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The Australian Prevention Partnership Centre

Preventing liver cancer: Scoping review on disease prevalence and transitions for MAFLD/MASH patients

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Contents

Definitions and Terminology

Body mass index (BMI) is the ratio of a person's weight in kilograms (or pounds) to the square of their height in meters, used as a proxy measure for a person's body size. For most adults, the World Health Organization (WHO) defines a BMI (in kg/m 2) of: ≥ 18.5 to <25 as normal weight; ≥ 25 to <30 as overweight, and ≥ 30 as obese.

Compensated cirrhosis refers to asymptomatic build-up of scar tissue in the liver.

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

Fibrosis refers to the formation of scar tissue in the liver. It can be further classified into stages: F0, there is no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis; F3, numerous septa without cirrhosis; F4, cirrhosis.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer diagnosed in Australia.(1)

Metabolic-associated fatty liver disease (MAFLD) is the presence of hepatic steatosis in combination with one or more of the following: overweight/obesity, T2DM, or two or more markers of metabolic dysregulation.

Metabolic-associated steatohepatitis (MASH) refers to the presence of hepatic steatosis with evidence of inflammation and hepatocellular injury the form of ballooning of the hepatocytes, with or without fibrosis, in patients with MAFLD.

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

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

Scoping Review

1. Purpose of report

This report describes the evidence review completed on disease prevalence and transitions for MAFLD/MASH patients, to support the *Preventing Liver Cancer: Assessing the benefits of risk assessment for patients with metabolic-associated fatty liver disease* report.(2) It is designed to be a supplement to be read in parallel to that report where further detail is required.

This report contains material previously included in the *Preventing Liver Cancer: Obesity and Alcohol Consumption* report.(3)

2. Background

Liver cancer is one of the most rapidly growing cancer types in Australia in terms of both incidence and mortality.(4) Hepatocellular carcinoma (HCC), the most common type of liver cancer,(1) often develops in people with underlying liver disease caused by modifiable risk factors.(5)

Categorised as a build-up of excess fat in the liver, metabolic-associated fatty liver disease (MAFLD), linked to excess body fatness, type 2 diabetes mellitus and/or metabolic abnormalities, is a major risk factor for the development of HCC.(6) Previously, patients with MAFLD were typically diagnosed with non-alcohol fatty liver disease (NAFLD) instead. From 2020, the MAFLD classification was introduced; proponents of the new classification argue that MAFLD better reflects the metabolic nature of the disease.(7)

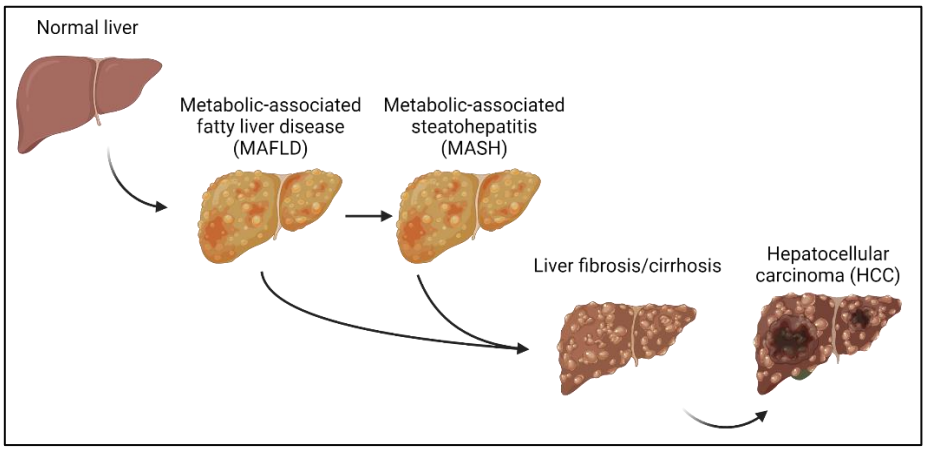
Whilst a benign condition on its own, the progression of MAFLD to metabolic-associated steatohepatitis (MASH)[1], categorised by inflammation of the liver, can lead to liver scarring (known as fibrosis, or at a later stage, cirrhosis), and a subsequently increased risk of HCC.(6) Patients with MASH are a subgroup of those with MAFLD (though some sources refer to them as mutually exclusive groupings), and, as with MAFLD and NAFLD, the term 'MASH' has been developed to replace the previous classification of non-alcoholic steatohepatitis (NASH). See Figure 1 for a diagram of the biological pathway of HCC through MAFLD and later MASH.

While MAFLD-related HCC has lower incidence than HCC related to viral Hepatitis B or alcohol-related liver disease (ARLD), recent Australian studies have shown that the incidence rate of NAFLD-related HCC has increased,(8,9) against decreases in the overall incidence rate of HCC.

Given this, the purpose of this review was to identify evidence available on disease transitions from MAFLD and MASH to HCC, with a focus on recent and/or Australian studies.

[1] We will refer to non-MASH MAFLD patients simply as MAFLD patients for convenience; terminology regarding the overlap between MAFLD and MASH patients differs across sources.

