03	NR		
			Asia	≥30	1.10 (0.63-1.92)	0.03	NR		
Yao et al. (2017) (27)	5,701,823	18,225	General	≥25 to <30	1.16 (1.08-1.25)	0.016	43	Incidence	RR
				≥30	1.83 (1.60-2.09)	<0.001	59		
	5,003,931	15,435	Men	≥25 to <30	1.18 (1.01-1.30)	0.004	59		
				≥30	2.04 (1.70-2.44)	<0.001	66		
	697,892	2,790	Women	≥25 to <30	1.11 (1.00-1.24)	0.500	0		
				≥30	1.56 (1.37-1.78)	0.414	3		
			Not Asia	≥25 to <30	1.21 (1.11-1.33)	0.365	8		
				≥30	1.95 (1.64-2.31)	<0.001	65		
			Asia	≥25 to <30	1.10 (1.00-1.22)	0.050	49		
				≥30	1.56 (1.64-2.31)	<0.01	0		

Author (year)	# Participants	# Cases	Group	BMI (kg/m ^{2}) categories	Relative risk (95% CI)	p-value	I^2 (%)	Outcome	Measure
Campbell et al. (2016) (18)	NR		General	Per 5 unit	1.41 (1.32-1.51)	NR	NR	Incidence	HR
			Men	Per 5 unit	1.37 (1.23-1.52)	NR	NR		
			Women	Per 5 unit	1.44 (1.32-1.56)	NR	NR		
			General	<18.5	1.67 (0.86-3.25)	NR	NR		
				≥25 to <30	1.31 (1.11-1.54)	NR	NR		
				≥30	2.32 (1.95-2.77)	NR	NR		
			Men	<18.5	1.06 (0.34-3.32)	NR	NR		
				≥25 to <30	1.35 (1.11-1.64)	NR	NR		
				≥30	2.36 (1.91-2.92)	NR	NR		
			Women	<18.5	2.33 (1.01-5.35)	NR	NR		
				≥25 to <30	1.17 (0.85-1.60)	NR	NR		
				≥30	2.17 (1.59-2.95)	NR	NR		

BMI; body mass index, NAFLD; non-alcoholic fatty liver disease NR; not reported, HCC; hepatocellular carcinoma, HR; hazard ratio, RR; risk ratio, WCRF; World Cancer Research Fund

Association between metabolic syndrome and risk of NAFLD

Results from Part A: systematic review and meta-analyses

Study Characteristics

One systematic review investigated the association between metabolic syndrome and risk of advanced NAFLD (19).

Table 6 Characteristics of systematic reviews with meta-analyses which examined the association between BMI and risk of NAFLD

Author (year)	Literature search to:	# Studies included	Participants	Exposure	Reference group	Outcome	AMSTAR-2 score
Jarvis et al. (2020) (19)	Jan 2020	4	Patients with and without existing NAFLD	MetS	No MetS	Advanced NAFLD	14

Research quality was assessed by the AMSTAR-2 tool for critical appraisal of systematic reviews and the score ranged from 0 to 16 points. AMSTAR-2; a measurement tool to assess systematic reviews, MetS; metabolic syndrome, NAFLD; non-alcoholic fatty liver disease, NR; not reported, ***Type of included study:*** *Jarvis: All cohort studies* ***Location:*** *Jarvis: 9 Europe; 5 North America; 2 Asia.*

Relevant outcomes

Jarvis et al. (2020) identified three cohort studies which used data from the same population to report on the association between metabolic syndrome and liver-related mortality (38–40), and one study that evaluated the risk of cirrhosis (41). Despite reporting on the same population, effect sizes were inconsistent with large confidence intervals which meant that pooling of results was not possible (19). One study found that metabolic risk factors had no association with risk of mortality (38), whilst two other studies found that metabolic syndrome was associated with higher risk of mortality (39,40). The study relating to cirrhosis was larger and identified that the relative risk of NAFLD-related cirrhosis ranged from 1.90-2.56 alongside increasing numbers of metabolic abnormalities (41).

Results from Part B: studies in the Australian context

No studies relating to the metabolic syndrome in the Australian context were identified.

Association between metabolic syndrome and risk of primary liver cancer

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

Study characteristics

Five systematic reviews with meta-analyses reported on the association between metabolic syndrome and risk of liver cancer as shown in Table 7 (33–37). While a formal quality assessment of included studies was beyond the scope of this review, the quality of the meta-analysis by Jinjuvadia et al. (2014) and Ren et al. (2019) were considered “moderate” and

the meta-analyses by Chen et al. (2018), Li et al. (2018) and Esposito et al. (2012) were considered “good” using the AMSTAR-2 tool for critical appraisal of systematic reviews.

Relevant outcomes

The most recent meta-analysis by Ren et al. (2019) found that patients with the metabolic syndrome had a statistically significant increased risk of HCC compared to those without metabolic syndrome (RR 1.76 (1.33-2.33), I^2=88%) and this result was supported by estimates from earlier meta-analyses by Chen et al. (2018), Li et al. (2018), Jinjuvadia et al. (2014) and Esposito et al. (2012) (33–37).

Estimates of the relative risk were similar for men and women. The relative risk ranged from 1.43 (1.23-1.65) to 1.91 (1.38-2.65) for men and 1.18 (0.76-1.84) to 2.10 (0.69-6.37) for women with the metabolic syndrome compared to those without (33,36,37). There was no clear difference by geographic location. The relative risk ranged from 1.58 (1.18-2.12) to 1.60 (0.88-2.89) for studies in Asia and from 1.34 (0.78-2.33) to 1.71 (1.09-2.67) for studies in Western countries as shown in Table 8.

Table 7 Characteristics of systematic reviews and meta-analyses which examined the association between metabolic syndrome and risk of liver cancer

Author (year)	Literature search to:	# Studies	Participants	Exposure	Reference group	Outcome	AMSTAR-2 score
Ren et al. (2019) (35)	Dec 2017	18	Patients with and without existing liver disease	MetS	No MetS	HCC	9
Chen et al. (2018) (36)	Oct 2017	6	Patients with and without existing liver disease	MetS	No MetS	HCC	12
Li et al. (2018) (37)	Sep 2017	8	Patients with and without existing liver disease	MetS	No MetS	HCC	12
Jinjuvadia et al. (2014) (34)	Jun 2012	4	Patients with and without existing liver disease	MetS	No MetS	HCC	9
Esposito et al. (2012) (33)	Oct 2011	7	NR	MetS	No MetS	Liver Cancer	12

Research quality was assessed by the AMSTAR-2 tool for critical appraisal of systematic reviews and the score ranged from 0 to 16 point. AMSTAR-2; a measurement tool to assess systematic reviews, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, NR; not reported, MetS; metabolic syndrome. ***Type of included studies****: Ren: 18 Cohort, 1 Case-control. Chen: All cohort. Li: Cohort, case-control. Jinjuvadia et al.: 3 Cohort; 1 Case-control. Esposito: 5 Cohort; 2 Case-control.* ***Location of included studies:*** *Ren: NR, Chen: 1 Italy; 2 Japan; 1 China; 1 Multinational; 1 Korea. Li: NR. Esposito: 1 Italy; 2 Japan; 2 US; 1 Multinational; 1 China.*

Table 8 Relative risk of liver cancer among patients with metabolic syndrome stratified by sub-group analyses where available

Author (year)	# Participants	# Cases	Group	Relative risk (95% CI)	p-value	I^2 (%)	Outcome	Measure
Ren et al. (2019) (35)	1,561,457	9,434	General	1.76 (1.33-2.33)	NR	88	HCC	RR
Chen et al. (2018) (36)	127,198	1,293	General	1.43 (1.19-1.72)	<0.001	29	HCC	RR
			Men	1.75 (1.28-2.38)	<0.001	65		
			Women	1.18 (0.76-1.84)	0.46	57		
			Asian	1.58 (1.18-2.12)	0.002	90		
			Western	1.34 (0.78-2.33)	0.29	90		
Li et al. (2018) (37)	363,093	8,124	General	1.60 (1.12-2.28)	0.01	90	HCC	RR
			Men	1.91 (1.38-2.65)	<0.001	0		
			Women	2.10 (0.69-6.37)	0.91	78		
			Asian	1.60 (0.88-2.89)	<0.001	85		
			Western	1.71 (1.09-2.67)	0.02	95		
Jinjuvadia et al. (2014) (34)	829,651	7,704	General	1.81 (1.37-2.41)	<0.001	79	HCC	RR

Author (year)	# Participants	# Cases	Group	Relative risk (95% CI)	p-value	I^2 (%)	Outcome	Measure
Esposito et al. (2012) (33)	NR	5,580	General	1.60 (1.32-1.94)	NR	79	Liver cancer	RR
			Men	1.43 (1.23-1.65)	NR	0		
			Women	1.42 (0.80-2.52)	NR	71		
			Men, US	1.62 (0.59-4.41)	NR	0		
			Men, Europe	1.36 (1.16-1.60)	NR	0		
			Men, Asia	1.81 (1.25-2.62)	NR	0		
			Women, Europe	1.01 (0.46-2.24)	NR	64		
			Women, Asia	2.09 (0.69-6.37)	NR	78		

HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, NR; not reported, RR; risk ratio, US; United States

Discussion

Brief overview of findings

This review found that excess body weight was consistently associated with increased risk of NAFLD and primary liver cancer. Among participants who carried excess weight, the relative risk of NAFLD ranged from 1.20 (1.12-1.28) to 3.58 (1.12-1.28) (19,20,22) and the relative risk of liver cancer incidence ranged from 1.16 (1.09-1.23) to 2.32 (1.95-2.77) (24,25,27). There appeared to be an association between metabolic syndrome and risk of NAFLD although there were limited studies in this area (19). Metabolic syndrome was consistently associated with increased risk of primary liver cancer, with the relative risk ranging from 1.43 (1.19-1.72) to 1.76 (1.33-2.33) (33–37). The review included meta-analyses which had large sample sizes (>10,000 participants in all but one study) (21) and covered a range of geographical locations.

Local evidence was limited with only two studies in the Australian context identified. One related to excess body weight and risk of NAFLD and one related to risk of liver cancer (32,10). No Australian studies were identified relating to metabolic syndrome or MAFLD. The confidence intervals for estimates of the relative risk in these two Australian studies were wide, indicating that they may not provide a precise estimate for the study population (32,10). Given that the evidence from international meta-analyses was consistent, statistically significant, and had limited heterogeneity, it is likely to be highly applicable to the Australian context.

