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SYSTEMATIC REVIEW

The Economic Burden of Non-Alcoholic Steatohepatitis: A Systematic Review

Michal Witkowski[1] · Søren Ilsøe Moreno[2] · João Fernandes[2] · Pierre Johansen[3] · Margarida Augusto[2] · Sunita Nair[4]

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Abstract

Background The global prevalence of non-alcoholic steatohepatitis (NASH) is increasing, such that NASH is predicted to become the leading cause of liver transplantation (LT) in the US by 2025. Despite this, data on the economic burden of NASH are limited.

Objectives This systematic literature review aimed to summarise and critically evaluate studies reporting on the economic burden of NASH and identify evidence gaps for subsequent research.

Methods Medline, EMBASE, the Cochrane Library and EconLit were searched up to 6 January 2021 for English language articles published from January 2010 to January 2021 inclusive that reported economic outcomes of a NASH population or subpopulation. Evidence was presented and synthesised using narrative data analysis, and quality was assessed by two reviewers using an 11-item checklist developed for economic evaluations and adapted to cost of illness.

Results Fourteen studies were included, of which five presented data on costs and resource use, four on costs only and five on resource use only. Overall, NASH is associated with a significant and increasing economic burden in terms of healthcare resource utilisation (HCRU) and direct and indirect costs. This burden was higher among NASH patients with advanced (fibrosis stage 3–4) versus early (fibrosis stage 0–2) disease, symptomatic versus asymptomatic disease and for patients with complications or comorbidities versus those without. In LT patients, those with NASH as the primary indication had greater HCRU and higher costs compared with non-NASH indications such as hepatitis B and C viruses. Considerable variability in HCRU and costs was seen across the US and Europe, with the highest costs seen in the US. The quality of the included studies was variable, and the studies themselves were heterogeneous in terms of study methodology, patient populations, comorbidities, follow-up time and outcomes measured.

Conclusions This review highlights a general scarcity of NASH-specific economic outcomes data. Despite this, the identified studies show that NASH is associated with a significant economic burden in terms of increased HCRU, and high direct medical and non-medical costs and societal burden that increases with disease severity or when patients have complications or comorbidity. More national-level NASH prevalence data are needed to generate accurate forecasts of HCRU and costs in the coming decades.

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Plain Language Summary

It is important to know the cost of treating different diseases because this helps to guide how healthcare resources and funds are used. Non-alcoholic steatohepatitis (NASH) is a serious liver disease that can lead to liver scarring (cirrhosis), liver transplantation and early death, and the number of people with NASH is growing around the world. Fourteen studies published over the past 10 years have investigated the costs of treating patients with NASH. Patients with NASH generally use more healthcare services with a higher cost than the general population or patients with type 2 diabetes. In people with more serious liver disease, such as liver transplant patients, NASH tends to be more expensive and use more healthcare services than other serious liver diseases such as hepatitis. Costs and use of health services are particularly high in patients with more severe NASH, or those who have other diseases or complications in addition to NASH (such as type 2 diabetes or kidney failure).

✉ Margarida Augusto
vmga@novonordisk.com

Extended author information available on the last page of the article

Key Points for Decision Makers

NASH is associated with a substantial economic burden in terms of healthcare resource utilisation, medical, non-medical and indirect costs, that increase with disease severity or when complications or comorbidity are present.

Available evidence on indirect costs (e.g. productivity losses, informal care) is scarce, but the limited reports suggest these may outweigh direct costs. Further research is justified to fully appreciate the impact of indirect and societal costs on the economic burden of NASH.

Studies evaluating economic outcomes were heterogeneous in terms of patient populations, comorbidities, follow-up time and outcomes measured, limiting comparability of studies, and varied in the quality of their analyses. More precise national-level prevalence data are needed for accurate forecasts of healthcare resource utilisation and costs in the coming decades.

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of related liver disorders, ranging from non-alcoholic fatty liver (NAFL; simple steatosis) to non-alcoholic steatohepatitis (NASH) [1]. NAFLD is the hepatic manifestation of the metabolic syndrome (MetS) and is closely linked with key components of MetS including central obesity [2]. Obesity is associated with a 10-fold increase in the risk of NAFLD [3]. Fuelled by increasing rates of obesity and other key components of MetS, the prevalence of NAFLD is growing rapidly [3–7], with an estimated global prevalence of 25% [6, 8]. NASH is likely to become the leading cause of end-stage liver disease in the coming decades [2].

NASH, the most severe form of NAFLD, is defined by the presence of liver damage in the form of steatosis, hepatocyte ballooning and lobular inflammation, with or without fibrosis [9, 10]. NASH is a progressive disease, and in some patients may progress to advanced fibrosis and cirrhosis [1, 7]. NASH is also associated with an increased risk of hepatocellular carcinoma (HCC), requirement for liver transplantation (LT) and liver-related mortality [11]. The prevalence of NASH as the primary indication for LT has increased in both Europe and the US over the past two decades [12, 13]. NASH is also associated with elevated risk of other extra-hepatic complications including chronic kidney disease, malignancy and cardiovascular disease (CVD) [9, 10].

Despite its high clinical burden, there are limited data on healthcare resource utilisation (HCRU) and direct medical costs associated with NASH. The national economic burden of NAFLD in terms of direct annual medical costs has been estimated at $103 billion in the US, €27.7 billion in three European countries combined (Germany, France, Italy) and £5.24 billion in the UK [14].

Economic burden analyses are pivotal for addressing key health policy and health system management questions [15, 16]. They provide information at a microeconomic (household, employer or government agency impact) and macroeconomic (societal impact, i.e. a country's gross domestic product [GDP]) level, and can inform decision makers about the overall magnitude of economic losses and their distribution across different categories of cost (e.g. health expenditure, labour and productivity losses). They can also be used for cost-effectiveness modelling and to guide healthcare resource allocation.

This review aimed to summarise and critically evaluate currently available evidence on the economic burden of NASH, focusing on direct medical and non-medical costs, indirect costs and HCRU, and identify evidence gaps for subsequent research.

2 Methods

A systematic literature review (SLR) was conducted using Medline, EMBASE, Cochrane Library and EconLit databases via the Ovid platform using pre-defined search strategies (see Supplementary Table 1 in the Electronic Supplementary Material [ESM]). The review was conducted in line with Cochrane guidelines [17] and is reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [18]. This review was not registered, and a protocol was not prepared. Further details on the review methodology are provided in Supplementary Methods in the ESM.

The primary SLR was conducted in 2020, with an update to the searches on 6 January 2021. Eligible studies were full-text English language publications of economic outcomes in NASH populations, with or without comorbidities, or a NASH subgroup within an NAFLD study, published from January 2010 to January 2021. Full eligibility criteria are described in Supplementary Table 2 in the ESM.

First-round screening of titles and abstracts was followed by second-round full-text screening of short-listed articles and data extraction of articles meeting the eligibility criteria. Both first- and second-round screening was performed by two independent researchers, and final inclusion was verified by the project lead.

Data extraction was performed using pre-designed data extraction tables by an analyst with a quality check on

all publications by an independent senior analyst. Any disagreements regarding study eligibility or data extraction were referred to a third party and were resolved through discussion or inclusion of additional referees. Data extracted from each study included, but were not limited to, reference, country/region, study design, baseline characteristics (including age, sex, body mass index, method of diagnosis and comorbidities), type of intervention (including dose, duration and frequency) and outcomes reported (as shown in Supplementary Table 2 in the ESM).