Figure 1 – Progression of liver disease to MAFLD, MASH, cirrhosis, and HCC (created with biorender.com)



2.1. Review questions and aims

1. What is known about the disease prevalence and transitions for patients with MAFLD, and/or MASH?
2. What are the prevalence and risk differences between patients diagnosed with MAFLD/MASH and patients diagnosed with NAFLD/NASH?

3. Methods

3.1. Search strategy

The search for this scoping review expanded upon a previous search on excess body fatness, the metabolic syndrome, and non-alcoholic fatty liver disease, as part of the *Preventing Liver Cancer* project.(3)

The evidence review was designed to:

1. Determine the Australian prevalence of excess body fatness, metabolic syndrome and NAFLD and/or MAFLD using data from the Australian Bureau of Statistics, and
2. Report the association between excess body fatness, metabolic syndrome, and risk of NAFLD, MAFLD and liver cancer, and
3. Quantify the progression from NAFLD and/or MAFLD to liver fibrosis, cirrhosis, liver cancer, and death.

Specifically, electronic literature searches were undertaken using the Ovid platform to search Embase and MEDLINE between January and May 2022. International evidence was assessed from systematic reviews, meta-analyses, pooled analyses and/or modelling studies published in the last ten years (2012 to 2022), as well as Australian studies of any type published to 2022.

Based on this, key outputs (e.g., fibrosis rates, fibrosis progression rates, or HCC/all-cause mortality risks by patient group) were identified, with additional data relating to disease prevalence and/or disease transitions extracted from the original sources where necessary. Other relevant studies identified by study team members were also included.

3.2. Eligibility criteria

The eligibility criteria and scope of the review were defined using the “Participant Concept Context” framework as described below.(10)

Participants

Studies could involve participants from the general population and/or participants with existing MAFLD/NAFLD or MASH/NASH. As literature on MASH and NASH were scarce, no exclusions were made for particular population groups.

Concept

To be included, studies needed to report prevalence, progression, incidence, or transitions. These could be measured as numbers of cases, proportions, probabilities, or rates. Both sources using the MAFLD/MASH and sources using the NAFLD/NASH classifications systems were included, as the literature was scarce. Relevant measures of disease transition risk and/or prevalence such as odds ratios, measures of interrater reliability etc. were extracted. Confidence intervals, measures of heterogeneity, and p-values were included when available. Data were collected and are included here as reported in the original study.

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. Data was extracted from relevant studies to a sufficient level of evidence to answer the research questions, with a focus on recency and relevance to the Australian MASH/MAFLD population.

3.3. Types of sources

Conference abstracts, letters, editorials, and narrative reviews were excluded. All other source types were considered (including preprints), with systematic reviews, meta-analyses, and pooled analyses identified as the preferred source type.

3.4. Study selection

In the initial search, all identified citations were collated and duplicates removed. Titles and abstracts were screened for assessment against the inclusion criteria, and potentially relevant articles were retrieved in full and assessed in detail. Reasons for exclusion at full text were recorded. 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.

One reviewer (AK) screened study titles which were included in the main project, retrieving the full text for potentially relevant sources, and extracting relevant data (including review of the reference lists of these studies for additional sources).

3.5. Data extraction

The following information was extracted from relevant studies:

- Study information (title, author, year published, study type, # of studies, study types included, and literature search date for systematic reviews, location)
- Participant information (total # participants, participant type, participant age)
- Information on outcome (outcome type, outcome measure)
- Data (estimates, confidence intervals, heterogeneity, p-values etc.)
- Quality assessment information
- Funding information
- Key conclusions
- Other comments

A formal critical appraisal and risk of bias assessment were not performed as this was outside the scope of this report.

4. Key findings

4.1. Search outcomes

The search yielded 17 relevant studies from which data was extracted. This included six systematic reviews with meta-analyses,(11–15) four modelling studies,(6,16–18) four cohort studies,(19–22), two cross-sectional studies,(23,24) and one systematic review.(25)

The characteristics of included studies are presented in Table 1.

Table 1. Characteristics of included studies

Author (year)	Type of study	Literature search to[2]	Participant type	Measure	Outcome(s)
Roskilly et al. (2020) (11)	Meta-analysis	Jan 2020	NASH patients in RCT studies	Progression	Fibrosis
Quek et al. (2023) (12)	Meta-analysis	Mar 2022	Overweight/obese population (including NAFLD and NASH sub-populations) in observational studies	Prevalence	NAFLD, NASH, Fibrosis
Singh et al. (2015) (13)	Meta-analysis	Jun 2013	NASH and NAFLD patients in cohort studies	Progression, Prevalence, Distribution	NASH, Fibrosis
Younossi et al. (2016) (14)	Meta-analysis	2015	NASH and NAFLD patients in cohort and cross-sectional studies	Progression, Incidence, Prevalence	NASH, Fibrosis
Younossi et al. (2019) (16)	Modelling	2018	55-year-old NASH patients with ≤ Fibrosis Stage 2 in the USA	Transition probabilities	Fibrosis
Glass et al. (2015) (19)	Cohort study	NR	NASH patients in the USA	Proportion	Fibrosis
Vilar-Gomez et al. (2015) (20)	Cohort study	NR	NASH patients in Cuba	Proportion	Fibrosis
Sanyal et al. (2019) (21)	Cohort study	NR	NASH patients with bridging fibrosis (F3) in the USA	Progression	Cirrhosis
Kemp et al. (2022) (23)	Cross-sectional study	NR	Regional Victorian, Australian population	Prevalence	NAFLD, MAFLD
Lim et al. (2021) (15)	Meta-analysis	2021	Global population	Prevalence, Odds Ratio	NAFLD, MAFLD
Younossi et al. (2022) (22)	Cohort study	NR	Fatty Liver Disease, NAFLD and MAFLD patients in the USA	Proportion, Prevalence, Interrater Reliability	NAFLD, MAFLD
Adams et al. (2020) (6)	Modelling	2019	Australian population (including NAFLD patients as sub-population)	Prevalence, Transition probabilities	NAFLD, NASH, Cirrhosis