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.

Though NAFLD may occur in patients who are lean or not obese (approximately 19% of NAFLD patients are lean) (9) we only included studies relating to excess body weight and the metabolic syndrome. Additionally, this review did not investigate the role of type 2 diabetes mellitus (T2DM). T2DM has been identified as an important predictive, although not necessarily causative, risk factor for NAFLD (19). (19). Following the inclusion of T2DM into the diagnostic criteria for MAFLD, and inclusion of NAFLD into clinical practice guidelines for T2DM in some countries (42), understanding the interplay between excess body weight, metabolic syndrome and T2DM will be important to capture and account for in future research.

Implications and future directions

The shift in terminology from NAFLD to MAFLD has significant implications for this review and future research. Firstly, no systematic reviews with meta-analyses were identified regarding the association between excess body weight or metabolic syndrome and risk of MAFLD. Secondly, MAFLD, with the inclusion of markers indicative of metabolic dysfunction,

appears to identify patients at higher risk of disease progression and may enable better stratification for non-obese patients with fatty liver, such as those with lean NAFLD (7,8). Thirdly, current estimates for the global and Australian prevalence of MAFLD are higher, thus including a larger proportion of patients compared with NAFLD (global prevalence: 39 vs. 37% and Australian prevalence: 37 vs. 22%, respectively) (4,12,43).

Future reviews could seek to identify evidence regarding the interplay between risk factors chronic liver disease and primary liver cancer. While the key risk factors chronic viral hepatitis, ARLD and NAFLD each have distinct pathways of disease progression, evidence increasingly shows that there is overlap and possible synergism between different risk factors. Presence of high BMI and metabolic syndrome can exacerbate disease progression in ARLD, for example, putting patients at heightened risk of primary liver cancer and mortality (40,38). Additionally, the change in terminology to MAFLD facilitates research in patients with concomitant liver disease as the exclusion of significant alcohol intake or other chronic liver disease is no longer a pre-requisite for its diagnosis (44).

Population-based interventions could be designed to target people with excess body weight and metabolic syndrome to reduce the prevalence of these modifiable risk factors. It is becoming increasingly important to monitor those with lean NAFLD. Identification of patients with T2DM may assist with risk stratification.

Conclusion

This report identified and reviewed evidence from recently published systematic reviews, meta-analyses and pooled analyses, and studies in the Australian context in relation to the association between excess body weight, metabolic syndrome, and the relative risk of NAFLD, MAFLD and primary liver cancer.

This body of literature substantiated that excess body weight and metabolic syndrome increase the risk of NAFLD and primary liver cancer but findings relating to MAFLD are not yet available.

As rates of obesity and the metabolic syndrome continue to increase, so too will the prevalence of NAFLD, MAFLD and primary liver cancer. It is important that efforts to understand the impact of preventable risk factors and the impact of MAFLD continue so that action can be taken to reduce the future burden of liver cancer.

Progression from NAFLD/MAFLD to liver fibrosis, cirrhosis, primary liver cancer and mortality

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects one-quarter (25.24%) of the global adult population, making it one of the most common chronic liver diseases worldwide (11). By 2030, it is estimated that the prevalence of NAFLD will have increased by a further 23% in Australia attributable to the obesity epidemic and rising rates of metabolic syndrome. Increased NAFLD prevalence will increase rates of non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, liver-related deaths, and primary liver cancer (12).

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer in Australia (45). In 85 to 90% of cases, HCC arises in the context of underlying cirrhosis (46). Risk factors for cirrhosis include chronic hepatitis C virus (HCV), alcohol-related liver disease (ARLD), chronic hepatitis B virus (HBV) and NAFLD which account for 29%, 25%, 23% and 13% of all cases in Australia, with the remaining 10% due to unknown causes (47). While NAFLD-related HCC is currently the least cited risk factor for liver cirrhosis and subsequent cases of HCC, recent Australian studies have shown that the incidence rate of NAFLD-related HCC has increased,(48) against decreases in the overall incidence rate of HCC.

A previous Australian review of the natural history and burden of NAFLD estimated transition rates from steatosis and NASH to cirrhosis, cirrhosis to HCC, cirrhosis to decompensation and HCC, and decompensation to mortality as shown in Figure 1 (49). There was limited Australian evidence to inform these rates and they were therefore based on international findings (49).

The purpose of this review was to identify if there was any additional evidence available from recently published international systematic reviews with meta-analyses, pooled analyses, and modelling studies or from studies of any type in the Australian context. Additionally, we sought to identify if there was any evidence relating to metabolic-associated fatty liver disease (MAFLD), the proposed updated terminology for NAFLD.

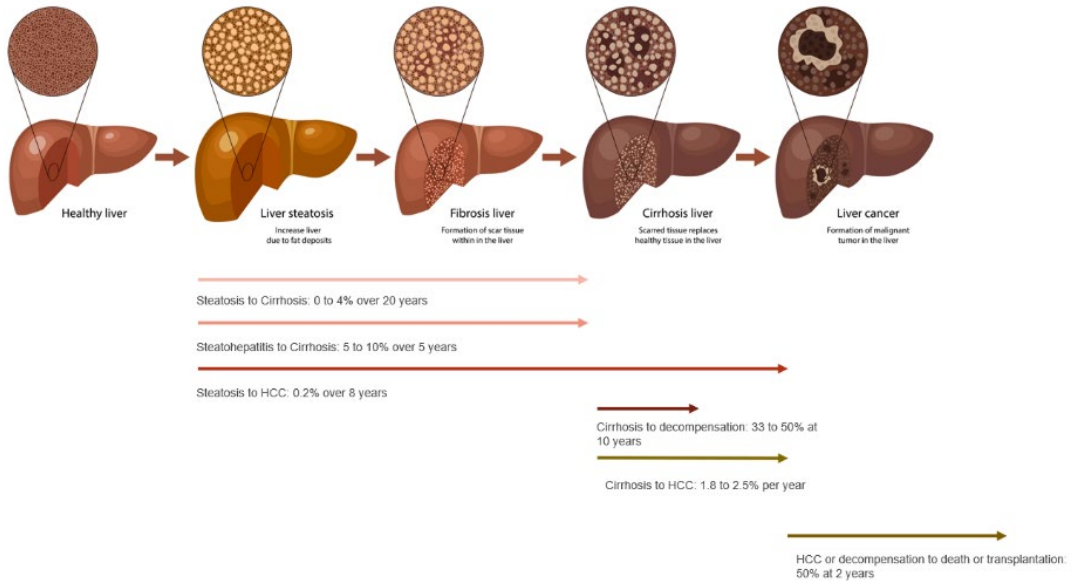

Figure 4 Stages of NAFLD

Review questions and aims

Question 1: What is known about the progression from NAFLD/NASH or MAFLD/MASH to liver fibrosis, cirrhosis, primary liver cancer and mortality?

Methods

Search strategy

Electronic literature searches were performed in March 2022 to search national and international literature for studies published in the last decade (March 2012 to March 2022). Key terms relating to NAFLD/NASH and MAFLD/MASH, fibrosis, cirrhosis, liver cancer, hepatocellular carcinoma and HCC were paired with terms relating to progression, risk, natural history, epidemiology, and burden as outlined in Table 1 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, and the International Prospective Register of Systematic Reviews (PROSPERO) were searched. Reference lists of all included papers were scanned manually for other relevant studies. The search strategy was adapted for each source, with complete details provided in the Appendix Tables 2-3.

Eligibility criteria

The eligibility criteria and scope of the review were defined using the "Participant Concept Context" framework as described below (50). Detailed summaries of the inclusion and exclusion criteria are provided in the Appendix 1.

Participants

Studies could involve adult participants (≥18 years) from the general population and/or participants with existing NAFLD/NASH or MAFLD/MASH. Studies reporting on liver function biomarkers such as alanine aminotransferase (AMT) or aspartate transaminase (ART) were excluded. Studies reporting on genetic polymorphisms or genome-wide association studies 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 transition probabilities or progression rates per 100 PYs where possible.

Studies which reported on 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-based interests or details about the setting 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 several existing systematic reviews with meta-analyses.(51,52) However, there were few studies in the Australian context. As such the literature search was conducted in 2 parts:

Part A: was restricted to review only systematic reviews, meta-analyses, and pooled analyses published in the last decade (March 2012 to March 2022). Additionally, the

PROSPERO database was searched for ongoing prospectively registered systematic reviews.

Part B: reviewed any relevant Australian literature published up to March 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 Table 18**. 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) (16).

Data extraction

The following data: study information; setting; number of participants; participant group; rate or progression or transition probability; funding information, and author's key conclusions were extracted. As this report is a scoping review 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 as shown in the **Appendix Table 19**. The AMSTAR-2 contains 16 domains and is not intended to generate an overall score but does assist in the identification of high-quality systematic reviews (17).

Key findings

Search outcomes

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

The literature search for Part A identified 7,980 potentially relevant records as shown in Figure 1. After removing duplicates and studies that were not a systematic review, meta-analysis, pooled analysis, or modelling study, 611 records were screened by their title and abstracts. Of these, 28 were retrieved and read full text. Ten records were included, and no additional studies identified by scanning reference lists.

Of these ten studies, eight were systematic reviews with meta-analyses (11,52–54,9,55–57) and two were systematic reviews.(58,59) One of the systematic reviews included 28 modelling studies.(58) Some of these modelling studies were identified during the literature search and would have met the inclusion criteria however they were excluded to avoid repetition.(60–64) Other reasons for exclusion at full text were not relevant exposure (e.g., impact of alcohol, obesity, diagnostic tool), not relevant population (e.g., patients with HCV), no liver-related outcomes were reported, or the study reported on the outcome of association between NAFLD and the relative risk of liver disease rather than rates of progression.

No studies relating to MAFLD/MASH were identified. No pooled analyses were eligible for inclusion. The characteristics of included systematic reviews and meta-analyses are presented in Table 9.

Ongoing systematic reviews and meta-analyses

Two systematic reviews with meta-analyses were registered in PROSPERO as shown in Table 11. Lim et al. proposed to investigate the natural history of MAFLD including prevalence, risk factors and outcomes. Zhang et al. proposed to investigate the incidence of HCC in patients with biopsy confirmed NAFLD.