Evidence was synthesised narratively, with outcomes categorised initially by type (resource use or costs), and further subdivided based on the range of components within each category. To allow comparison of like-for-like data, resource use was further categorised into hospital admissions, hospital length-of-stay (LOS) and other HCRU, and data were organised according to NASH population type (LT-related populations, cirrhosis-related populations and NASH populations with or without comorbidities). Cost data were separated into direct and indirect costs, with direct costs further subdivided into individual costs or estimates of national cost burdens.

Quality assessment was performed for all studies within the SLR. The quality of included cost of illness/economic burden studies was assessed using an 11-item checklist of questions that evaluated the methodological quality of the studies using a four-point answer scale (yes, no, partially, not specified). The checklist was developed from a model described by Drummond et al. [19] and adapted to cost of illness by Molinier et al. [20]. Questions within the checklist encompassed whether a clear definition of the illness was given; whether epidemiological sources, activity data, methodology, and cost values were appropriately described and/or assessed; whether costs were discounted, unit costs appropriately valued, and direct/indirect costs sufficiently disaggregated; whether major assumptions were tested in a sensitivity analysis; and whether presentation of the study results was consistent with the study methodology. Two reviewers independently assessed the likelihood of bias and any disagreements were resolved by discussion and/or additional referees.

3 Results

The electronic database search identified 4672 citations, of which 370 were identified as duplicates and excluded, 4046 were excluded based on title and abstract and a further 242 publications were excluded during full-text screening. The reasons for exclusion at first and second pass are summarised in Fig. 1. Overall, 14 unique publications were included (see Supplementary Table 3 in the ESM).

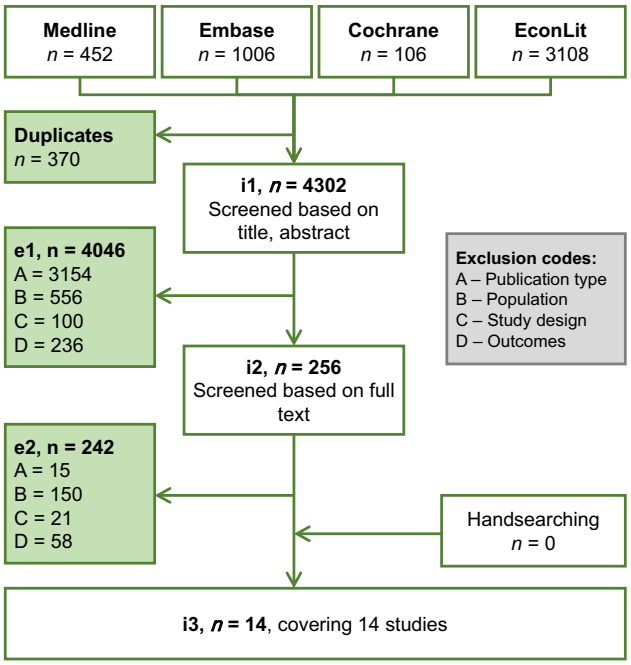

Fig. 1 Flow diagram of publications included and excluded from systematic review. *e1* excluded studies after title/abstract screening stage, *e2* excluded studies after full-text review stage, *i1* studies to screen at title/abstract stage, *i2* studies to screen at full-text review stage, *i3* included studies after full-text review stage

3.1 Study and Patient Characteristics

Overall, the included studies were heterogeneous in terms of study methodology, patient populations, comorbidities, follow-up time and outcomes measured.

Most of the identified studies were retrospective in nature, and over half of the studies were US-based (see Supplementary Table 3 in the ESM). Patient populations across the studies included general NASH populations or sub-populations, NASH with or without coexisting conditions (type 2 diabetes [T2D], sarcopenia, kidney failure), LT recipients and patients hospitalised for NASH/NASH-cirrhosis (see Supplementary Table 3 in the ESM). Approximately equal proportions of studies reported on resource use alone, costs alone or both costs and resource use. Cost perspectives were applicable for nine studies; these included patient, societal, payer and national healthcare system perspectives in seven studies, with two studies not reporting the cost perspective (see Supplementary Table 4 in the ESM).

3.2 Resource Use

3.2.1 Hospitalisations and Length of Stay

Ten studies reported hospitalisation (Table 1) and/or hospital LOS (Table 2) data associated with NASH, half of which

Table 1 Hospital admissions reported across included studies

Study	Country	Population	*N*	Outcome	Hospital admissions
LT-related hospitalisations					
Aby et al. [21]	US	LT recipients with NASH cirrhosis or cryptogenic cirrhosis, 2002–2015		1-year post-transplant hospital admissions, median (IQR)	**Sarcopenia vs no sarcopenia:** 1 (0.2–2) vs 1 (0–2); $p = 0.402$
		With sarcopenia	90		
		Wthout sarcopenia	56		
Agopian et al. [22]	US	Patients who underwent primary LT, 1993–2011		NASH as primary indication for LT, %	**2002 vs 2011:** 3 vs 19
		NASH aetiology	144		
		Non-NASH aetiology	1150		
		HBV	691		
		HCV	127		
		ALD	185		
		CC	58		
		PBC/PSC	89	Pre-transplant hospitalisations, %	**NASH vs non-NASH:** 62 vs 41 **HCV:** 37; **HBV:** 25; **ALD:** 60; **CC:** 67; **PBC/PSC:** 43
Barbas et al. [23]	Canada	NASH patients undergoing primary LT, 2000–2014		Pre-transplant hospitalisations, %	**LDLT vs DDLT:**
		LDLT	48	Home/hospital	69.6/30.4 vs 50.8/49.2; $p = 0.03$
		DDLT	128	Home/ward/ICU	69.6/28.3/2.2 vs 50.8/39.2/10.0; $p = 0.06$
Morris et al. [24]	US	Patients who underwent LSG following LT, 2014–2018	15	Post-transplant LSG ICU admissions, *n* (%)	1 (6.7)
		NASH	14		
Cirrhosis-related hospitalisations					
Axley et al. [27]	US	Hospital admissions for cirrhosis (2006–2014)	1,928,764	Proportion of cirrhosis admissions with NASH aetiology, %	**2006–8 vs 2012–14:** 6 vs 12; $p < 0.001$
		NASH-related	179,104	NASH-related admissions:	
				Proportion of NASH cirrhosis hospitalisations that developed ACLF, n (%)	**2006–14:** 8903 (5)
				ACLF admissions in NASH cirrhosis patients, %	**2006–8 vs 2012–14:** 3.5 vs 5.7; $p < 0.001$
				Frequency of ACLF admissions for NASH (proportion of total ACLF admissions in NASH cirrhosis patients), %	**2006–8/2009–11/2012–14:** 12/33/55

Table 1 (continued)

Study	Country	Population	*N*	Outcome	Hospital admissions
		CC subgroup with discharge diagnosis of NASH	699,668	CC subgroup:	
				Proportion of CC admissions with discharge diagnosis of NASH, %	**2006–8 vs 2012–14:** 49 vs 54; *p* NR
				ACLF admissions with NASH cirrhosis, %	**2006–8 vs 2012–14:** 4.5 vs 6.2; $p < 0.001$
				Frequency of ACLF admissions in NASH cirrhosis (proportion of total ACLF admissions with NASH cirrhosis), %	**2006–8/2009–11/2012–14:** 23/NR/43
Hospitalisation rates in NASH patients alone or versus general population and/or patients with T2D					
Balp et al. [26]	EU5[a]	Respondents to the National Health and Wellness Survey		Hospitalisations in past 6 months, mean	**NASH vs general population:** 0.47 vs 0.17; $p < 0.001$ **NASH vs T2D:** 0.39 vs 0.19; $p = 0.033$
		NASH	184		
		Unmatched general population	79.267		
		Unmatched T2D	4783		
Carruthers et al. [28]	England	Patients with biopsy-proven NASH and diabetes (inpatient and day-case admissions to NHS hospitals 2004–2015)	2004/05: 1303	Number of admissions	**2004–5 vs 2014–15:** 1303 vs 2341