[2] For studies which included a literature search

Swain et al. (2020) (17)	Modelling	2019	Canadian population (including NAFLD patients as sub-population)	Prevalence, Transition Probability	NAFLD, NASH, Fibrosis, Cirrhosis
Younossi et al. (2023) (26)	Meta-analysis	2022	Global NAFLD population (including North America & Australasian sub-population) in observational studies	Prevalence	NAFLD, NASH
Farrell et al. (2022) (24)	Cross-sectional study	NR	Australian population, aged between 34 and 97 years-old	Prevalence	MAFLD
Estes et al. (2018) (18)	Modelling	2016	NAFLD patients in the USA	Proportion	NASH
Gruneau et al. (2023) (25)	Systematic Review	Jun 2021	NAFLD patients in modelling studies	Transition Probabilities	Fibrosis, Cirrhosis

NR; not relevant/not retrieved.

4.2. Prevalence of fibrosis in patients diagnosed with MASH/NASH

Study characteristics

One systematic review with meta-analysis reported on the prevalence of fibrosis in NASH,(12) which focused on the overweight/obese NASH population.

Relevant outcomes

Within the overweight/obese NASH population, the prevalence of F1, F2, F3 and F4 was estimated at 26.55%, 20.95%, 11.66% and 1.71%, respectively.(12)

Table 2 Prevalence of fibrosis in NASH

Author (year)	# Participants	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	I^2	P-value
Quek et al. (2023) (12)	497	Overweight/obese NASH	F1	Prevalence (%)	26.55	15.5	41.6	84	<0.0001
	497		F2		20.95	10.14	38.38	75	NR
	497		F3		11.66	6.35	20.43	48	
	594		F4		1.71	0.43	6.59	0	
	753		F1-4		72.57	49.4	87.76	89	<0.0001
	897		F2-4		35.14	21.9	51.15	91	NR
	601		F3-4		19.35	7.61	41.11	77	

NR; not relevant/not retrieved, F1-4; Fibrosis Stages 1-4.

4.3. Risk of developing fibrosis in MASH/NASH patients

Study characteristics

Three systematic reviews with meta-analyses,(11,13,14) two cohort studies,(19,20) and one modelling study (16) reported on the risk of developing fibrosis in NASH patients, as shown in Table 3.

Relevant outcomes

In NASH patients, the annual rate of fibrosis progression was estimated at 0.14, 0.09, and 0.03 stages, by Singh et al., Younossi et al. (2016), and Roskilly, respectively.(11,13,14) Younossi et al. (2019) modelled annual fibrosis transition probabilities within a model 55-year

old NASH patient, such as the probability of transitioning from no fibrosis (F0) to stage 1 fibrosis (F1) or stage 2 fibrosis (F2), which was estimated at 6.1% and 1.7%, respectively.(16) Both Glass et al. and Vilar-Gomez et al. investigated the association between weight loss and changes in fibrosis stage, finding that fibrosis regression occurred in NASH patients with over 10% total body weight loss.(19,20)

Table 3 Risk of developing fibrosis in NASH patients

Author (year)	# Participants	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	I2	P-value	P (heterogeneity)	Time period
Singh et al. (2015) (13)	116	NASH	F	Progression Rate (stages)	0.14	0.07	0.21	21.1	0.283	NR	Per year
			FP	Proportion (%)	34.5		NR				NR
Younossi et al. (2016) (14)	8,515,431	NASH	F	Progression Rate (stages)	0.09	0.06	0.12	0	NR		Per year
			FP	Proportion (%)	41	34.69	47.13	NR			NR
			AF	Incidence Rate (%)	67.95	46.84	98.56	9.80			Per 1,000 PYs
Roskilly et al. (2020) (11)	952	NASH	F	Progression Rate (stages progressed per year)	0.03	-0.02	0.07	59	NR	<0.01	Per year
	825					-0.01	0.08	72			
	639	NASH F≥1			-0.01	-0.09	0.06	90			
Younossi et al. (2019) (16)	NR	NASH F0	NASH F0	Transition Probabilities (%)	90			NR			Per year
			NASH F1		6.1						
			NASH F2		1.7						
			NASH F3		0.9						
		NASH F1	NASH F2		2.3						
		NASH F2	NASH F3		3.8						
Glass et al. (2015) (19)	16	NASH ≥ 10% TBW loss	FR (≥1 F stage decrease)	Proportion (%)	75		NR		<0.001	NR	4.6 years
			FS		18.75						
			FP (≥1 F stage increase)		6.25						
	17	NASH 0-10% TBW loss	FR		35.29						
			FS		29.41						
			FP		35.29						
Vilar-Gomez et al. (2015) (20)	73	NASH <5% TBW loss	FR (≥1 F stage decrease)	Proportion (%)	45		NR		0.4	NR	Per year
			FS		45						
			FP (≥1 F stage increase)		10						
	16	NASH 5-7% TBW loss	FR		38						
			FS		44						
			FP		18						
	8	NASH 7-10% TBW loss	FR		50						
			FS		50						
			FP		0						
	16	NASH ≥10% TBW loss	FR		81						
			FS		19						
			FP		0						