Part B Search for studies in the Australian context

The literature search for Part B identified 71 potentially relevant records as shown in Figure 1. No duplicates were identified so all 71 records were screened by their titles and abstracts. Of these, three studies were retrieved and read full text, and all three studies were included in the review. Two additional studies were identified by scanning reference lists and one more was known to the reviewers (48) to give a total of six studies in this section of the review.

Of the six included studies, one study modelled the projected burden of NAFLD over 2019-30 (12), three were multinational cohort studies which included Australian participants (65–67), one was cohort study conducted in New South Wales (NSW), (68) and one was a cohort study conducted in South Australia (SA) (48).

No Australian studies relating to MAFLD/MASH were identified. The characteristics of included studies in the Australian context are presented in Table 10.

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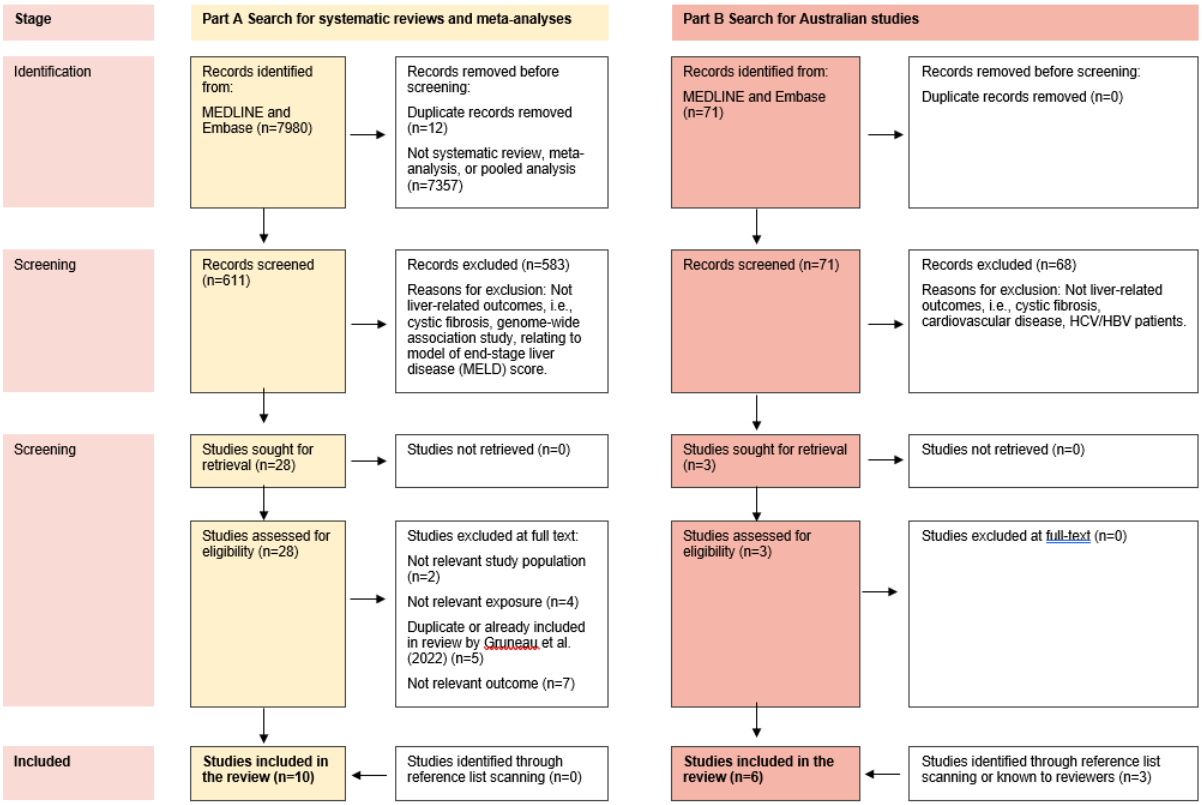

Figure 5 Search outcomes

Table 9 Characteristics of systematic reviews and meta-analyses

Author (year)	Type of study	Literature search to:	# Studies included	Participants	Stage(s) of NAFLD	Measure	Outcome(s)	AMSTAR-2 Rating
Gruneau et al. (2021) (58)	Systematic review	Jun 2021	28	NAFLD patients in modelling studies	NAFLD F0-3; CC DC; HCC	Transition probability (%)	F1-3; CC; DC; HCC; Mortality (liver-related)	Moderate
Orci et al. (2022) (52)	Meta-analysis	Jan 2020	18	NAFLD patients in observational studies	NAFLD non cirrhotic, cirrhotic, cirrhotic screening, cirrhotic no screening	Incidence rate per 100 PYs	HCC	High
Ito et al. (2021) (53)	Meta-analysis	May 2019	73	NAFLD patients in Japan	NAFLD lean, NAFLD non lean	Incidence and mortality rate per 1,000 PYs	HCC, Mortality (all-cause, liver and non-liver related)	Moderate
Roskilly et al. (2020) (54)	Meta-analysis	Jan 2020	35	Biopsy-proven NASH patients in placebo-arm of RCTs	NASH	Progression rate per year	Fibrosis, Cirrhosis	Moderate
Ye et al. (2020) (9)	Meta-analysis	May 2019	8	Lean NAFLD patients in observational studies	NAFLD non-obese or lean	Mortality rate per 1,000 PYs	Mortality (all-cause, liver-, and CVD-related)	Moderate
Li et al. (2019) (57)	Meta-analysis	Jan 2019	237	NAFLD patients in Asia	NAFLD	Incidence rate per 1,000 PYs	HCC; Mortality (all-cause)	Moderate
Dulai et al. (2017) (55)	Meta-analysis	Nov 2016	5	NAFLD patients in observational studies	NAFLD F0-4	Mortality rate per 1,000 PYs	Mortality (all-cause, liver-related)	Moderate
Younossi et al. (2016) (11)	Meta-analysis	2015	85	NAFLD patients in observational studies	NAFLD; NASH	Progression. Incidence, and mortality rate	Fibrosis; HCC; Mortality (all cause, liver-related).	Moderate
Singh et al. (2015) (56)	Meta-analysis	Jun 2013	11	Biopsy-proven NAFLD patients in observational studies	NAFLD F0, F1, F0/1 combined	Progression rate per year	Fibrosis stage progression	Moderate
White et al. (2012) (59)	Systematic review	Dec 2012	61	NAFLD cirrhotic; NAFLD non-cirrhotic	Non cirrhotic, cirrhotic	Mortality cumulative risk	HCC	Moderate

Research quality was assessed by the AMSTAR-2 tool for critical appraisal of systematic reviews and the score ranged from 0 to 16 points. AMSTAR-2; a measurement tool to assess systematic reviews, CC; compensated cirrhosis, CI; confidence interval, DC; decompensated cirrhosis, F0-4; fibrosis stage 0-4, HCC; hepatocellular carcinoma, Lean NAFLD; refers to patients with BMI <25.; NAFLD; non-alcoholic fatty liver disease, NAS; NAFLD Activity Score, NASH; non-alcoholic steatohepatitis, NR; not reported, PY; person-years.

Table 10 Characteristics of studies in the Australian context

Author (year)	Study period	Type of study	Participants	Stage(s) of NAFLD	Measure	Outcome(s)
Chandran et al. (2022) (48)	Jan 2014 to Dec 2019	Cohort retrospective	SA	NAFLD	AAPC of the ASIR	HCC
Adams et al. (2022) (12)	2019-2030	Model	Australian population	NAFLD F0-3, CC, DC, HCC	Transition probability (%)	NAFLD F1-3, CC, DC, HCC, Mortality (1st year, subsequent years)
Vilar-Gomez et al. (2018) (65)	Apr 1995 to Nov 2013	Cohort prospective	Multinational	NAFLD F3-4	Proportion (%)	Mortality (liver, non-liver related), liver transplant, DC, HCC
Anuglo et al. (2015) (66)	1975-2005 to 2012	Cohort prospective	Multinational	NAFLD F0-4; NASH	Proportion (%)	Mortality (overall), liver transplant, HCC
Bhala et al. (2011) (67)	1984 to 2006	Cohort prospective	Multinational	NAFLD	Proportion (%)	Mortality and liver transplant, HCC
Hui et al. (2003) (68)	NR	Cohort prospective	NSW	NASH cirrhosis	Proportion (%), probability of survival (%)	1-, 3-, and 10-year survival (complication free, overall)

Liver-related complications included ascites, hepatic encephalopathy, variceal bleeding and, in some cases, HCC. The study by Vilar-Gomez et al. (2018) included 458 NAFLD patients (116 Australian). The study by Anuglo et al. (2015) included 619 patients (119 Australian). The study by Bhala et al. (2011) included 247 patients (51 Australian). AAPC; average annual percentage change; ASIR; age-standardized incidence rate, CC; compensated cirrhosis, DC; decompensated cirrhosis, F0-4; fibrosis stage 0 to 4, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, NR; not reported, NSW; New South Wales. SA; South Australia

Table 11 Characteristics of studies registered in PROSPERO

Author (year registered)	Title	Population	Outcome	Measure	PROSPERO ID	Status
Zhang et al. (2022)	Incidence of hepatocellular carcinoma and extrahepatic cancers in patients with biopsy-confirmed non-alcoholic fatty liver disease: a systematic review, meta-analysis	Biopsy-confirmed NAFLD By distinct stages of NAFLD i.e., non-cirrhotic patients, cirrhotic patients, screening, not regular surveillance	HCC	Incidence rate	CRD42022301458	Review Ongoing as of March 2022
Lim et al. (2021)	The natural history of metabolic associated fatty liver disease: a meta-analysis on prevalence, risk factors and outcomes	MAFLD or MASH	Clinical outcomes	Mean difference, odds ratio	CRD42021279304	Review Ongoing as of March 2022

HCC; hepatocellular carcinoma, HR; hazards ratio, NAFLD; non-alcoholic fatty liver disease, OR; odds ratio, RR; risk ratio

Progression to fibrosis in patients with NAFLD/NASH

Results from Part A: systematic reviews and meta-analyses

Study characteristics

Three systematic reviews with meta-analyses (54,11,56) investigated the annual fibrosis progression rate (number of stages progressed per year) in patients with NAFLD/NASH. One systematic review of modelling studies reported on NAFLD transition probabilities (58). While a formal quality assessment was beyond the scope of this report, studies included in this section of the review were rated "good" using the AMSTAR-2 critical appraisal tool (11,54,56,58) as shown in Table 9.