Table 1 (continued)

Study	Country	Population	*N*	Outcome	Hospital admissions
			2014/15: 2341	Hospital admission rates from 2004–2014 (rate per 100,000 population)	**Overall:** **2004:** 73.8; **2005:** 76.8; **2006:** 73.4; **2007:** 71.4; **2008:** 71.9; **2009:** 75.6; **2010:** 79.2; **2011:** 79.7; **2012:** 83.5; **2013:** 78; **2014:** 80.4 Rate ratio: 1.01 (1.00–1.02); $p = 0.04$ **Male:** **2004:** 41.5; **2005:** 44; **2006:** 43.9; **2007:** 42.6; **2008:** 43.8; **2009:** 43.7; **2010:** 47.9; **2011:** 46.5; **2012:** 48.2; **2013:** 45; **2014:** 47.6 Rate ratio: 1.01 (1.00–1.02); $p = 0.03$ **Female:** **2004:** 32.2; **2005:** 32.8; **2006:** 29.5; **2007:** 28.8; **2008:** 28.1; **2009:** 31.9; **2010:** 31.3; **2011:** 33.2; **2012:** 35.3; **2013:** 33; **2014:** 32.8 Rate ratio: 1.00 (0.99–1.02); $p = 0.37$ **17–44 years:** **2004:** 7.5; **2005:** 8.2; **2006:** 7.3; **2007:** 7.5; **2008:** 6.3; **2009:** 7.4; **2010:** 8.3; **2011:** 7.3; **2012:** 10.7; **2013:** 7.5; **2014:** 7.2 Rate ratio: 1.01 (0.98–1.03); $p = 0.54$ **44–64 years:** **2004:** 33.7; **2005:** 37.1; **2006:** 33.6; **2007:** 30.9; **2008:** 33.3; **2009:** 30; **2010:** 31.8; **2011:** 31.8; **2012:** 30.9; **2013:** 32.8; **2014:** 29.7 Rate ratio: 0.99 (0.97–0.99); $p = 0.002$ **65+ years:** **2004:** 32.5; **2005:** 31.5; **2006:** 32.5; **2007:** 33; **2008:** 32.3; **2009:** 38.2; **2010:** 39.1; **2011:** 40.6; **2012:** 41.8; **2013:** 37.7; **2014:** 43.5 Rate ratio: 1.03 (1.02–1.04); $p < 0.001$

Table 1 (continued)

Study	Country	Population	*N*	Outcome	Hospital admissions
Carruthers et al. [28]	England	Patients with biopsy-proven NASH without diabetes (inpatient and day-case admissions to NHS hospitals 2004–2015)	2004/05: 12,758 2014/15: 10,988	Number of admissions Hospital admission rates from 2004–2014 (rate per 100,000 population)	**2004–5 vs 2014–15:** 12,758 vs 10,988 **Overall:** **2004:** 33.6; **2005:** 35.7; **2006:** 34.7; **2007:** 33.5; **2008:** 32.6; **2009:** 31.3; **2010:** 31.4; **2011:** 30.7; **2012:** 30.1; **2013:** 28.3; **2014:** 21.7 Rate ratio: 0.97 (0.96–0.98); $p < 0.001$ **Male:** **2004:** 18.9; **2005:** 20.1; **2006:** 19.4; **2007:** 18.3; **2008:** 17.6; **2009:** 17.3; **2010:** 17.3; **2011:** 16.2; **2012:** 15.8; **2013:** 14.3; **2014:** 11 Rate ratio: 0.96 (0.95–0.97); $p < 0.001$ **Female:** **2004:** 14.7; **2005:** 15.6; **2006:** 15.3; **2007:** 15.2; **2008:** 15; **2009:** 14; **2010:** 14.1; **2011:** 14.5; **2012:** 14.3; **2013:** 14; **2014:** 10.7 Rate ratio: 0.98 (0.97–0.99); $p < 0.001$ **17–44 years:** **2004:** 10.5; **2005:** 11.1; **2006:** 10.7; **2007:** 9.4; **2008:** 9.1; **2009:** 8.8; **2010:** 8.5; **2011:** 8.5; **2012:** 8.3; **2013:** 7.3; **2014:** 5.4 Rate ratio: 0.95 (0.94–0.96); $p < 0.001$ **44–64 years:** **2004:** 14; **2005:** 15.1; **2006:** 14.5; **2007:** 14.3; **2008:** 13.7; **2009:** 12.6; **2010:** 12.9; **2011:** 12.5; **2012:** 12.1; **2013:** 10.9; **2014:** 8.5 Rate ratio: 0.96 (0.95–0.97); $p < 0.001$ **65+ years:** **2004**: 9.1; **2005**: 9.5; **2006:** 9.5; **2007:**9.8; **2008:** 9.8; **2009:** 9.9; **2010:** 10; **2011:** 9.7; **2012:** 9.7; **2013:** 10.1; **2014:** 7.8 Rate ratio: 1.00 (0.99–1.00); $p = 0.45$
Geier et al. [29]	US, France, Germany	NASH patients (NASH-Atlas program July–November 2017) Total BC NASH Phenotypic NASH French NASH population German NASH population US NASH population	 1216 786 430 227 287 702	Number of inpatient visits, mean (SD)	**Total population: 0.3 (3.9)** **BC vs phenotypic NASH:** 0.3 (NR) vs 0.3 (NR) **FR vs DE vs US:** 0.5 (NR) vs 0.5 (NR) vs 0.1 (NR)

[a]EU5 includes France, Germany, Italy, Spain and the UK

ACLF acute-on-chronic liver failure, *ALD* alcoholic liver disease, *BC* biopsy-confirmed, *CC* compensated cirrhosis, *CI* confidence interval, *DDLT* deceased donor liver transplant, *DE* German cohort, *FR* French cohort, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICU* intensive care unit, *IQR* interquartile range, *LDLT* living donor liver transplantation, *LSG* laparoscopic sleeve gastrectomy, *LT* liver transplantation, *NASH* non-alcoholic steatohepatitis, *NASH-Atlas* Growth from Knowledge (currently Ipsos) Disease Atlas Real-World Evidence program, *NHS* National Health Service, *NR* not reported, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *SD* standard deviation, *T2D* type 2 diabetes, *US* US cohort