NR; not relevant/not retrieved, F; Fibrosis, AF; Advanced Fibrosis, FR; Fibrosis Regression, FS; Fibrosis Stabilised, FP; Fibrosis Progression, TBW; Total Body Weight, PY; Person-Years, F0; No Fibrosis.

4.4. Risk of developing cirrhosis in MASH/NASH

Study characteristics

One systematic review with meta-analysis,(11) one modelling study,(16) and one cohort study (21) reported on the risk of developing cirrhosis in MASH/NASH patients, as shown in Table 4.

Relevant outcomes

The proportion of NASH patients likely to develop cirrhosis over their lifetime was estimated at 13% and 28% based on a fibrosis progression rate of 0.03 and 0.14, respectively.(11) Younossi et al. (2019) reported the annual transition probability of developing compensated cirrhosis as a 55-year-old NASH patient with F0, F1, F2 or F3 at 0.9%, 0.3%, 1.8%, 11%, respectively.(16) Sanyal et al. estimated that a NASH patient with F3 would have a 22% chance of developing cirrhosis over a median follow-up period of 29-months.(21)

Table 4 Risk of developing cirrhosis in NASH

Author (year)	# Participants	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	Time period
Roskilly et al. (2020) (11)	116	NASH with 0.14 FPR	Cirrhosis	Proportion (%)	28	NR		NR
	825	NASH with 0.03 FPR			13			
	NR	NASH			24			Lifetime
Younossi et al. (2019) (16)	NR	NASH F0	CC	Transition Probabilities (%)	0.9	NR		Per year
		NASH F1			0.3			
		NASH F2			1.8			
		NASH F3			11			
		NASH CC	DC		6.6			
Sanyal et al. (2019) (21)	475	NASH F3	Cirrhosis	Transition Probabilities	22	8	14	29 months

NR; not relevant/not retrieved, F; Fibrosis, F0-4; Fibrosis Stages 0-4, CC; Compensated Cirrhosis, DC; Decompensated Cirrhosis, FPR; Fibrosis Progression Rate.

4.5. Overlap between patients who would be diagnosed with MAFLD and patients who would be diagnosed with NAFLD

Study characteristics

Two systematic reviews with meta-analysis,(15,22) and one cross-sectional study (23) reported on the overlap between patients who would be diagnosed with MAFLD vs. NAFLD.

Relevant outcomes

Kemp et al. reported that whilst all NAFLD patients fall under the criterion for MAFLD, 17.5% of patients with MAFLD do not meet the criterion to be diagnosed with NAFLD.(23) Correspondingly, Lim et al. found that the prevalence of NAFLD in MAFLD patients was estimated around 81.59%.(15) Younossi et al. (2022) reported an interrater reliability ranging from 0.83-0.94 between NAFLD and MAFLD in fatty liver disease patients in two different datasets. See Table 5 for full results.(22)

Table 5 MAFLD vs. NAFLD overlap

Author (year)	# Participants	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	P-value
Kemp et al. (2022) (23)	722	NR	NAFLD	Prevalence (%)	38.70	NR		
			MAFLD		47.20			
			MAFLD but not NAFLD		17.5			
			NAFLD but not MAFLD		0			
Lim et al. (2021) (15)	379,801	MAFLD	NAFLD	Prevalence (%)	81.59	66.51	90.82	NR
		NR	MAFLD vs. NAFLD	Odds Ratio	1.37	1.16	1.63	<0.001
Younossi et al. (2022) (22)	2617	FLD	MAFLD but not NAFLD	Relative Proportion (%)	16	NR		
			NAFLD but not MAFLD		7.9			
			Both NAFLD and MAFLD		73.2			
			NAFLD vs. MAFLD (Dataset 1)	Cohen's kappa coefficient	0.83	0.82	0.85	NR
	1594	FLD	NAFLD vs. MAFLD (Dataset 2)		0.94	0.93	0.95	
	2332	MAFLD	NAFLD	Weighted percentages (%)	82.11	78.91	85.3	
	2122	NAFLD	MAFLD		90.26	88.09	92.43	

NR; not relevant/not retrieved, FLD; Fatty Liver Disease

4.6. Prevalence of MAFLD/NAFLD (in Australia or similar contexts)

Study characteristics

Data was extracted from two systematic reviews with meta-analysis,(12,26) two modelling studies (6,17) and one cross-sectional analysis.(24) Four studies reported on NAFLD prevalence,(6,12,17,26) whilst one reported on MAFLD.(24) Three provided prevalence estimates within the Australian population,(6,12,24) and data was also collected on prevalence within similar or wider contexts, such as the Canadian population,(17) the Western Pacific population,(12) and the combined North America and Australasian population.(26)