Relevant outcomes

The most recent meta-analysis by Roskilly et al. (2020) involving 1,419 biopsy-proven NASH patients from the placebo arm of 35 RCTs found that NASH patients had an annual fibrosis progression rate of 0.00 (95% CI -0.05-0.06), I^2=68% as shown in Table 12 (54). This estimated rate of progression is substantially lower than estimated in previous meta-analyses of observational studies (11,56). Younossi et al. in a meta-analysis of 85 cohort or cross-sectional studies with 8,515,431 participants found an annual fibrosis progression rate of 0.09 (95% CI 0.06-0.12), I^2=0% among NASH patients (Table 12) (11). Singh et al. in a meta-analysis of 11 cohort studies with 411 biopsy-proven NAFLD patients found the annual fibrosis progression rate was 0.13 (95% CI 0.07-0.18), I^2=88% (Table 12) (56).

It should be noted that the time intervals between biopsy for participants involved in the RCTs in the meta-analysis by Roskilly et al. were short (54). The interval ranged from 16 to 96 weeks (with most biopsies undertaken at 48 weeks or greater) (54). The meta-analysis of observational studies by Singh et al. only included studies which identified NAFLD patients who had undergone paired liver biopsies at least 52 weeks apart (56).

In the systematic review of modelling studies, Gruneau et al. reported that the transition probabilities from NAFLD F0 to F1, F1 to F2, F2 to F3, and F3 to F4 ranged between 5.9 to 9.5%, 2.3 to 14%, 1.8 to 7.0% and 4.0 to 11.8% respectively (58).

Results from Part B: studies in the Australian context

One modelling study by Adams et al. reported transition probabilities for the progression to fibrosis in Australian patients with NAFLD as shown in Table 13 Progression from NAFLD/NASH to fibrosis, results from Part A systematic review of modelling studies

Author (year)	# Participants	# Cases	Initial disease stage:	Progression to:	Group	Transition probability (95% CI)	I2 (%)
Gruneau et al. (2021) (58)	NR	NR	NAFLD F0	NAFLD F1	Overall	5-9.5	NR
	NR	NR	NAFLD F1	NAFLD F2		2.3-14	NR
	NR	NR	NAFLD F2	NAFLD F3		1.8-7.0	NR
	NR	NR	NAFLD F3	NAFLD F4		4.0-11.8	NR

CI; confidence interval, F0-4; fibrosis stage 0-4, NAFLD; non-alcoholic fatty liver disease, NR; not reported

Table 14 (12). The probabilities of progression from F0 to F1, F1 to F2, and F2 to F3 were 0.60%, 3.65% and 3.65% respectively in men aged 0 to 44 years, and 0.50%, 3.04% and 3.04% in women aged 0 to 44 years (12). The probabilities of progression were 1.57%, 9.64% and 9.64%, and 1.31%, 8.04% and 8.04% for men and women respectively aged 45 to more than 85 years (12).

Table 12 Progression from NAFLD/NASH to fibrosis, results from Part A systematic reviews with meta-analyses

Author (year)	# Participants	# Cases	Initial disease stage:	Progression to:	Group	Annual rate (95% CI)	I^2 (%)
Roskilly et al. (2020) (54)	1,419	NR	NASH	Next fibrosis stage	Overall	0.00 (-0.05-0.06)	NR
Younossi et al. (2016) (11)	8,515,431	NR	NASH	Next fibrosis stage	Overall	0.09 (0.06-0.12)	NR
Singh et al. (2015) (56)	366	132	NAFLD F0	Next fibrosis stage	Overall	0.13 (0.07-0.18)	88
	133	52	NAFL F0			0.07 (0.02-0.11)	81
	116	40	NASH F0			0.14 (0.07-0.21)	21
	NR	NR	NAFLD F0		Western	0.12 (0.06-0.18)	NR
	NR	NR	NAFL F0			0.05 (0.0-0.10)	NR
	NR	NR	NASH F0			0.14 (0.0-0.29)	NR
	NR	NR	NAFLD F0		Asia	0.14 (-0.06-0.18)	NR
	NR	NR	NAFL F0			0.11 (0.01-0.22)	NR
	NR	NR	NASH F0			0.17 (0.03-0.31)	NR

CI; confidence interval, F0-4; fibrosis stage 0-4, NAFLD; non-alcoholic fatty liver disease, NAFL; non-alcoholic fatty liver or steatosis, NASH; non-alcoholic steatohepatitis, NR; not reported

Table 13 Progression from NAFLD/NASH to fibrosis, results from Part A systematic review of modelling studies

Author (year)	# Participants	# Cases	Initial disease stage:	Progression to:	Group	Transition probability (95% CI)	I^2 (%)
Gruneau et al. (2021) (58)	NR	NR	NAFLD F0	NAFLD F1	Overall	5-9.5	NR
	NR	NR	NAFLD F1	NAFLD F2		2.3-14	NR
	NR	NR	NAFLD F2	NAFLD F3		1.8-7.0	NR
	NR	NR	NAFLD F3	NAFLD F4		4.0-11.8	NR

CI; confidence interval, F0-4; fibrosis stage 0-4, NAFLD; non-alcoholic fatty liver disease, NR; not reported

Table 14 Progression from NAFLD/NASH to fibrosis, results from Part B

Author (year)	# Participants	# Cases	Initial disease stage:	Annual progression to:	Group	Transition probability (%)
Adams et al. (2020) (12)	NR	NR	NAFLD F0	NAFLD F1	Men, aged 0-44	0.60
					Men, aged 45 -85+	1.57
					Women, aged 0-44	0.50
					Women, aged 45-85+	1.31
			NAFLD F1	NAFLD F2	Men, aged 0-44	3.65
					Men, aged 45 -85+	9.64
					Women, aged 0-44	3.04
					Women, aged 45-85+	8.04
			NAFLD F2	NAFLD F3	Men, aged 0-44	3.65
					Men, aged 45 -85+	9.64
					Women, aged 0-44	3.04
					Women, aged 45-85+	8.04

The study by Adams et al. was a modelling study of the NAFLD burden in Australia 2019-30 and reported the progression rate as transition probabilities (%) (12). *F0-4; fibrosis stage 0-4, NAFLD; non-alcoholic fatty liver disease, NR; not reported*

Progression to cirrhosis in patients with NAFLD/NASH

Results from Part A: systematic reviews and meta-analyses

Study characteristics

Two systematic reviews with meta-analysis (11,54) and one systematic review (58) reported on the incidence rate of cirrhosis among patients with NAFLD/NASH. While a formal quality assessment was beyond the scope of this report, studies included in this section of the review were rated "good" using the AMSTAR-2 critical appraisal tool (11,54,58) as shown in Table 9.

Relevant outcomes

The proportion of NASH patients who developed cirrhosis was found to be 13% of 1,419 patients over 28 years (equivalent to an incidence rate of 0.46 per 100 PYs) in the meta-analysis of RCTs by Roskilly et al. (54). The incidence rate of NAFLD-related advanced fibrosis was estimated at 6.8 (95% CI 4.68-9.86) per 100 PYs for NASH patients in a meta-analysis of observational studies (11). In the systematic review of modelling studies, Gruneau et al. found that modelling studies recorded the annual transition probability from NAFLD F3 to NAFLD-related compensated cirrhosis as ranging between 4-11.8% and from NAFLD-related compensated to decompensated cirrhosis as ranging between 1-9% (58).

Table 15 Progression from NAFLD/NASH to cirrhosis, results from Part A systematic review with meta-analyses

Author (year)	# Participants	# Cases	Initial disease stage	Progression to:	Rate per 100 PYs (95% CI)	I2 (%)
Younossi et al. (2016) (11)	NR	NR	NASH	NAFLD Advanced fibrosis	6.8 (4.68-9.86)	10

CI; confidence interval, DC; decompensated cirrhosis, F0-4; fibrosis stage 0-4, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, NR; not reported, PY; person-years

Table 16 Progression from NAFLD/NASH to cirrhosis, results from Part A systematic review of modelling studies

Author (year)	# Participants	# Cases	Initial disease stage	Progression to:	Rate per 100 PYs (95% CI)	I2 (%)
Gruneau et al. (2021) (58)	NR	NR	NAFLD F3	NAFLD CC	4-11.8%	NR
			NAFLD CC	NAFLD CC	1-9%	

CC; compensated cirrhosis, CI; confidence interval, DC; decompensated cirrhosis, F0-4; fibrosis stage 0-4, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, NR; not reported, PY; person-years

Results from Part B: Studies in the Australian context

Study characteristics

One modelling study (12) and one cohort study (65) reported on the proportion of patients with NAFLD who progressed to cirrhosis as shown in Table 10.

Relevant outcomes

Adams et al. reported transition probabilities for patients with NAFLD F3 to compensated cirrhosis and for patients with compensated to decompensated cirrhosis by age and gender as shown in Table 17. Transition probabilities from NAFLD F3 to compensated cirrhosis ranged from 3.68 to 7.21 and the transition probability form compensated to decompensated cirrhosis was 3.71. The cohort study by Vilar-Gomez et al. included 458 NAFLD patients (116 Australian) with bridging (F3) or compensated cirrhosis (F4) (65). Vilar-Gomez et al. found that 19% of NAFLD F3-4 patients developed decompensated cirrhosis over the 10-year

study follow-up (3% and 28% of patients with NAFLD F3 and F4 respectively, equivalent to an incidence rate of 0.19 per 100 PYs.) (65).