Table 2 Hospital length of stay across included studies

Study	Country	Population	*N*	Outcome	Length of stay
LT-related hospitalisations					
Aby et al. [21]	US	LT recipients with NASH cirrhosis or cryptogenic cirrhosis, 2002–2015		Post-transplant LOS, median days (IQR)	**Sarcopenia vs no sarcopenia:** 44.5 (23.2–81.2) vs 46 (27–69.2); $p = 0.812$
				Post-transplant hospital days in 1-yr, median (IQR)	53 (31.2–89.8) vs 55.5 (33.5–80); $p = 0.777$
		With sarcopenia	90		
		Without sarcopenia	56		
Agopian et al. [22]	US	Patients who underwent primary LT, 1993–2011		All patients:	
				Total LOS, days	**NASH vs non-NASH:** 47 vs 36
		NASH aetiology	144		**HCV:** 34; **HBV:** 27; **ALD:** 47; **CC:** 47; **PBC/PSC:** 35
		Non-NASH aetiology	1150		
		HBV	691	Post-transplant LOS, days	**NASH vs non-NASH:** 35 vs 29
		HCV	127		**HCV:** 28; **HBV:** 23; **ALD:** 36; **CC:** 36; **PBC/PSC:** 27
		ALD	185		
		CC	58		
		PBC/PSC	89	Patients from home pre-transplant:	
				Post-transplant LOS, days	**NASH vs non-NASH:** 28 vs 20
					HCV: 17; **HBV:** 17; **ALD:** 21; **CC:** 33; **PBC/PSC:** 22
				Hospitalised patients pre-transplant:	
				Pre-transplant LOS, days	**NASH vs non-NASH:** 18 vs 18
					HCV: 16; **HBV:** 16; **ALD:** 18; **CC:** 17; **PBC/PSC:** 18
				Post-transplant LOS, days	**NASH vs non-NASH:** 40 vs 42
					HCV: 38; **HBV:** 38; **ALD:** 46; **CC:** 37; **PBC/PSC:** 29
Barbas et al. [23]	Canada	NASH patients undergoing primary LT, 2000–2014			**LDLT vs DDLT:**
				Post-transplant LOS, median days (IQR)	11 (8–16) vs 17 (10–31)
		LDLT	48	Post-transplant ICU LOS, mean days (SD)	3.2 (9.7) vs 6.3 (14.2)
		DDLT	128		
				Total LOS for index admission, median days (IQR)	12.5 (9–18) vs 19 (10–34)
Hoehn et al. [25]	US	Patients with diabetes who underwent LT, 2007–2011		Proportion of patients discharged home, %	**NASH vs non-NASH[a]:** **Obese:** 71% vs 83%; $p < 0.005$ **Non-obese:** 79% vs 85%; $p < 0.005$
		Total	2971	LOS	**NASH vs non-NASH[a]:** **Non-obese:** 10 vs 9 days; $p < 0.05$
		NASH	713		
Morris et al. [24]	US	Patients who underwent LSG following LT, 2014–2018	1	Post-transplant LSG LOS, median days (IQR)	2 (1–2)
		Total	15		
		NASH	14		
Cirrhosis-related hospitalisations					
Axley et al. [27]	US	Hospital admissions for cirrhosis with ACLF (2006–2014)		LOS, mean days	**Total:** **2006–8:** 13; **2009–11:** 13; **2012–14:** 12 **NASH:** **2006–14:** 14
		Total	112,174		
		NASH-related	8903		

Table 2 (continued)

Study	Country	Population	*N*	Outcome	Length of stay
NASH-related hospitalisations with or without comorbidities					
Carruthers et al. [28]	England	Patients with biopsy-proven NASH (inpatient and day-case admissions to NHS hospitals 2004–2015)		LOS, median days (IQR)	**2004–5 vs 2014–15:** **With diabetes:** 2 (0–16) vs 0 (0–8); $p < 0.001$ **Without diabetes:** 1 (0–7) vs 0 (0–5); $p < 0.001$
		With diabetes (2004–5)	1303		
		With diabetes (2014–15)	2341		
		Without diabetes (2004–5)	12,758		
		Without diabetes (2014–15)	10,988		
Geier et al. [29]	US, France, Germany	NASH patients (NASH-Atlas program July–November 2017)		LOS,[b] mean (SD)	**Total population:** 3.7 (7.1) **BC vs phenotypic NASH:** 2.7 vs 6.0; $p < 0.05$ **FR vs DE vs US:** 5.0 vs 4.3 vs 2.1
		Total	1216		
		BC NASH	786		
		Phenotypic NASH	430	ICU LOS,[b] mean (SD)	**Total population:** 0.4 (1.2) **BC vs phenotypic NASH:** 0.4 vs 0.4; p = ns **FR vs DE vs US:** 0.5 vs 0.3 vs 0.4
		French NASH population	227		
		German NASH population	287		
		US NASH population	702		
Reja et al. [31]	US	Hospitalised NASH patients with or without kidney failure, 2016		LOS, mean days (SD)	**Total NASH:** 4.8 (7.1) **With vs without kidney failure:** 6.4 (9.1) vs 3.1 (3.4), β/OR = 3.02 (95% CI 2.54–3.50; $p < 0.0001$)
		Total	1196		
		With kidney failure	598		
		Without kidney failure	598		

[a]Comparator inferred, but not explicitly stated in publication

[b]Nights in hospital/ICU

ACLF acute-on-chronic liver failure, *ALD* alcoholic liver disease, *BC* biopsy-confirmed, *CC* compensated cirrhosis, *CI* confidence interval, *DDLT* deceased donor liver transplant, *DE* German cohort, *FR* French cohort, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICU* intensive care unit, *IQR* interquartile range, *LDLT* living donor liver transplantation, *LOS* length of stay, *LSG* laparoscopic sleeve gastrectomy, *LT* liver transplantation, *NASH* non-alcoholic steatohepatitis, *NASH-Atlas* Growth from Knowledge (currently Ipsos) Disease Atlas Real-World Evidence program, *NHS* National Health Service, *ns* non-significant, *OR* odds ratio, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *SD* standard deviation, *US* US cohort, *yr* year

reported on LT-related hospitalisations [21–25]. Most studies scored highly in all applicable categories of the quality assessment while two studies scored poorly in multiple categories (see section 3.4 for further details).

NASH was associated with a two- to three-fold higher rate of hospital admissions over 6 months compared with the general population or patients with T2D [26]. A pattern of increasing prevalence of hospitalisations due to NASH was seen across the studies, including an increase in the proportion of late-stage liver complications due to NASH relative to other liver diseases [27], an increase in the proportion of cirrhosis admissions of NASH aetiology over 8 years [27] and a five-fold increase in the frequency of NASH as primary indication for LT over 10 years [22]. The frequency of hospital admissions among patients with comorbid diabetes has increased relative to patients without diabetes over time [28].

The presence of comorbid diabetes does not appear to increase LOS among inpatient or day-case admissions (Table 2). Equivalent median LOS was reported for patients with and without diabetes in 2014–2015 following an overall decrease in median LOS in both populations over 11 years [28]. In LT recipients, one Canadian study found that patients receiving deceased donor LT had longer post-transplant and intensive care LOS than patients receiving living donor LT (LDLT), leading the study authors to conclude that LDLT for NASH facilitates transplantation of patients at a less severe stage of disease, which appears to promote a faster recovery and decreased HCRU [23].

The results of two studies suggest that LOS is longer in patients with NASH compared with other serious liver diseases (Table 2) [22, 27]. A higher rate of pre-transplant hospitalisations and longer total and post-transplant LOS were reported for NASH versus non-NASH LT recipients [22], and similarly, a longer mean LOS was reported among acute-on-chronic liver failure (ACLF) admissions of NASH-cirrhosis aetiology compared with alcohol- or viral-related cirrhosis [27].