Relevant outcomes

The prevalence of NAFLD within the overweight Australian population was estimated at 70.27% by Quek et al.(12) NAFLD prevalence in the Australian population was modelled at 5,710,000 cases in 2020, a prevalence rate of 22.2%, increasing to 6,424,000 cases in 2025, a prevalence rate of 23.1%.(6) Of Australian adults aged 34-97 years, MAFLD prevalence was estimated at 37% in a 2022 study.(24)

Table 6 Prevalence of MAFLD/NAFLD

Author (year)	# Participants	Population	Outcome	Measure	Est.	LCI	UCI	I2	Time-period
Quek et al. (2023) (12)	NR	Overweight Australian population	NAFLD	Prevalence (%)	70.27	NR			NR
	49220	Overweight Western Pacific population			59.18	51.67	66.29	99	
	23163	Obese Western Pacific population			65.22	57.09	72.56		
Adams et al. (2020) (6)	NR	Australian population	NAFLD	Prevalence cases (n)	4,915,000	4,220,000	5,605,000	NR	2015
					5,710,000	4,879,000	6,483,000		2020
					6,424,000	5,387,000	7,253,000		2025

					7,026,000	5,842,000	7,890,000		2030
				Prevalence rate (%)	20.6	17.7	23.5		2015
					22.2	19.0	25.2		2020
					23.1	19.4	26.1		2025
					23.6	19.6	26.5		2030
Swain et al. (2020) (17)	NR	Canadian population	NAFLD	Crude prevalence rate (%)	21.1	19.4	22.4	NR	2020
					22.2	20.5	23.6		2025
					22.9	21.1	24.3		2030
				Adjusted prevalence rate (%)	21.0	19.4	22.3		2020
					22.0	20.2	23.4		2025
					22.3	20.5	23.7		2030
Younossi et al. (2023) (26)	56133	North America and Australasia population	NAFLD	Pooled prevalence (%)	31.2	25.86	37.08	99.49	1990-2019
	114,045,578				38.47	22.68	57.13	NR	2019
Farrell et al. (2022) (24)	4749	Australian population, aged 34-97	MAFLD	Prevalence (%)	37	NR			

NR; not relevant/not retrieved.

4.7. Prevalence of MASH/NASH (in Australia or similar contexts)

Study characteristics

One systematic review with meta-analysis,(26) and two modelling studies (6,17) reported on the prevalence of NASH. One of the modelling studies focused specifically on prevalence within the Australian population,(6) whilst the other two studies investigated prevalence within the Canadian,(17) and North American and Australasian population.(26)

Relevant outcomes

In 2020, there were 1,366,000 NASH cases in the Australian population.(6) This will increase to 1,612,000 in 2025; a change in prevalence rate from 5.3% to 5.8% over the 5 years.(6)

Table 7 Prevalence of NASH

Author (year)	Population	Measure	Est.	LCI	UCI	Time period
Adams et al. (2020) (6)	Australian population	Prevalence cases (n)	1,119,000	886,000	1,380,000	2015
			1,366,000	1,078,000	1,681,000	2020
			1,612,000	1,264,000	1,974,000	2025
			1,848,000	1,439,000	2,256,000	2030
		Prevalence rate (%)	4.7	3.7	5.8	2015
			5.3	4.2	6.5	2020
			5.8	4.5	7.1	2025
			6.2	4.8	7.6	2030
Swain et al. (2020) (17)	Canadian population	Crude prevalence rate (%)	5.4	4.3	6.4	2020
			6	4.8	7.1	2025
			6.5	5.2	7.7	2030
		Adjusted prevalence rate (%)	5.3	4.3	6.3	2020
			5.8	4.7	6.9	2025
			6.1	4.9	7.2	2030
Younossi et al. (2023) (26)	North America and Australasia population	Prevalence (%)	5.00	NR		1990-2019

NR; not relevant/not retrieved.

4.8. Prevalence of MASH/NASH in MAFLD/NAFLD patients

Study characteristics

Three systematic reviews with meta-analyses (12,14,26) and one modelling study (18) reported on the prevalence of NASH in NAFLD patients.

Relevant outcomes

The prevalence of NASH in the global population was estimated at 16.02% in a recent study.(26) Prevalence of the disease in the overweight and obese population was found to be much higher, at 45.5% and 44.05%, respectively.(12) Two studies predicted NASH prevalence in 2015 with great disparities; one estimating a prevalence of 20% in the USA population,(18) and the other estimating a prevalence of 59.1%.(14) The latter study acknowledged that this estimation was around double of that reported in previous studies, concluding that this may be due to a selection bias, with NAFLD patients typically selected for biopsy after showing signs of being at high risk of steatohepatitis.

Table 8 Prevalence of NASH in NAFLD patients

Author (year)	# Participants	NAFLD Population	Est. (%)	LCI	UCI	I2	Time-period
Younossi et al. (2016) (14)	8,515,431	Patients identified as being at high-risk of developing steatohepatitis	59.1	47.55	69.73		NR
Quek et al. (2023) (12)	11,683	Overweight patients	45.5	38.84	52.32	96	NR
	10,995	Obese patients	44.05	37.42	50.9	96.1	
Younossi et al. (2023) (26)	9,361,716	Global population	16.02	3.24	52.08		NR
Estes et al. (2018) (18)	NR	USA patients	20		NR		2015
			27				2030

NR; not relevant/not retrieved.