Table 17 Progression from NAFLD/NASH to cirrhosis, results from Part B

Author (year)	# Participants	# Cases	Initial disease stage	Progression to:	Group	Progression rate (%)
Adams et al. (2020) (12)	NR	NR	NAFLD F3	NAFLD CC	Men, aged 0-44	4.42
					Men, aged 45 -85+	7.21
					Women, aged 0-44	3.68
					Women, aged 45-85+	6.00
			NAFLD CC	NAFLD DC	Men, aged 0-44	3.71
					Men, aged 45 -85+	3.71
					Women, aged 0-44	3.71
					Women, aged 45-85+	3.71
Vilar-Gomez et al. (2018) (65)	458	88	NAFLD F3-4	NAFLD DC	Overall	19
	159	5	NAFLD F3	NAFLD DC	Overall	3
	299	38	NAFLD F4	NAFLD DC	Overall	28

The study by Adams et al. was a modelling study of the NAFLD burden in Australia 2019-30 and reported the progression rate as transition probabilities (%) (12). *The study by Vilar-Gomez et al. reported on the proportion of patients who progressed to decompensated cirrhosis over the mean follow-up period of 10 years* (65). *CC; compensated cirrhosis, DC; decompensated cirrhosis, F0-4; fibrosis stage, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis.*

Progression to HCC in patients with NAFLD/NASH

Results from Part A: systematic reviews and meta-analyses

Study characteristics

Four systematic reviews with meta-analyses (11,52,53,57), and two systematic reviews (58,59) reported on the incidence rate of HCC in patients with NAFLD/NASH as shown in Table 9. While a formal quality assessment was beyond the scope of this report, five studies included in this section of the review were rated “good” (11,52,53,57,58) and one “moderate” (59) using the AMSTAR-2 critical appraisal tool.

Relevant outcomes

The most recent global meta-analysis by Orci et al. reported that the incidence rate of HCC in non-cirrhotic NAFLD patients was 0.03 (95% CI 0.01-0.07), I^2 =98% per 100 PYs (52). These results are in line with findings of an earlier global meta-analysis by Younossi et al. which found an incidence rate of 0.044 (95% CI 0.029-0.066), I^2 =0% per 100 PYs for patients with NAFLD (11). A meta-analysis of studies in Asia found an incidence rate of 0.180 (95% CI 0.080-0.310), I^2 =97% per 100 PYs among NAFLD patients (57), and a subsequent meta-analysis studies in Japan reported an incidence rate of 0.76 (95% CI 0.21-1.62), I^2 =93% per 100 PYs (53).

For cirrhotic NAFLD patients, the incidence rate was 3.78 (95% CI 2.47-5.78), I^2 =81% per 100 PYs (52). For cirrhotic NAFLD undergoing regular screening it was 4.62 (95% CI 2.77-7.72), I^2 =77% per 100 PYs and for cirrhotic NAFLD not undergoing regular screening it was 4.35 (95% CI 0.99-5.10), I^2 =56% per 100 PYs (52). As above, it appeared that cirrhotic NAFLD patients in Asian countries had a higher incidence of HCC compared to patients in the US and other countries with incidence rates of 5.82 (95% CI 2.09-15.01), I^2 =86%, 2.31 (95% CI 1.13-4.72), I^2 =94% and 1.50 (95% CI 0.57-3.93), I^2 =81% per 100 PYs for Asian, United States and other countries respectively (52).

In the systematic review of modelling studies, Gruneau et al. reported that annual? transition probabilities from compensated and decompensated cirrhosis to HCC ranged between 0.002-0.06% and 0.02- 0.04% respectively (58).

Table 18 Progression from NAFLD/NASH to HCC, results from Part A

Author (year)	# Participants	# Cases	Initial disease stage	Group	HCC incidence rate per 100 PYs (95% CI)	I^2 (%)
Gruneau et al. (2021) (58)	NR	NR	NAFLD	NAFLD CC	0.002 to 0.06	NR
	NR	NR	NAFLD	NAFLD DC	0.02 to 0.04	NR
Orci et al. (2022) (52)	470,404	563	NAFLD	Non-cirrhotic	0.03 (0.01-0.07)	98
		112	NAFLD	Cirrhotic	3.78 (2.47-5.78)	81
		68	NAFLD	Cirrhotic regular screening	4.62 (2.77-7.72)	77
		19	NAFLD	Cirrhotic no regular screening	2.35 (0.99-5.10)	56
		NR	NAFLD	Cirrhotic, Asia	5.82 (2.09-15.10)	86
		NR	NAFLD	Cirrhotic, US	2.31 (1.13-4.72)	94
		NR	NAFLD	Cirrhotic, other countries	1.50 (0.57-3.93)	81
Ito et al. (2021) (53)	8,318	114	NAFLD	NAFLD, Japan	0.76 (0.21-1.62)	97
Li et al. (2019) (57)	NR	NR	NAFLD	NAFLD, Asia	0.18 (0.08-0.31)	93
Younossi et al. (2016) (11)	8,515,431	NR	NAFLD	Overall	0.044 (0.029-0.066)	0
			NASH	Overall	0.529 (0.075-3.756)	NR
White et al. (2012) (59)	NR	NR	NASH Cirrhotic	Overall	2.4% over 7 years to 12.8% over 3 years	NR

The study by Gruneau et al. was a systematic review of modelling studies and reported the progression rate as a transition probability (%) (58). *All other studies reported on incidence rate of HCC per 100 PYs. CC; compensated cirrhosis, CI; confidence interval, DC; decompensated cirrhosis, F0-4; fibrosis stage 0 to 4, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, NR; not reported, PY; person-years, US; United States.*

Results from Part B: studies in the Australian context

Four studies in the Australian context were identified as shown in Table 19 (12,48,65,67). The most recent study by Chandran et al. (2022) was a retrospective cohort study conducted in South Australia, involving 626 patients (48). Over January 2014 to December 2019, Chandran et al. analysed trends in the age-standardised incidence rate (ASIR) of HCC (48). Although the ASIR for HCC overall decreased over this period (from 7.50 to 5.60 cases per 100,000 persons), there was an increase in the average annual percentage change (AAPC) of NASH-related HCC (+7.0%). The AAPC for all other HCC aetiologies (HBV-, HCV-, and alcohol-related) decreased over this period (AAPC -8.00%, -8.2% and -2.30% respectively) (48).

Vilar-Gomez et al. (2018) in a multinational prospective cohort study with 458 NAFLD patients (of whom 116 were Australian) found that 41 participants (9% of the cohort) developed HCC over the 10-year follow-up period(65). An earlier multinational prospective cohort study by Bhala et al. (2011) with 247 NAFLD patients (of whom 51 were Australian) found that 6 participants (2.4% of the cohort) developed HCC over the mean follow-up of 85.6 months (67).

Table 19 Progression from NAFLD/NASH to HCC, results from Part B

Author (year)	# Participants	# Cases	Initial disease stage	Progression rate	Follow-up	Measure
Chandran et al. (2022) (48)	NR	626	NASH	+7.0	NR	AAPC of the ASIR (%)
Adams et al. (2020) (12)	NR	NR	NAFLD F0	0	NR	Annual Transition probability (%)
			NAFLD F1	1		
			NAFLD F2	2		
			NAFLD F3	4		
			NAFLD CC	48		
Vilar-Gomez et al. (2018) (65)	458	41	NAFLD F3-4	9	Mean 10-years	Proportion (%)
	159	2	NAFLD F3	6		
	299	21	NAFLD F4	9		
Bhala et al. (2011) (67)	247	6	NAFLD F3-4	2	Mean 7 years	Proportion (%)

The study by Chandran et al. was a trends analysis and reported on the annual percentage change in the age-standardised incidence rate of HCC in South Australia (48). *The study by Adams et al. was a modelling study of the NAFLD burden in Australia 2019-30 and reported the progression rate as transition probabilities (%)* (12). *The study by Vilar-Gomez et al. reported on the proportion of patients who progressed to HCC over the mean follow-up period of 10 years* (65). *The study by Bhala et al. reported on the proportion of patients who progressed to HCC over the mean follow-up period of 7 years* (67). *AAPC; average annual percentage change, ASIR; age-standardized incidence rate, F0-4; fibrosis stage, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis.*

Progression to mortality in patients with NAFLD/NASH

Results from Part A: systematic reviews and meta-analyses

Study characteristics

Five systematic reviews with meta-analyses (9,11,53,55,57), and one systematic review (58) reported on the progression from NAFLD/NASH to mortality. While a formal quality assessment was beyond the scope of this report, all studies included in this section of the review were rated “good” (9,11,53,55,57,58) using the AMSTAR-2 critical appraisal tool as shown in Table 9.

Relevant outcomes

The most recent global meta-analysis found all-cause, liver-related and cardiovascular disease (CVD)-related mortality rates of 1.21 (95% CI 0.05-3.88), 0.41 (95% CI 0.19-0.71), 0.04 (95% CI 0.01-1.49) per 100 PYs respectively for patients with lean NAFLD (9). Meta-analyses of only Japanese (53) or only Asian studies (57) reported lower all-cause mortality rates of 0.62 (95% CI 0.54-0.72) and 0.53 (95% CI 0.015-1.14), I^2 =97% per 100 PYs. Dulai et al. (2017) estimated rates of mortality by stage of NAFLD fibrosis and found that mortality rates increased by increasing fibrosis stage and ranged from 1.52 to 4.58 for all-cause mortality and 0.03 to 2.33 for liver-related mortality as detailed in Table 20.

Results from Part B: studies in the Australian context

Five studies with Australian patients reported on outcomes related to mortality (12,65–68). Adams et al. reported that the probability of liver-related mortality was 61% for NAFLD HCC patients in the first year and 16.2% in subsequent years (12). Vilar-Gomez et al. found that the proportion of NAFLD F3-4 patients who died over the course of the study due to liver and non-liver related causes, ranged from 1-8% (65). Angulo et al. reported on the proportion of patients who died or underwent liver transplant as a combined outcome (66). Depending on NALFD F0-4 stage or presence of NASH, between 23-78% of patients died or underwent liver transplant over the 12.6-year follow-up (66). Bhala et al. (2011) and Hui et al. (2003) reported 1-, 3-, and 10-year survival probabilities as outlined in Table 21(67,68).