Table 3 Resource use (excluding inpatient visits) across included studies

Study	Country	Population	*N*	Outcome	Resource use
LT-related					
Agopian et al. [22]	US	Patients who underwent primary LT, 1993–2011		Mechanical ventilator use before LT, %	**NASH vs non-NASH:** 16 vs 17 **HCV:** 15; **HBV:** 12; **ALD:** 24; **CC:** 22; **PBC/PSC:** 12
		NASH aetiology	144	Vasopressor use before LT, %	**NASH vs non-NASH:** 17 vs 10* **HCV:** 8*; **HBV:** 8*; **ALD:** 19; **CC:** 16; **PBC/PSC:** 7
		Non-NASH aetiology	1150		
		HBV	691		
		HCV	127	Dialysis before LT, %	**NASH vs non-NASH:** 45 vs 31* **HCV:** 26*; **HBV:** 16*; **ALD:** 47; **CC:** 37; **PBC/PSC:** 28*
		ALD	185		
		CC	58		
		PBC/PSC	89	Operative time, mins	**NASH vs non-NASH:** 402 vs 322* **HCV:** 323*; **HBV:** 308*; **ALD:** 330*; **CC:** 315*; **PBC/PSC:** 322*
				Intraoperative transfusion, uPRBC, %	**NASH vs non-NASH:** 18 vs 14* **HCV:** 14*; **HBV:** 13*; **ALD:** 16; **CC:** 14*; **PBC/PSC:** 12*
				Retransplantation, %	**NASH vs non-NASH:** 7 vs 7 **HCV:** 8; **HBV:** 2; **ALD:** 6; **CC:** 3; **PBC/PSC:** 6
Cirrhosis-related					
Axley et al. [27]	US	Hospital admissions for cirrhosis with ACLF (2006–2014)			**NASH vs non-NASH:**
		Total	112,174	Endoscopic evaluation, %	5 vs 2–10; *p* NR
		NASH aetiology	8903	Dialysis use, %	45 vs 36; $p < 0.0001$
		Non-NASH	103,271[b]	Ventilator use, %	78 vs 76–82; *p* NR
				Long-term care, %	32 vs 26; $p = 0.0001$
NASH-related with or without comorbidities					
Balp et al. [26]	EU5[a]	Respondents to the National Health and Wellness Survey		Healthcare resource use in past 6 months, adjusted mean (SE):	**NASH vs matched general population:**
		NASH	184	General/family practitioner visits	3.80 (0.33) vs 2.23 (0.10); $p < 0.001$
		Unmatched general pop.	79,267		
		Matched general pop.	736	Specialists (any type) visits	6.94 (0.69) vs 3.77 (0.19); $p < 0.001$
		Unmatched T2D	4783	Cardiologist visits	0.32 (0.05) vs 0.19 (0.02); $p = 0.013$
		Matched T2D`	368	Gastroenterologist visits	0.28 (0.06) vs 0.07 (0.01); $p < 0.001$
				Endocrinologist visits	0.27 (0.05) vs 0.04 (0.01); $p < 0.001$
				Internist visits	0.28 (0.06) vs 0.12 (0.02); $p = 0.002$
				Diabetologist visits	0.22 (0.06) vs 0.09 (0.02); $p = 0.007$
				Psychiatrist visits	0.37 (0.12) vs 0.16 (0.04); $p = 0.034$
				Hepatologist visits	0.07 (0.02) vs 0.01 (0.00); $p = 0.000$
				HCP visits	10.73 (NR) vs 6.01 (NR); $p < 0.001$
				ER visits	0.57 (NR) vs 0.22 (NR); $p < 0.001$
				Healthcare resource use in past 6 months, adjusted mean (SE):	**NASH vs matched T2D:**
				General/family practitioner visits	3.68 (0.36) vs 2.81 (0.19); $p = 0.033$
				Specialists (any type) visits	7.13 (0.73) vs 5.01 (0.35); $p = 0.008$
				Cardiologist visits	0.31 (0.07) vs 0.23 (0.04); $p = 0.333$
				Gastroenterologist visits	0.28 (0.07) vs 0.08 (0.02); $p = 0.001$
				Endocrinologist visits	0.27 (0.07) vs 0.09 (0.02); $p = 0.004$
				Internist visits	0.26 (0.09) vs 0.23 (0.05); $p = 0.740$

Table 3 (continued)

Study	Country	Population	*N*	Outcome	Resource use
				Diabetologist visits	0.26 (0.05) vs 0.27 (0.04); $p = 0.964$
				Psychiatrist visits	0.38 (0.11) vs 0.16 (0.04); $p = 0.041$
				Hepatologist visits	0.09 (0.03) vs 0.00 (0.00); $p < 0.001$
				HCP visits	10.85 (NR) vs 7.86 (NR); $p = 0.006$
				ER visits	0.65 (NR) vs 0.23 (NR); $p = 0.009$
				Prescription treatment for T2D, %	**NASH vs general population vs T2D:**
				Use of a prescription	20.1 vs 5.0 vs 82.6
				Use of insulin prescription	5.4 vs 1.4 vs 23.0
				Use of non-insulin prescription	19.6 vs 4.5 vs 75.1
Geier et al. [29]	US, France, Germany	NASH patients (NASH-Atlas program July–November 2017)		**Annual non-routine HCRU, mean (SD)**	**Total population:** 4.2 (3.1)
		Total	1216	Physician visits	**BC vs phenotypic NASH:** 4.5 vs 3.7 **FR vs DE vs US:** 4.6 vs 4.6 vs 3.9
		BC NASH	786		
		Phenotypic NASH	430		
		French NASH population	227	Outpatient visits	**Total population:** 1.6 (2.0) **BC vs phenotypic NASH:** 1.8 vs 1.4 **FR vs DE vs US:** 2.3 vs 1.3 vs 1.5
		German NASH population	287		
		US NASH population	702		
		F1 fibrosis	175	ER visits	**Total population:** 0.3 (1.0) **BC vs phenotypic NASH:** 0.4 vs 0.4 **FR vs DE vs US:** 0.4 vs 0.5 vs 0.2
		F2 fibrosis	278		
		F3 fibrosis	211		
		F4 fibrosis	47	**Tests/procedures used for NASH diagnosis, %**	
				Liver biopsy	**Total NASH vs BC NASH:** 66.0 vs 100 **FR vs DE vs US:** 47.1 vs 65.9** vs 72.1**
				Ultrasound	**Total NASH vs BC NASH:** 62.5 vs 59.0 **FR vs DE vs US:** 67.4** vs 57.1 vs 63.1
				FibroScan (transient elastography)	**Total NASH vs BC NASH:** 23.2 vs 21.1 **FR vs DE vs US:** 54.6*** vs 23.7** vs 12.8
				Serum transaminase (ALT, AST)	**Total NASH vs BC NASH:** 65.3 vs 64.5 **FR vs DE vs US:** 72.7*** vs 62.0 vs 64.2
				GGT	**Total NASH vs BC NASH:** 43.8 vs 38.3 **FR vs DE vs US:** 70.0*** vs 58.2** vs 29.3
				Lipid profile	**Total NASH vs BC NASH:** 49.3 vs 37.3 **FR vs DE vs US:** 58.1** vs 57.8** vs 43.0
				Platelet count	**Total NASH vs BC NASH:** 44.4 vs 40.4 **FR vs DE vs US:** 59.9*** vs 43.9 vs 39.6
				Clotting studies[d]	**Total NASH vs BC NASH:** 33.1 vs 27.1 **FR vs DE vs US:** 32.6 vs 45.6*** vs 28.2

Table 3 (continued)