4.9. Prevalence of fibrosis in MAFLD/NAFLD patients

Study characteristics

Two systematic reviews with meta-analyses reported on the prevalence of fibrosis in NAFLD patients;(12,13) no data was found on prevalence in the MAFLD population.

Relevant outcomes

Over one third of NAFLD patients (35.8%) reportedly had no fibrosis.(13) The prevalence of F1, F2, F3 and F4 was estimated at 32.5%, 16.7%, 9.3% and 5.7% in the general NAFLD population,(13) 14.89%, 13.39%, 5.07%, and 2.46%, in the overweight NAFLD population, and 13.84%, 14.05%, 5.15%, and 2.06% in the obese NAFLD population.(12)

Table 9 Prevalence of fibrosis in NAFLD patients

Author (year)	# Participants	Initial disease stage	Outcome	Measure (%)	Est.	LCI	UCI	I2	P-value
Singh et al. (2015) (13)	366	NAFLD	F0	Proportion	35.8	NR			
			F1		32.5				
			F2		16.7				
			F3		9.3				
			F4		5.7				
Quek et al. (2023) (12)	1,939	Overweight NAFLD	F1	Prevalence	14.89	6.17	31.76	96	<0.0001
	1,939		F2		13.39	5.52	29.02	93	NR
	2,136		F3		5.07	3.1	8.19	58	
	2151		F4		2.46	1.62	3.73	0	
	2870		F1-4		46.56	26.56	67.74	97	<0.0001
	3227		F2-4		20.27	11.32	33.62	93	NR
	2197		F3-4		6.65	4.35	10.01	58	
	1604	Obese NAFLD	F1		13.84	5.83	29.44	97	<0.0001
	1604		F2		14.05	5.68	30.76	94	NR
	1801		F3		5.15	2.82	9.22	83	
	1816		F4		2.06	1.02	4.12	72	
	2472		F1-4		50.21	27.67	72.66	97	<0.0001
	2829		F2-4		21.60	11.47	36.92	95	NR
	1862		F3-4		6.85	3.85	11.9	90	

NR; not relevant/not retrieved, F; Fibrosis, F0-4; Fibrosis Stages 0-4.

4.10. Risk of developing fibrosis in MAFLD/NAFLD patients

Study characteristics

One systematic review with meta-analysis,(13) one systematic review of modelling studies,(25) and one modelling study (17) reported on the risk of developing fibrosis in NAFLD patients.

Relevant outcomes

In NAFLD patients, the proportion experiencing fibrosis progression and the annual rate of fibrosis progression was 36.1% and 0.13 stages, as reported by Singh et al.(13) Gruneau et al. estimated that the probability of NAFLD patients transitioning from F0 to F1, F1 to F2, and F2 to F3 ranged from 0.05 to 0.095, 0.023 to 0.14, and 0.018 to 0.07, respectively.(25) Swain et al. also reported transition probabilities for NAFLD patients, broken down by sex and age.(17)

Table 10 Risk of developing fibrosis in NAFLD patients

Author (year)	Population	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	I2	P-value	Time period
Singh et al. (2015) (13)	NAFLD	F0	F	Progression rate (stages)	0.13	0.07	0.18	88	<0.01	Per year
		NR	FP	Proportion (%)	36.1		NR			
Gruneau et al. (2022) (25)	NAFLD	F0	F1	Transition probability	0.05 to 0.095			NR		
		F1	F2		0.023 to 0.140					
		F2	F3		0.018 to 0.070					
Swain et al. (2020) (17)	0-39yo males with NAFLD	F0	F1	Transition probability	0.006	0.0035	0.0091	NR		Per year
	40+ males NAFLD				0.0158	0.0093	0.0241			
	0-39yo females NAFLD				0.005	0.0029	0.0076			
	40+ females NAFLD				0.0131	0.0077	0.0201			
	0-39yo males NAFLD	F1	F2		0.0366	0.0216	0.0561			
	40+ males NAFLD				0.0967	0.0569	0.1481			
	0-39yo females NAFLD				0.0305	0.018	0.0468			
	40+ females NAFLD				0.0806	0.0474	0.1235			
	0-39yo males NAFLD	F2	F3		0.0366	0.0216	0.0561			
	40+ males NAFLD				0.0967	0.0569	0.1481			
	0-39yo females NAFLD				0.0305	0.018	0.0468			
	40+ females NAFLD				0.0806	0.0474	0.1235			

NR; not relevant/not retrieved, F; Fibrosis, FP; Fibrosis Progression, F0-4; Fibrosis Stages 0-4.

4.11. Risk of developing cirrhosis in MAFLD/NAFLD patients

Study characteristics

Two modelling studies (6,17) and one systematic review of modelling studies (25) reported on the risk of developing cirrhosis in NAFLD patients; no data was found within the MAFLD population.