Table 20 Progression from NAFLD/NASH to mortality, results from Part A

Author (year)	# Participants	# Cases	Initial disease stage	Type of mortality	Mortality rate per 100 PYs (95% CI)	I^2 (%)
Gruneau et al. (2021) (58)	NR	NR	NAFLD DC	Liver-related	0.13 to 0.25	NR
			NAFLD HCC		0.068 to 0.61	NR
Ito et al. (2021) (53)	4,307	187	NAFLD, Japan	All-cause	0.62 (0.54-0.72)	NR
		15		Liver-related	0.05 (0.03-0.08)	NR
		172		Non-liver-related	0.57 (0.49-0.66)	NR
Ye et al. (2020) (9)	36,954	NR	Lean NAFLD	All-cause	1.21 (0.05-3.88)	NR
				Liver-related	0.41 (0.19-0.71)	NR
Li et al. (2019) (57)	NR	NR	NAFLD, Asia	All-cause	0.53 (0.015-1.14)	97
Dulai et al. (2017) (55)	570	113	NAFLD F0	All-cause	1.52	NR
	432	84	NAFLD F1		1.71	NR
	203	69	NAFLD F2		2.79	NR
	179	65	NAFLD F3		3.60	NR
	111	36	NAFLD F4		4.58	NR
	570	6	NAFLD F0	Liver-related	0.03	NR
	432	6	NAFLD F1		0.064	NR
	203	12	NAFLD F2		0.428	NR
	179	16	NAFLD F3		0.792	NR
	111	17	NAFLD F4		2.33	NR
Younossi et al. (2016) (11)	8,515,431	NR	NAFLD	All-cause	1.54 (1.17-2.03)	97
				Liver-related	0.08 (0.03-0.18)	92
				CVD-related	0.48 (0.34-0.67)	91
			NASH	All-cause	2.56 (0.63-10.4)	8
				Liver-related	1.18 (0.71-1.95)	0

The study by Gruneau et al. was a systematic review of modelling studies and reported the progression rate as a transition probability (%) (58)*. All other studies reported on the mortality rate per 100 PYs. CI; confidence interval, CVD; cardiovascular disease, DC; decompensated cirrhosis, F0-4; fibrosis stage, Lean NAFLD; patients with BMI <25; NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis; NR; not reported*

Table 21 Progression from NAFLD/NASH to mortality, results from Part B

Author (year)	# Participants	# Cases	Initial disease stage	Group	Outcome	Probability or progression rate (%)
Adams et al. (2020) (12)	NR	NR	NAFLD HCC	Overall	1st year mortality	61
					Subsequent mortality	16.2
Vilar-Gomez et al. (2018) (65)	458	31	NAFLD F3-4	Liver-related	Mortality	8
	458	3		Non-liver related		7
	159	2	NAFLD F3	Liver-related		1
	159	2		Non-liver related		1
	299	11	NAFLD F4	Liver-related		7
	299	54		Non-liver related		5
Angulo et al. (2015) (66)	322	74	NAFLD F0	Overall	Mortality or liver transplant	23
	141	42	NAFLD F1			30
	85	36	NAFLD F2			42
	53	27	NAFLD F3			51
	18	14	NAFLD F4			78
	335	85	NAFLD	No NASH		25
	105	42	NAFLD	Suspected NASH		40
	179	66	NAFLD	Definite NASH		37
Bhala et al. (2011) (67)	247	14	NAFLD F3-4	Overall	1-year survival	98
	NR	NR			3-year survival	93
	NR	NR			10-year survival	82
Hui et al. (2003) (68)	23	NR	NASH cirrhosis	Overall	1-year survival	95
	NR	NR			3-year survival	9
	NR	NR			10-year survival	84
	NR	NR		Complication free	1-year survival	83
	NR	NR			3-year survival	77
	NR	NR			10-year survival	48

The study by Adams et al. was a modelling study of the NAFLD burden in Australia 2019-30 and reported the mortality rates as transition probabilities (%) (12)*. The study by Vilar-Gomez et al., Angulo et al., and Bhala et al., were cohort studies that reported the proportion of patients who progressed to mortality over the mean follow-up periods of 10, 12.6 and 7 years respectively* (65–67)*. The study by Hui et al. reported on overall and complication free survival* (68)*. F0-4; fibrosis stage, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis.*

Discussion

Brief overview of findings

There was evidence from systematic reviews with meta-analyses of RCTs (54), observational studies (11,56) and modelling studies (58) that the fibrosis progression rate in patients with NAFLD/NASH ranges from 0.00 (95% CI -0.05-0.06) to 0.13 95% CI (0.07-0.18) stages per year. The incidence rate of cirrhosis among patients with NASH ranged from 0.46 to 6.80 (95% CI 4.68-9.86) per 100 PYs (11,54). The incidence rate of HCC ranged from 0.03 (95% CI 0.01-0.07) to 0.76 (95% CI 0.21-1.62) among patients with NAFLD (11,52,53,57), and from 2.35 (95% CI 0.99-5.10) to 3.78 (95% CI 2.47-5.78) among patients with cirrhotic NAFLD (52). It is noteworthy that the rates of progression to HCC align with international guidelines for HCC surveillance which recommend surveillance when the annual incidence rate of HCC exceeds 1.5% for patients with cirrhosis (52). The rate of liver-related mortality ranged from 0.05 (95% CI 0.03-0.08) to 2.33 (9,11,53,55). The rate of all-cause mortality ranged from 0.62 (95% CI 0.54-0.72) to 4.58 (9,11,53,55,57). Interestingly, several meta-analyses demonstrated higher rates of progression to mortality (all-cause and liver-related) compared to rates of progression to HCC (11,9,57). The review included meta-analyses conducted on a large scale, involving participants from a wide range of geographical locations and various ethnicities (11,52–54,9,55–59). High heterogeneity (I^2>50%) was a key limitation of the included meta-analyses (43,52,53,56).

There was substantive evidence in the Australian context, from a recent Australian modelling study of the NAFLD burden over 2019-30 as well as a series of multinational cohort studies which involved Australian patients (48,65–68). In the Australian modelling study fibrosis transition probabilities were back-calculated based on published odds of NAFLD progression from a 2007 cohort study (69) and expert consensus (12).

It appeared that studies involving NAFLD patients from Asian countries had a higher incidence of HCC compared to those located in Non-Asian countries (52,53,57). Whereas rates of liver-related and all-cause mortality were lower for NAFLD patients located in Japan and Asian countries (53,57). Li et al. acknowledged that these results were surprising and suggested that increasing incidence of NAFLD was due to the urbanisation of Asian populations and that higher NAFLD mortality rates may be seen in future years (57).

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

Differences in fibrosis and cirrhosis progression rates estimated in the meta-analyses by Roskilly et al. compared to Younossi and Singh et al. were explained by the study types included (1,2,17). There may be a degree of selection bias among persons who undergo repeat liver biopsy in observational studies as they comprise a subset of patients prone to progression, while patients in RCTs are generally followed-up for a shorter duration and undergo repeat biopsy at shorter intervals (70). Future studies could attempt to quantify the expected difference in NAFLD progression rates between meta-analyses of observational studies and meta-analyses of RCTs. This would help to identify real-world estimates of progression in the NAFLD population.

During the literature search, two meta-analyses were identified that estimated the proportion of patients with NASH who experienced improvement in fibrosis (71,72). Ng et al. found that 10% of patients with NASH had resolution of NASH without worsening of fibrosis (71). Han et al. found that 25% of NASH patients experienced two-point improvement in NAFLD

histological scores over trial durations ranging between 8-96 weeks (72). These studies were excluded as they did not meet our selection criteria however given the large proportion of NAFLD patients who experienced regression, this is an area that requires further investigation.

Four of the included meta-analyses reported on sub-group analyses by geographic location (52,53,56,57), and Orci et al. reported on sub-group analyses by surveillance groups in cirrhotic NAFLD patients (cirrhotic NAFLD no regular surveillance, cirrhotic NAFLD regular surveillance) (52). None of the included meta-analyses analysed results by sex or age sub-groups. Given that existing NAFLD modelling studies have estimated disease state transition probabilities by age and gender (e.g., Adams et al., calculated transition probabilities for men and women aged 0 to 44 and aged 45 to 85 years and older (12)), it will be important for future meta-analyses to determine accurate estimates of the relative risk in these groups.

There was a clear gap in the literature in that no studies were identified relating to rates of disease progression in MAFLD. The term MAFLD was put forward by expert consensus in 2020 (7,8), and has been endorsed in letter of more than 1,000 signatories from professional bodies as well as specialist and primary care physicians (73). The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver are yet to endorse the change in terminology. Until MAFLD is accepted into standard practice it is likely that literature will refer to both NAFLD and MAFLD. Current estimates for the global and Australian prevalence of MAFLD are higher compared with NAFLD (global: 39 vs. 37% and Australia: 37 vs. 22%, respectively) (4,12,43). MAFLD, with the inclusion of markers indicative of metabolic dysfunction, appears to identify patients at higher risk of disease progression including those with concomitant liver disease (44). It will be important for future studies to determine if there are any differences in rates of progression for NAFLD compared to MAFLD patients which are likely to encompass a broad and more heterogenous patient group.

Conclusion

This scoping report identified and reviewed evidence from recently published systematic reviews, meta-analyses and modelling analyses, and studies in the Australian context in relation to rates of disease progression in NAFLD and MAFLD.

This body of literature substantiated that, among patients with NAFLD, rates of progression to mortality (all-cause and liver-related) were generally higher than rates of progression to HCC. There is a substantive body of evidence in the Australian context relating to NAFLD and not yet local nor international literature relating to MAFLD.

As rates of obesity and the metabolic syndrome rise, so too will the prevalence of NAFLD, MAFLD and related primary liver cancer. It is important that efforts continue to understand rates disease progression, and which stages of NAFLD or MAFLD are high-risk, so that action can be taken to reduce the future burden of liver disease and liver cancer in Australia.