Study	Country	Population	*N*	Outcome	Resource use
				ARFI imaging	**Total NASH vs BC NASH:** 2.2 vs 2.4 **FR vs DE vs US:** 1.9 vs 1.3 vs 3.8
				CT scan	**Total NASH vs BC NASH:** 16.2 vs 17.2 **FR vs DE vs US:** 19.2 vs 9.3 vs 14.3
				MRI	**Total NASH vs BC NASH:** 9.5 vs 9.0 **FR vs DE vs US:** 7.1 vs 9.7 vs 15.0
				MRE	**Total NASH vs BC NASH:** 4.5 vs 5.0 **FR vs DE vs US:** 4.3 vs 3.5 vs 5.9
				FibroTest/FibroSure	**Total NASH vs BC NASH:** 19.6 vs 17.4 **FR vs DE vs US:** 15.7 vs 40.1 vs 12.9
				Fibrosis-4 index	**Total NASH vs BC NASH:** 6.2 vs 6.6 **FR vs DE vs US:** 5.7 vs 5.7 vs 7.7
				APRI	**Total NASH vs BC NASH:** 20.6 vs 21.6 **FR vs DE vs US:** 22.6 vs 18.5 vs 17.1
				Steatosis, activity and fibrosis score	**Total NASH vs BC NASH:** 8.1 vs 8.9 **FR vs DE vs US:** 8.3 vs 6.2 vs 9.1
				NashTest	**Total NASH vs BC NASH:** 9.5 vs 10.2 **FR vs DE vs US:** 5.3 vs 13.2 vs 17.1
				NAFLD fibrosis score	**Total NASH vs BC NASH:** 14.8 vs 15.5 **FR vs DE vs US:** 14.4 vs 13.2 vs 17.1
				NAFLD activity score	**Total NASH vs BC NASH:** 15.9 vs 18.7 **FR vs DE vs US:** 15.7 vs 9.7 vs 21.3
				Enhanced liver fibrosis panel score	**Total NASH vs BC NASH:** 3.9 vs 3.4 **FR vs DE vs US:** 3.3 vs 0.4 vs 8.4
				Circulating levels of CK-18	**Total NASH vs BC NASH:** 4.4 vs 5.2 **FR vs DE vs US:** 2.4 vs 2.6 vs 10.5
				Tests/procedures used for NASH monitoring, %	
				Liver biopsy	**Total NASH vs BC NASH:** 11.6 vs 16.7 **FR vs DE vs US:** 13.1 vs 2.6 vs 15.0
				Ultrasound	**Total NASH vs BC NASH:** 54.4 vs 57.3 **FR vs DE vs US:** 53.7 vs 48.9 vs 60.6
				FibroScan (transient elastography)	**Total NASH vs BC NASH:** 17.6 vs 18.2 **FR vs DE vs US:** 11.7 vs 49.3 vs 21.6

Table 3 (continued)

Study	Country	Population	*N*	Outcome	Resource use
				Serum transaminase (ALT, AST)	**Total NASH vs BC NASH:** 61.8 vs 61.6 **FR vs DE vs US:** 64.1 vs 69.2 vs 61.7
				GGT	**Total NASH vs BC NASH:** 41.1 vs 38.8 **FR vs DE vs US:** 22.8 vs 62.1 vs 57.5
				Lipid profile	**Total NASH vs BC NASH:** 49.3 vs 37.3 **FR vs DE vs US:** 30.5 vs 31.7 vs 58.5
				Platelet count	**Total NASH vs BC NASH:** 44.4 vs 40.4 **FR vs DE vs US:** 37.7 vs 45.4 vs 42.9
				Clotting studies[d]	**Total NASH vs BC NASH:** 33.1 vs 27.1 **FR vs DE vs US:** 22.9 vs 19.4 vs 43.2
				ARFI imaging	**Total NASH vs BC NASH:** 2.5 vs 3.4 **FR vs DE vs US:** 2.1 vs 1.3 vs 4.2
				CT scan	**Total NASH vs BC NASH:** 8.2 vs 9.5 **FR vs DE vs US:** 9.8 vs 1.8 vs 9.4
				MRI	**Total NASH vs BC NASH:** 5.9 vs 6.0 **FR vs DE vs US:** 4.8 vs 4.0 vs 10.1
				MRE	**Total NASH vs BC NASH:** 5.0 vs 3.8 **FR vs DE vs US:** 1.6 vs 3.1 vs 7.3
				FibroTest/FibroSure	**Total NASH vs BC NASH:** 17.4 vs 16.3 **FR vs DE vs US:** 12.7 vs 29.1 vs 12.9
				Fibrosis-4 index	**Total NASH vs BC NASH:** 6.6 vs 7.8 **FR vs DE vs US:** 6.0 vs 4.0 vs 8.7
				APRI	**Total NASH vs BC NASH:** 21.6 vs 18.6 **FR vs DE vs US:** 18.7 vs 10.1 vs 20.2
				Steatosis, activity and fibrosis score	**Total NASH vs BC NASH:** 8.9 vs 6.2 **FR vs DE vs US:** 5.7 vs 4.0 vs 8.0
				NashTest	**Total NASH vs BC NASH:** 10.2 vs 9.3 **FR vs DE vs US:** 5.3 vs 5.3 vs 16.4
				NAFLD fibrosis score	**Total NASH vs BC NASH:** 15.5 vs 12.9 **FR vs DE vs US:** 9.3 vs 9.3 vs 18.1
				NAFLD activity score	**Total NASH vs BC NASH:** 18.7 vs 15.9 **FR vs DE vs US:** 11.5 vs 8.4 vs 23.3

Table 3 (continued)

Study	Country	Population	*N*	Outcome	Resource use
				Enhanced liver fibrosis panel score	**Total NASH vs BC NASH:** 3.4 vs 4.3 **FR vs DE vs US:** 3.6 vs 0.4 vs 7.7
				Circulating levels of CK-18	**Total NASH vs BC NASH:** 5.2 vs 5.3 **FR vs DE vs US:** 2.8 vs 2.2 vs 8.4
				NASH diagnosis and monitoring tests, mean number (SD)	
				Liver biopsy	**Total NASH vs BC NASH:** 1.2 (0.7) vs 1.2 (0.7) **FR vs DE vs US:** 1.2 (0.8) vs 1.1 (0.5) vs 1.2 (0.5)
				Ultrasound	**Total NASH vs BC NASH:** 2.7 (2.3) vs 2.9 (2.5) **FR vs DE vs US:** 2.4 (2.4) vs 2.5 (1.4) vs 3.7 (2.5)
				ARFI imaging	**Total NASH vs BC NASH:** 1.5 (1.2) vs 1.6 (1.2) **FR vs DE vs US:** 1.5 (1.0) vs 1.0 (1.2) vs 1.8 (1.3)
				CT scan	**Total NASH vs BC NASH:** 1.4 (0.8) vs 1.5 (0.8) **FR vs DE vs US:** 1.4 (0.8) vs 1.6 (0.9) vs 1.4 (0.8)
				MRI	**Total NASH vs BC NASH:** 1.5 (1.2) vs 1.7 (1.4) **FR vs DE vs US:** 1.6 (1.4) vs 1.5 (0.7) vs 1.6 (1.0)
				MRE	**Total NASH vs BC NASH:** 1.7 (1.1) vs 1.8 (1.3) **FR vs DE vs US:** 1.6 (1.2) vs 1.6 (1.0) vs 1.9 (1.1)
				Fibroscan (transient elastography)	**Total NASH vs BC NASH:** 2.0 (1.4) vs 2.1 (1.5) **FR vs DE vs US:** 2.0 (1.6) vs 2.1 (1.3) vs 2.0 (1.1)
				Serum transaminases (AST, ALT)	**Total NASH vs BC NASH:** 5.0 (4.0) vs 5.0 (4.2) **FR vs DE vs US:** 4.7 (4.2) vs 5.3 (3.2) vs 5.4 (4.2)
				GGT	**Total NASH vs BC NASH:** 4.7 (3.6) vs 5.0 (3.9) **FR vs DE vs US:** 3.8 (3.6) vs 5.1 (3.1) vs 5.5 (3.9)
				FibroTest/FibroSure	**Total NASH vs BC NASH:** 2.0 (1.4) vs 2.2 (1.3) **FR vs DE vs US:** 2.0 (1.4) vs 2.3 (1.5) vs 1.7 (1.1)
				Fibrosis-4 Index	**Total NASH vs BC NASH:** 2.3 (1.6) vs 2.3 (1.7) **FR vs DE vs US:** 2.4 (1.8) vs 2.8 (1.7) vs 1.9 (1.2)
				APRI	**Total NASH vs BC NASH:** 3.5 (2.6) vs 3.4 (2.7) **FR vs DE vs US:** 3.6 (2.8) vs 3.1 (2.0) vs 3.3 (2.1)