Relevant outcomes

The probability of a NAFLD patient transitioning from F3 to compensated cirrhosis (CC) was estimated at 0.0721 per year by Adams et al.,(6) and between the range of 0.04 and 0.118 in studies included in the systematic review by Gruneau et al.(25)

Table 11 Risk of developing cirrhosis in NAFLD patients

Author (year)	Population	Initial disease stage	Outcome	Measure	Est.	LCI	UCI	Time period
Adams et al. (2020) (6)	NAFLD	F3	CC	TP	0.0721	NR		Per year
		CC	DC		0.0371			
Swain et al. (2020) (17)	0-39yo males with NAFLD	F3	CC	TP	0.0443	0.0253	0.0842	Per year
	40+ males with NAFLD				0.0723	0.0412	0.1374	
	0-39yo females with NAFLD				0.0369	0.0211	0.0702	
	40+ females with NAFLD				0.0602	0.0344	0.1145	
	NAFLD	CC	DC		0.0371	0.026	0.0503	
Gruneau et al. (2022) (25)	NAFLD	F3	CC	TP	0.040 to 0.118	NR		

NR; not relevant/not retrieved, F; Fibrosis, F0-4; Fibrosis Stages 0-4, CC; Compensated Cirrhosis, DC; Decompensated Cirrhosis, TP; Transition Probability

5. Discussion

Overall, data was extracted on disease prevalence and transitions for MAFLD/NAFLD and MASH/NASH patients from 17 studies, including six systematic reviews with meta-analyses,(11–15) four modelling studies,(6,16–18) four cohort studies,(19–22), two cross-sectional studies,(23,24) and one systematic review.(25) Meta-analysis/systematic review evidence on these disease transitions was available from large scale studies involving participants from a wide range of geographical locations and various ethnicities.(11–15,25,26) There was a substantive evidence in the Australian context,(6,23,24) as well as from the USA,(16,18,19,21,22) and Canada.(17)

Overview of findings

Prevalence of MAFLD/NAFLD (in Australia or similar contexts)

In Australia, the prevalence of NAFLD was estimated at 22.2% in 2020,(6) a similar proportion to the Canadian population,(17) but much lower than the reported North American and Australasian population (estimated at 38.47%).(26)

NAFLD prevalence has dramatically increased over time in Australia,(8,9) with one New South Wales-based study reporting an increase in NAFLD/NASH HCC from 13% in 2008 to 19% in 2016.(9) These trends have been driven by increases in overweight and obesity, with Australians who have been born more recently at higher risk of being overweight and/or obese than if they were born earlier.(27)

Prevalence of MASH/NASH (in Australia or similar contexts)

The prevalence of NASH in the Australian population was estimated at 5.3% in 2020, increasing to 5.8% and 6.2% in 2025 and 2030, respectively, with similar estimates reported in the Canadian population.(6,17)

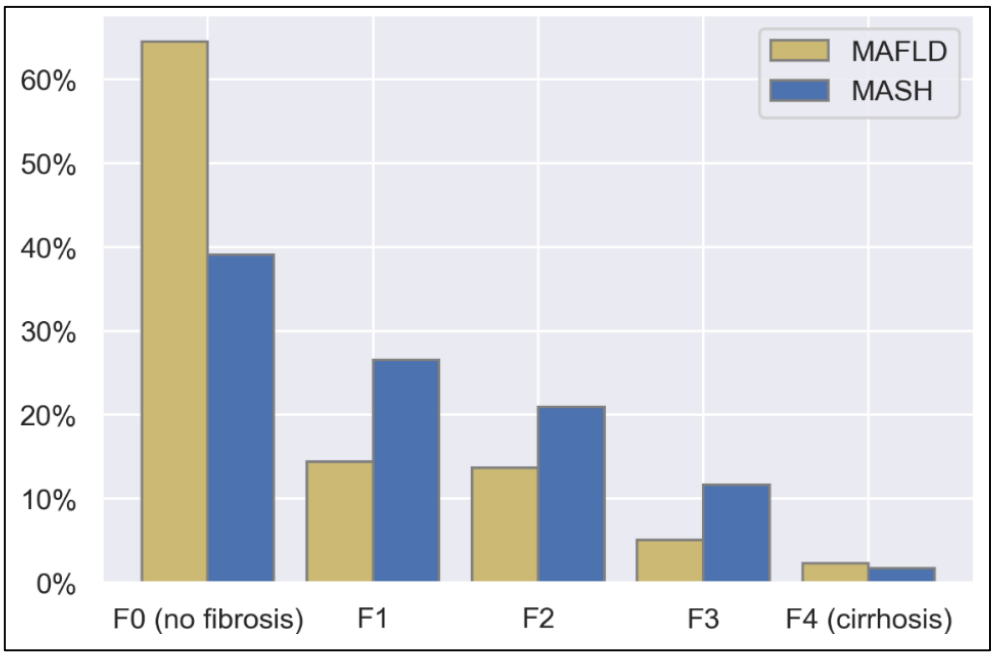
Prevalence of MASH/NASH in MAFLD/NAFLD patients

The global prevalence of NASH in NAFLD patients was estimated at 16.02% in 2023,(26) and projected to reach 27% in the USA in 2030.(18) As expected, prevalence was significantly higher in the overweight and obese population, at 45.5% and 44.05% (globally), respectively.(12) In contrast to these findings, Younossi et al. (14) reported an extremely high prevalence of NASH in NAFLD at 59.1%. The authors acknowledged that this high estimate was likely a result of selection bias, with the study population typically selected for biopsy due to showing signs of being at high risk of steatohepatitis.