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Appendix

Appendix Table 1 Database search for Part A, excess body weight

#	Search for systematic reviews with meta-analyses and pooled analyses	# Results
1	(liver disease* or liver fibrosis or fibrotic liver or steatosis or steatohepatitis or nonalcoholic fatty liver or non-alcoholic fatty liver or NAFLD or NASH or metabolic associated fatty liver or MAFLD or MASH or cirrhosis or cirrhotic liver or hepatocellular or HCC or liver cancer).tw.	717385
2	(obese or obesity or overweight).tw.	901489
3	(body fatness or body weight or body mass index or BMI).tw.	1293272
4	(non-lean or lean).tw.	104732
5	2 or 3 or 4	1891205
6	1 and 5	71854
7	Limit 6 to English language	69068
8	Limit 7 to human	48398
9	limit 8 to yr="2012 -Current"	38954
10	limit 9 to conference abstracts	25581
11	9 not 10	13373
12	(Systematic review or meta-analysis or meta analysis or pooled analysis or random* control* trial or RCT).tw.	1065036
13	11 and 12	554
14	Remove duplicates from 13	546

BMI; body mass index, HCC; hepatocellular carcinoma NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, MAFLD; metabolic-associated fatty liver disease, MASH; metabolic associated steatohepatitis, Database(s): Embase Classic+Embase 1947 to May 2022, Ovid MEDLINE® ALL 1946 to May 2022

Appendix Table 2 Database search for Part B, excess body weight

#	Search for studies in the Australian context	# Results
1	(liver disease* or liver fibrosis or fibrotic liver or steatosis or steatohepatitis or nonalcoholic fatty liver or non-alcoholic fatty liver or NAFLD or NASH or metabolic associated fatty liver or MAFLD or MASH or cirrhosis or cirrhotic liver or hepatocellular or HCC or liver cancer).tw.	810610
2	(obese or obesity or overweight).tw.	902949
3	(body fatness or body weight or body mass index or BMI).tw.	1295212
4	(non-lean or lean).tw.	104945
5	2 or 3 or 4	1894104
6	1 and 5	74849
7	Limit 6 to English language	71968
8	Limit 7 to human	49416
9	limit 8 to yr="2012 -Current"	39698
10	limit 9 to conference abstracts	26028
11	9 not 10	13670
12	(Australia or Australian).tw.	375439
13	11 and 12	51
14	Remove duplicates from 13	50

BMI; body mass index, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, MAFLD; metabolic-associated fatty liver disease, MASH; metabolic associated steatohepatitis. Database(s): Embase Classic+Embase 1947 to May 2022, Ovid MEDLINE® ALL 1946 to May 2022

Appendix Table 3 Database search for Part A, metabolic syndrome

#	Search for systematic reviews with meta-analyses and pooled analyses	# Results
1	(liver disease* or liver fibrosis or fibrotic liver or steatosis or steatohepatitis or nonalcoholic fatty liver or non-alcoholic fatty liver or NAFLD or NASH or metabolic associated fatty liver or MAFLD or MASH or cirrhosis or cirrhotic liver or hepatocellular or HCC or liver cancer).tw.	810610
2	(metabolic syndrome or metabolic traits or metabolic components or metabolic status).tw.	160780
3	1 and 2	17987
4	Limit 3 to English language	17229
5	Limit 4 to humans	12633
6	Limit 5 to yr=”2012-current”	10193
7	Limit 6 to conference abstracts	6353
8	6 not 7	3840
9	(Systematic review or meta-analysis or meta analysis or pooled analysis or random* control* trial or RCT).tw.	1066993
10	8 and 9	119
11	Remove duplicates from 10	117

BMI; body mass index, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic-associated fatty liver disease Database(s): Embase Classic+Embase 1947 to May 2022, Ovid MEDLINE® ALL 1946 to May 2022

Appendix Table 4 Database search for Part B, metabolic syndrome

#	Search for studies in the Australian context	# Results
1	(liver disease* or liver fibrosis or fibrotic liver or steatosis or steatohepatitis or nonalcoholic fatty liver or non-alcoholic fatty liver or NAFLD or NASH or metabolic associated fatty liver or MAFLD or MASH or cirrhosis or cirrhotic liver or hepatocellular or HCC or liver cancer).tw.	810610
2	(metabolic syndrome or metabolic traits or metabolic components or metabolic status).tw.	160780
3	1 and 2	17987
4	Limit 3 to English language	17229
5	Limit 4 to humans	12633
6	Limit 5 to yr="2012-current"	10193
7	Limit 6 to conference abstracts	6353
8	6 not 7	3840
9	(Australia or Australian).tw.	375439
10	8 and 9	7
11	Remove duplicates from 10	7

BMI; body mass index, HCC; hepatocellular carcinoma, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic-associated fatty liver disease Database(s): Embase Classic+Embase 1947 to May 2022, Ovid MEDLINE® ALL 1946 to May 2022

Appendix Table 5 Cochrane, PROSPERO and clinical trial registry search

Database	Search terms	# Results
Cochrane Database of Systematic Reviews	(NAFLD or "liver disease" or liver fibrosis" or cirrhosis or liver cancer or HCC) AND (obese or obesity or overweight or BMI or body mass index or metabolic syndrome)	10
PROSPERO database for registered prospective systematic reviews	NAFLD or liver disease or liver cancer	306
Australian New Zealand Clinical Trials Registry	Condition: liver disease	0

BMI; body mass index, HCC; hepatocellular carcinoma, NA; not applicable, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic-associated fatty liver disease, PROSPERO; The International Prospective Register of Systematic Reviews

Appendix Table 6 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	Studies involving participants with or without existing NAFLD. Stage of liver disease (normal, NAFL, NASH, fibrosis, cirrhosis, or primary liver cancer) had to be reported.	Studies involving 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 only involving participants who had liver disease of other etiologies such as HBV, HCV, ARLD were excluded.
Intervention	**For question 1 BMI classified as obese or overweight. For adults, the WHO defines:** ≥ 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 **For question 2 metabolic syndrome defined as:** a cluster of 3 or more metabolic risk factors. according to the BMC Joint Interim Statement (which incorporates International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHALBI) criteria,	**For question 1 BMI not reported.** Studies which reported alternative measures of obesity e.g., waist circumference or waist-to-hip ratio were excluded **For question 2 metabolic syndrome not reported;** only reported on components of the metabolic syndrome, not as a whole.
Comparator	**For question 1** BMI not obese or overweight, and/or BMI normal **For question 2** no metabolic syndrome	Comparator is unclear
Outcome	Incidence, morbidity, or mortality due to liver disease (any stage) or primary liver cancer (e.g., HCC).	Rare liver cancers (e.g., ICC), liver transplantation, post-surgical outcomes.

Outcome measures	Hazard ratios; risk ratios; odds ratios and their 95% confidence or information allowing us to compute them.	Studies that did not report any odds, risk, or hazard ratios for the outcome of interest.
Language	English	Not in English
Publication period	Systematic reviews, meta-analyses and pooled analyses undertaken in the past 10 years (May 2012 to May 2022).	Prior to 2012*

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

Appendix Table 7 Studies excluded at full text from Part A, with reason for exclusion

Author (date)	Title	Reason excluded
Lim et al. (2022)	An Observational Data Meta-analysis on the Differences in Prevalence and Risk Factors Between MAFLD vs NAFLD.	Not relevant outcome (mean difference in BMI)
Alam et al. (2021)	Risk factors of nonalcoholic fatty liver disease in lean body mass population: A systematic review and meta-analysis.	Not relevant outcome (mean difference in BMI)
Cholangitas et al. (2021)	Epidemiology of nonalcoholic fatty liver disease in europe: A systematic review and meta-analysis.	Not relevant outcome (prevalence study)
Shi et al. (2020)	The Prevalence of Lean/Nonobese Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis.	Not relevant outcome (prevalence study)
Ye et al. (2020)	Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis.	Not relevant outcome (prevalence study)
Souza et al. (2012)	Metabolic syndrome and risk factors for non-alcoholic fatty liver disease.	Not relevant study type (narrative reviews)
Li et al. (2019)	Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis.	Not relevant outcome
Ukawa et al. (2018)	Pooled Analysis of the Associations between Body Mass Index, Total Cholesterol, and Liver Cancer-related Mortality in Japan.	Not relevant exposure (grouped BMI with total cholesterol in analysis)
Rinella et al. (2015)	Nonalcoholic fatty liver disease a systematic review.	Not relevant study type (narrative review)
Li et al. (2018)	Nonalcoholic Fatty Liver Disease Cirrhosis: A Review of Its Epidemiology, Risk Factors, Clinical Presentation, Diagnosis, Management, and Prognosis.	Not relevant study type
Dyal et al. (2015)	Concurrent Obesity, Diabetes, and Steatosis Increase Risk of Advanced Fibrosis Among HCV Patients: A Systematic Review.	Not relevant population
Stocks et al. (2017)	Metabolic risk score and cancer risk: Pooled analysis of seven cohorts.	Not relevant exposure
Sookoian et al. (2017)	Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients.	Not relevant outcome
Wang et al. (2012)	Body mass index and risk of primary liver cancer: A meta-analysis of prospective studies.	Pre WCRF report
Tanaka et al. (2012)	Obesity and liver cancer risk: An evaluation based on a systematic review of epidemiologic evidence among the Japanese population.	Pre WCRF report
Rui et al. (2012)	Excess Body Mass Index and Risk of Liver Cancer: A Nonlinear Dose-Response Meta-Analysis of Prospective Studies.	Pre WCRF report
Chen et al. (2012)	Excess body weight and the risk of primary liver cancer: An updated meta-analysis of prospective studies.	Pre WCRF report
Glyn-Owen et al. (2021)	The combined effect of alcohol and body mass index on risk of chronic liver disease: A systematic review and meta-analysis of cohort studies.	Not relevant outcome (not specific to NAFLD)

BMI; body mass index, NAFLD; non-alcoholic fatty liver disease, WCRF; World Cancer Research Fund

Appendix Table 8 Studies excluded at full text from Part B, with reason for exclusion

Author (year)	Title	Reason excluded
Kemp et al. (2022)	Impact of renaming NAFLD to MAFLD in an Australian regional cohort: Results from a prospective population-based study.	Not relevant outcome (difference in mean BMI between NAFLD and MAFLD patients)
Farrell et al. (2022)	A problem of proportions: estimates of metabolic associated fatty liver disease and liver fibrosis in Australian adults in the nationwide 2012 AusDiab Study.	Not relevant outcome (ALT levels)
George et al. (2018)	Non-alcoholic fatty liver disease patients attending two metropolitan hospitals in Melbourne, Australia: high risk status and low prevalence.	Not relevant outcome (liver stiff ness measure
Adams et al. (2008)	Body mass index is a stronger predictor of alanine aminotransaminase levels than alcohol consumption	Not relevant outcome (ALT levels)
Mahady et al. (2017)	Prevalence of elevated alanine transaminase in Australia and its relationship to metabolic risk factors: A cross-sectional study of 9,447 people	Not relevant outcome (ALT levels)

ALT; alanine aminotransferase, BMI; body mass index, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic associated fatty liver disease

Appendix Table 9 Studies excluded at full text from Part A, with reason for exclusion