Table 3 (continued)

Study	Country	Population	*N*	Outcome	Resource use
				Steatosis, activity and fibrosis score	**Total NASH vs BC NASH:** 2.0 (1.4) vs 1.9 (1.3) **FR vs DE vs US:** 1.7 (1.2) vs 3.0 (1.1) vs 2.2 (1.6)
				NashTest	**Total NASH vs BC NASH:** 1.7 (1.3) vs 1.8 (1.4) **FR vs DE vs US:** 2.0 (1.8) vs 1.5 (0.7) vs 1.6 (0.9)
				NAFLD fibrosis score	**Total NASH vs BC NASH:** 2.5 (2.1) vs 2.4 (2.2) **FR vs DE vs US:** 2.7 (2.4) vs 2.7 (1.6) vs 1.8 (1.2)
				NAFLD activity score	**Total NASH vs BC NASH:** 2.6 (2.8) vs 2.6 (2.8) **FR vs DE vs US:** 2.8 (3.1) vs 2.8 (3.6) vs 2.3 (1.5)
				Enhanced liver fibrosis panel score	**Total NASH vs BC NASH:** 2.0 (1.3) vs 1.9 (1.3) **FR vs DE vs US:** 2.1 (1.3) vs 2.0 (1.4) vs 1.8 (1.3)
				Circulating levels of CK-18	**Total NASH vs BC NASH:** 2.4 (1.5) vs 2.6 (1.6) **FR vs DE vs US:** 2.3 (2.0) vs 2.5 (1.2) vs 2.5 (1.3)
				Lipid profile[c]	**Total NASH vs BC NASH:** 4.1 (3.6) vs 4.1 (3.6) **FR vs DE vs US:** 3.4 (3.4) vs 4.3 (3.0) vs 5.1 (4.0)
				Platelet count	**Total NASH vs BC NASH:** 5.0 (4.2) vs 5.0 (4.0) **FR vs DE vs US:** 4.8 (4.8) vs 5.1 (3.3) vs 5.2 (3.6)
				Clotting studies[d]	**Total NASH vs BC NASH:** 4.4 (4.0) vs 4.4 (3.6) **FR vs DE vs US:** 4.0 (4.6) vs 4.4 (2.9) vs 4.8 (3.6)
				Non-invasive laboratory tests by fibrosis stage, mean number while under physician management	**F1 vs F2 vs F3 vs F4:**
				Platelet count	3.9 vs 5.1 vs 5.1 vs 7.1
				Serum transaminases	4.1 vs 5.1 vs 5.4 vs 6.9
				GGT	4.4 vs 4.9 vs 4.9 vs 7.5
				Clotting studies	4.0 vs 4.4 vs 4.2 vs 6.9
				Lipid profile	3.3 vs 4.2 vs 4.3 vs 5.8
				APRI	3.5 vs 3.1 vs 3.4 vs 5.5
				CK-18	2.3 vs 2.8 vs 2.6 vs NR
				Non-invasive procedures by fibrosis stage, mean number while under physician management	**F1 vs F2 vs F3 vs F4:**
				Ultrasound	2.4 vs 3.1 vs 2.7 vs 4.0
				Fibroscan (transient elastography)	1.6 vs 2.2 vs 2.3 vs 2.6

Table 3 (continued)

Study	Country	Population	*N*	Outcome	Resource use
				MRE	2.3 vs 1.8 vs 1.8 vs 0.7
				MRI	1.3 vs 1.9 vs 1.9 vs 1.3
				ARFI	1.3 vs 1.6 vs 1.4 vs 3.0
				CT scan	1.3 vs 1.6 vs 1.4 vs 1.7
				Current pharmacological interventions, % of total population	
				Statins	2.5
				Vitamin E	23.8
				Metformin	20.2
				Vitamin D	10.4
				Ursodeoxycholic acid	9.3
				Omega-3 fatty acids	7.5
				Thiazolidinediones	5.5
				Fibrates (fenofibrate)	4.5
				Orlistat	3.9
				GLP-1 analogues	4.0
				Pentoxifylline	3.7
				Betaine	1.2
				Current non-pharmacological interventions, % of total population	
				Lifestyle modification	64.6
				Watchful waiting	14.6
				Bariatric surgery	6.3
				Endoscopic intervention	5.7
				Put on a waiting list for a liver transplant	3.6
O'Hara et al. [30]	US and EU5[a]	NASH		**Diagnostic/imaging tests, %**	
		Total	3754	Liver biopsy	**Total:** NR; **US vs ES:** 57 vs 25
		US	1221	Ultrasound imaging	**Total:** 68; **EU5 vs US:** 76 vs 51
		EU5	2533	Fibroscan (transient elastography)	**Total:** 33; **EU5 vs US:** 42 vs 13
		Spain	522	AST/ALT ratio	**Total:** 23
				NAFLD fibrosis score	**Total:** 9
				BARD score[e]	**Total:** 3
				FIB-4 score	**Total:** 3
				CK-18	**Total:** 3

[a]EU5 includes France, Germany, Italy, Spain and the UK

[b]Non-NASH total is sum of alcohol-related cirrhosis ($n = 27{,}890$), viral hepatitis cirrhosis ($n = 9491$) and 'other' cirrhosis ($n = 65{,}890$)

[c]Cholesterol, LDL, HDL and triglycerides

[d]Prothrombin time, international normalised ratio

[e]BARD score is a simple clinical score based on **B**MI ≥28 kg/m^2, **A**ST/ALT **R**atio ≥0.8 and **D**iabetes mellitus

ACLF acute-on-chronic liver failure, *ALD* alcoholic liver disease, *ALT* alanine aminotransferase, *APRI* AST to Platelet Ratio Index, *ARFI* acoustic radiation force impulse, *AST* aspartate aminotransferase, *BC* biopsy-confirmed, *CC* compensated cirrhosis, *CK-18* cytokeratin-18, *CT* computed tomography, *DE* German cohort, *ER* emergency room, *ES* Spanish cohort, *F* fibrosis stage, *FIB-4* Fibrosis-4, *FR* French cohort, *GGT* gamma-glutamyl transferase, *GLP* glucagon-like peptide, *HBV* hepatitis B virus, *HCP* healthcare professional, *HCRU* healthcare resource utilisation, *HCV* hepatitis C virus, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LT* liver transplantation, *MRE* magnetic resonance enterography, *MRI* magnetic resonance imaging, *NAFLD* non-alcoholic fatty liver disease, *NASH* non-alcoholic steatohepatitis, *NASH-Atlas* Growth from Knowledge (currently Ipsos) Disease Atlas Real-World Evidence program, *NR* not reported, *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *SD* standard deviation, *SE* standard error, *T2D* type 2 diabetes, *uPRBC* units packed red blood cells, *US* US cohort

*$p < 0.05$ versus NASH or NAFLD/NASH; **$p < 0.05$ versus lowest reporting country; ***$p < 0.05$ versus all other countries

3.2.2 Healthcare Resource Utilisation

Five studies reported HCRU data, which included healthcare visits (excluding inpatient admissions), use of drugs, devices, tests, procedures and non-pharmacological interventions (Table 3). All five studies scored highly in all or most relevant quality assessment categories (see section 3.4 for further details).