Prevalence of fibrosis in MAFLD/NAFLD patients

The prevalence of NAFLD with no fibrosis was estimated at 35.8% in the general NAFLD population.(13) The prevalence of NAFLD F1 was reported at 32.5% (or 14.89% and 13.84% in overweight and obese patients, respectively), and the prevalence of NAFLD F2, F3 and F4 was estimated at 16.7%, 9.3% and 5.7%, respectively.(12)

Figure 2 – Fibrosis stage distribution in patients with MAFLD and MASH



Prevalence of fibrosis in patients diagnosed with MASH/NASH

The prevalence of fibrosis within the overweight and obese NASH population was estimated at 26.55% (F1), 20.95% (F2), 11.6% (F3) and 1.71% (F4),(12) with MASH patients more likely to have advanced fibrosis than MAFLD patients. The distributions for each group are shown in Figure 2.

Risk of developing fibrosis in MAFLD/NAFLD patients

The risk of fibrosis progression within the NAFLD population was estimated at a rate of 0.13 stages per year,(13) and at a transition probability ranging from 0.0131 to 0.095 from F0 to F1, 0.023 to 0.14 from F1 to F2, and 0.018 to 0.07 from F2 to F3.(17,25)

Risk of developing fibrosis in MASH/NASH patients

The risk of fibrosis progression within the NASH population was estimated at a rate of 0.03-0.14 stages per year,(11,13,14) and at a transition probability from F0 (no fibrosis) to F1, F2 and F3 of 6.1%, 1.7% and 0.9% per year, respectively.(16) Notably, over 10% total body weight loss was associated with fibrosis regression in NASH patients.(19,20) Although both these studies had small sample sizes, these results indicate that weight loss is an effective treatment for the regression of fibrosis, even in advanced stages.

Risk of developing cirrhosis in MAFLD/NAFLD patients

The risk of cirrhosis within the NAFLD population was estimated at a transition probability of 0.04 to 0.118.(6,17,25)

Risk of developing cirrhosis in MASH/NASH patients

The risk of compensated cirrhosis within the NASH population was estimated at an annual transition probability of 0.9% in F0 patients, 0.3% in F1 patients, 1.8% in F2 patients, and 11% in F3 patients,(16) with F3 patients at a 22% risk of developing cirrhosis over 29-months.(21)

Overlap between patients who would be diagnosed with MAFLD and patients who would be diagnosed with NAFLD

The overlap between NAFLD and MAFLD was estimated at a relative proportion of 73.2%,(22) and excellent interrater reliability was reported between the two definitions, with a

Cohen's kappa ranging from a 0.83 to 0.94.(22) Notably, the prevalence of MAFLD in Australian adults was estimated to be higher than NAFLD prevalence, at 37% in 2022,(24) aligning with other studies which have reported a higher overall prevalence of MAFLD vs NAFLD.(23)

Strengths and limitations of the review

A strength of this scoping review is the comprehensive nature of the search across all types of research studies published in both the international and national literature.

As this report was a scoping and not systematic review, no formal critical appraisal or risk of bias assessment was performed. Data was extracted from relevant studies to a sufficient level of evidence to address the research questions; this is, by design, not exhaustive of literature published on the disease transitions in NAFLD, MAFLD, NASH and MASH patients within the last decade.

Implications and future directions

Whilst a considerable amount of evidence was found on the NAFLD/NASH population, there were only a few studies conducted in the MAFLD/MASH population, as these classifications are more recent and there has not been sufficient time for large-scale data collection or studies. The term MAFLD was put forward by expert consensus in 2020,(28,29) and has been endorsed in letter of more than 1,000 signatories from professional bodies as well as specialist and primary care physicians.(7) 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, and there remains some controversy over the new definition.(7) As this new definition becomes accepted into standard practice, research which utilises these new classifications will be critical to help guide liver disease treatment and modelling.

A notable finding of this scoping review was the potential effectiveness of lifestyle interventions aimed at total body weight loss for the regression of fibrosis in NASH patients. As the two studies which showed associations between fibrosis regression and over 10% total body weight loss were conducted retrospectively and with small sample sizes, larger prospective studies, including longitudinal studies and randomized controlled trials, should be conducted to further explore this relationship, including predictive modelling.

6. Conclusion

This scoping report identified and reviewed evidence from recently published national and international studies on disease prevalence and transitions for MAFLD/MASH patients.

Overall, there is a substantive body of evidence relating to NAFLD/NASH, including three based in the Australian context. However, literature focusing on the MAFLD/MASH population remains scarce due to the relatively recent adoption of these classifications; this will be a key area of future research.

As rates of obesity and the metabolic syndrome rise in Australia, so too will the prevalence of MAFLD/NAFLD, MASH/NASH and related primary liver cancer. It is important that efforts continue to understand these diseases, so that action can be taken to reduce the future burden of liver disease and liver cancer in Australia.

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