Author (date)	Title	Reason excluded
Lu et al.(2020)	Global epidemiology of lean non-alcoholic fatty liver disease: A systematic review and meta-analysis.	Not relevant outcome – prevalence study
Sookoian et al. (2017)	Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients.	Not relevant outcome – referred to components only of the metabolic syndrome
Li et al. (2018)	Nonalcoholic Fatty Liver Disease Cirrhosis: A Review of Its Epidemiology, Risk Factors, Clinical Presentation, Diagnosis, Management, and Prognosis.	Not relevant study type – review article
Souza et al. (2012)	Metabolic syndrome and risk factors for non-alcoholic fatty liver disease.	Not relevant study type – review article

NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic associated fatty liver disease

Appendix Table 10 Studies excluded at full text from Part B, with reason for exclusion

Author (date)	Title	Reason excluded
Farrell et al. (2022)	A problem of proportions: estimates of metabolic associated fatty liver disease and liver fibrosis in Australian adults in the nationwide 2012 AusDiab Study.	Not relevant outcome (ALT levels)

ALT; alanine aminotransferase, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic associated fatty liver disease

Appendix Table 11 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 12 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 13 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	Score:
Sohn et al. (2021)	y	y	y	y	y	y	n	y	y	n	y	y	y	y	y	y	
Jarvis et al. (2020)	y	y	y	y	y	y	n	y	y	n	y	y	y	y	y	y	
Yang et al. (2019)	y	n	n	y	y	y	n	y	y	n	y	y	y	y	y	y	
Ren et al. (2019)	y	n	n	y	n	n	n	y	y	n	y	y	y	y	y	n	
Gupta et al. (2019)	y	n	y	y	y	y	n	y	y	n	y	y	y	y	y	n	
Lu et al. (2018)	y	n	y	y	y	y	n	y	n	n	y	n	y	y	y	y	
Yao et al. (2017)	y	y	y	y	y	y	n	y	y	n	y	y	y	y	y	n	
Dyal et al. (2015)	y	n	y	y	n	y	n	y	y	n	NA	NA	n	y	NA	n	
Li et al. (2016)	y	y	y	y	y	y	n	y	y	n	y	y	y	y	y	n	

**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 14 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, randomised 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, NAFL, NASH, 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 NAFLD/MAFLD 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., ARLD, 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. **For this review,** studies reporting on relative risk i.e., risk ratios, hazard ratios, odds ratios were excluded.
Language	English	Not in English
Publication period	Systematic reviews and meta-analyses undertaken in the past 10 years (March 2012-March 2022).	Prior to March 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 15 Database search for Part A

#	Searches	# Results
1	(liver disease* or steatosis or steatohepatitis or nonalcoholic fatty liver disease or non-alcoholic fatty liver disease or NAFLD or NAFL or NASH or metabolic associated fatty liver disease or MAFLD or MAFL or MASH or fibrosis or fibrotic liver or cirrhosis or cirrhotic liver or hepatocellullar or HCC or liver cancer).ti.	441203
2	(incidence or mortality or morbidity or burden or epidemiology or natural history or progression or association or risk*).ti.	2908931
3	1 and 2	34690
4	limit 3 to english language	327333
5	Limit 4 to human	27716
6	Limit 5 to yr="2012-Current"	20694
7	Limit 6 to conference abstracts	12714
8	6 not 7	7980

#	Searches	# Results
9	(systematic review or meta-analysis or meta-analytic or pooled analysis or randomised control* trial or RCT or model or modelling or modeling).ti	1801334
10	8 and 9	623
11	Remove duplicates from 10	611

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

Appendix Table 16 Database search for Part B

#	Searches	# Results
1	(liver disease* or steatosis or steatohepatitis or nonalcoholic fatty liver disease or non-alcoholic fatty liver disease or NAFLD or NAFL or NASH or metabolic associated fatty liver disease or MAFLD or MAFL or MASH or fibrosis or fibrotic liver or cirrhosis or cirrhotic liver or hepatocellullar or HCC or liver cancer).ti.	441882
2	(incidence or mortality or morbidity or burden or epidemiology or natural history or progression or association or risk*).ti.	2914926
3	1 and 2	34778
4	limit 3 to english language	32819
5	Limit 4 to human	27806
6	Limit 5 to conference abstracts	16439
7	5 not 6	11367
8	(Australia or Australian).tw.	371085
9	7 and 8	71
10	Remove duplicates from 9	71
11		

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

Appendix Table 17 Cochrane, PROSPERO and Clinical trial registry search

Database	Search terms	# Results
Cochrane Database of Systematic Reviews	("liver disease*" or steatosis or steatohepatitis or "nonalcoholic fatty liver disease" or "non-alcoholic fatty liver disease" or NAFLD or NAFL or NASH or "metabolic associated fatty liver disease" or MAFLD or MAFL or MASH 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.	98
PROSPERO database for registered prospective systematic reviews	liver disease or steatosis or steatohepatitis or nonalcoholic fatty liver disease or non-alcoholic fatty liver disease or NAFLD or NAFL or NASH or metabolic associated fatty liver disease or MAFLD or MAFL or MASH or fibrosis or cirrhosis or hepatocellular or HCC or liver cancer: titles only and (review ongoing or completed not published or completed published being updated), in cancer or digestive system or endocrine and metabolic disorders from 28/03/2012 to 28/03/2022	470
Australian New Zealand Clinical Trials Registry	liver disease* or steatosis or steatohepatitis or nonalcoholic fatty liver disease or non-alcoholic fatty liver disease or NAFLD or NAFL or NASH or metabolic associated fatty liver disease or MAFLD or MAFL or MASH 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

HCC; hepatocellular carcinoma, MAFLD; metabolic associated fatty liver disease, MASH; metabolic associated steatohepatitis, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis, PROSPERO; The International Prospective Register for Systematic Reviews

Appendix Table 18 Studies excluded at full text from 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 - Not relevant exposure - exposure was alcohol/no alcohol
Andersson et al. (2022)	Clinical Utility of Magnetic Resonance Imaging Biomarkers for Identifying Nonalcoholic Steatohepatitis Patients at High Risk of Progression: A Multicenter Pooled Data and Meta-Analysis.	Exclude - Not relevant exposure - assessment of diagnostic tools
Balakrishna et al. (2021)	Women Have a Lower Risk of Nonalcoholic Fatty Liver Disease but Higher Risk of Nonalcoholic Fatty Liver Disease Fibrosis Than Men: Summary of the Findings of a Systematic Review and Meta-analysis.	Exclude - Not relevant exposure – the exposure was men versus women not whether patients had NAFLD or not
Younossi et al. (2019)	Burden of Illness and Economic Model for Patients With Nonalcoholic Steatohepatitis in the United States.	Exclude - Already included in review by Gruneau et al. (2022)
Tampi et al. (2020)	Modelling the economic and clinical burden of non-alcoholic steatohepatitis in East Asia: Data from Hong Kong.	Exclude - Already included in review by Gruneau et al. (2022)
Balakrishna et al. (2021)	Women Have a Lower Risk of Nonalcoholic Fatty Liver Disease but a Higher Risk of Progression vs Men: A Systematic Review and Meta-analysis.	Exclude - Duplicate of above
Khalid et al. (2020)	Increased cardiovascular events and mortality in females with nafld: A meta-analysis.	Exclude - not relevant outcome - no liver related outcomes were reported

Author (date)	Title	Reason excluded
Estes et al. (2020)	Modelling NAFLD disease burden in four Asian regions-2019-2030.	Exclude - Already included in review by Gruneau et al. (2022)
Estes et al. (2018)	Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030.	Exclude - Already included in review by Gruneau et al. (2022)
Xiong et al. (2017)	Hepatitis B virus infection and the risk of nonalcoholic fatty liver disease: A meta-analysis.	Exclude - not relevant population - patients with HCV
Estes et al. (2018)	Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease.	Exclude - Already included in review by Gruneau et al. (2022)
Dyal et al. (2015)	Concurrent Obesity, Diabetes, and Steatosis Increase Risk of Advanced Fibrosis Among HCV Patients: A Systematic Review.	Exclude - not relevant population – patients with HCV
Wu et al. (2020)	The epidemiology of NAFLD in Mainland China with analysis by adjusted gross regional domestic product: a meta-analysis.	Exclude - not relevant outcome - no liver related outcomes were reported
Taylor et al. (2020)	Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis.	Exclude – not relevant outcome – reported on the association between liver disease and risk of progression
Liu et al. (2019)	Nonalcoholic fatty liver disease and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis.	Exclude – not relevant outcome – reported on the association between liver disease and risk of progression
Liu et al. (2021)	Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: A modelling study.	Exclude – not specifically related to NAFLD
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 – not relevant outcome – reported on the association between liver disease and risk of progression

HCV; hepatitis C virus, NAFLD; non-alcoholic fatty liver disease

Appendix Table 19 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 20 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 21 AMSTAR-2 checklist 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:
Gruneau et al. (2021)	yes	yes	yes	yes	yes	yes	no	yes	yes	no	NA	NA	NA	NA	NA	yes	Moderate
Orci et al. (2021)	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	High
Ito et al. (2021)	yes	yes	no	yes	yes	yes	no	yes	yes	no	yes	yes	yes	yes	yes	yes	Moderate
Roskilly et al. (2020)	yes	no	yes	yes	yes	yes	no	yes	yes	no	yes	yes	yes	yes	yes	yes	Moderate
Ye et al. (2020)	yes	no	yes	yes	yes	yes	no	yes	yes	no	yes	yes	yes	yes	yes	yes	Moderate
Li et al. (2019)	yes	no	yes	yes	yes	yes	no	yes	yes	no	yes	yes	yes	yes	yes	yes	Moderate
Dulai et al. (2017)	yes	yes	yes	yes	yes	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes	Moderate
Younossi et al. (2016)	yes	no	yes	yes	yes	yes	no	yes	yes	no	yes	yes	yes	yes	yes	yes	Moderate
Singh et al. (2015)	yes	yes	yes	yes	yes	no	no	yes	yes	no	yes	yes	yes	yes	yes	yes	Moderate
White et al. (2012)	yes	no	no	yes	no	no	no	yes	yes	no	NA	NA	yes	yes	NA	yes	Moderate

**Critical domains that seriously impact on the validity of findings. AMSTAR-2; A MeaSurement Tool to Assess systematic Reviews, Y; yes, N; no, NA; not applicable, P; partial yes*