Studies indicate a high demand for pharmacological and non-pharmacological interventions, as well as diagnosis and monitoring tests (Table 3) [22, 27, 29, 30]. Use of tests and procedures varied depending on disease severity, as shown by one multinational study that showed increased utilisation of non-invasive tests and procedures in patients with more advanced fibrosis (stage 4 [F4]) [29]. Differences in use of different diagnostic tests were also seen depending on country, with higher rates of liver biopsy, NashTest, NAFLD fibrosis score, NAFLD activity score, enhanced liver fibrosis score and less frequent use of FibroScan and some laboratory tests (e.g. GGT, lipid profile) reported in the US compared with European countries [29, 30].

Drug and device use in patients with late-stage complications often included dialysis and ventilation [22, 27]. Patients with NASH as primary indication for LT had greater device use, longer operative time and higher operative blood loss versus non-NASH LT [22], and ACLF patients with NASH aetiology required more dialysis use and long-term care versus non-NASH ACLF [27].

Two studies reporting on the frequency of healthcare provider visits in NASH populations (Table 3) showed that visits are more frequent in patients with NASH versus the general population [26], and in patients with biopsy-confirmed NASH compared with suspected NASH [29].

3.3 Costs

3.3.1 Direct Healthcare Costs

Direct healthcare costs were evaluated in six studies, of which three reported per-person costs [27, 30, 31] and four estimated national cost burdens [14, 30, 32, 33] (Table 4 and Supplementary Table 6 in the ESM). All six studies scored positively in all or most categories of the quality assessment (see section 3.4 for further details).

Overall, studies showed that direct costs are correlated with disease severity and vary significantly by country, with notably high costs in the US. The GAIN study, which assessed direct costs in a real-world setting in five European countries (EU5) and the US, reported mean annual costs per patient of €4754 in total (per 2019 valuation), composed of €2763 of NASH-related and €1991 of non-NASH costs (Table 4) [30]. Greater direct medical costs and non-medical costs were incurred by patients with advanced disease (F3–4 fibrosis) compared with early-stage disease. Presence of comorbidities also led to higher costs, with two-fold higher total hospitalisation charges reported for patients with versus without kidney failure [31]. Higher per patient hospital charges were reported in patients with NASH-related versus non-NASH-ACLF [27].

Total direct costs (including NASH-related and non-NASH-related costs relating to procedures/tests, NASH treatment, surgery, consultation and hospitalisation) varied considerably by country, with two- to three-fold higher annual costs per person in the US compared with each of the EU5 countries (Table 4) [30]. Higher costs in the US were driven mainly by NASH treatment, surgery and non-medical costs. Total direct costs across the EU5 countries were similar but there was variability in terms of individual direct cost components. For example, the UK reported the highest annual costs for tests/procedures and consultation fees, but the lowest annual costs for surgery and hospitalisations. Non-medical direct costs were lowest in France and highest in Spain followed by the US [30].

Four studies predicted the national cost burden of NASH alone or NASH plus T2D (Supplementary Table 6 in the ESM). In the US and EU5, the GAIN study reported national medical costs ranging from €2.5–5 billion annually across the EU5 countries, rising to €80 billion per year in the US due to higher per person costs and its larger population compared with EU5 countries [30]. For most countries, early-stage NASH (F0–2) appears to account for most of the estimated national medical cost burden, resulting from a greater prevalence of early-stage versus advanced-stage (F3–4) cases, though in Spain and Germany, where higher per person costs were reported for advanced-stage cases compared with the other EU5 countries, the national medical cost burdens were similar for early and advanced (F3–4) NASH. Another study predicted the annual economic burden of NAFLD, broken down by different liver disease health states in the US, Germany, France, Italy and the UK [14]. Direct medical costs attributable to NASH with or without fibrosis ranged from €332 million in Germany to $7.35 billion in the US (calculated as the sum of costs for NASH with fibrosis and NASH without fibrosis), with the cost burden more than doubling when including costs attributed to later stage complications (compensated and decompensated cirrhosis, HCC, LT and post-LT).

Two studies used Markov modelling to estimate the economic burden of NASH direct medical costs in Hong Kong [32] and of NASH with T2D in the US [33] (Supplementary Table 6 in the ESM). Tampi et al. [32] estimated that the average cost of NASH per person-year in Hong Kong is USD$257, with the highest cost seen in those aged ≥80 years. This equated to a 20-year national cost burden of $1.3 billion. Direct medical costs in the US for patients with NASH plus T2D were estimated to be $7349 and $9379

per person-year in incident and prevalent patient cohorts, respectively, of which liver-related costs accounted for 25% or less of the total costs [33]. Total liver-related care costs in the US over 20 years were estimated to be $3.4 billion for the NASH incident cohort and $160 billion for the NASH prevalent cohort.

3.3.2 Indirect Costs

Three studies assessed the indirect costs associated with NASH (Table 5), each of which scored positively in all or most relevant categories of the quality assessment (see section 3.4 for further details). Two studies assessed productivity-related costs associated with employed patients with NASH using the Work Productivity and Activity Impairment-General Health (WPAI-GH) or WPAI-Specific Health Problem (WPAI-SHP) instruments [26, 29]. The WPAI assesses absenteeism, presenteeism, overall work impairment (for employed respondents) and overall activity impairment (for all respondents) in the previous 7 days, with WPAI-SHP completed for NASH impairment specifically. Higher WPAI scores indicate greater impairment. These studies demonstrate that patients with NASH have significantly greater productivity losses versus the general population in terms of absenteeism, presenteeism, overall work impairment (for employed persons) and activity impairment [26], and this is more apparent in symptomatic versus asymptomatic patients [29]. When comparing NASH with T2D, similar WPAI impairment was reported in both groups across all categories [26].

The GAIN study calculated the monetary burden of productivity-related costs, averaging at €7871 per person annually and correlating with disease severity [30]. Costs were largely attributed to stopping work (74%), followed by time off work in the previous 12 months (26%). There was a large variability between countries, with two-to five-fold greater costs reported in France and the US compared with Germany, Italy and Spain.

3.4 Quality of Included Studies

All 14 included studies were assessed in 11 quality assessment domains (see Supplementary Table 7 in the ESM). One study scored positively in all 11 categories [33], with other high-scoring studies achieving positive scores in 10 [6, 32], nine [30], eight [27, 31] or seven [22, 23, 26, 28] categories. One study that assessed resource use in NASH cirrhosis LT recipients achieved positive scores in six categories, while four categories were not applicable to the study [21]. A multi-national real-world burden study also scored positively in six categories with the remaining four categories not specified within the publication [29]. One single-centre database study of 15 patients undergoing laparoscopic sleeve gastrectomy following LT scored poorly in six of 11 categories [24], while a multicentre database study assessing 12,442 post-LT patients scored poorly in four areas [25]. The latter two studies both failed to carefully describe and appropriately assess activity data sources, to analytically describe sources of all cost values and to appropriately value unit costs. The most frequently failed or non-evaluable questions were whether direct and indirect costs were sufficiently disaggregated, and whether costs were discounted.

4 Discussion

Overall, the findings of this study demonstrate that NASH places a significant demand on healthcare resources, and the increasing prevalence of NASH globally suggests that this will worsen in the future. This SLR includes results from large, well-designed database studies that indicate a high economic burden of NASH, but also highlight a general paucity of publications reporting economic outcomes data associated with NASH. This data gap, indicative of an unmet need to better understand the economic burden of NASH, is in line with other recent publications, including an SLR that discusses NASH health economic models [34]. One-third of included studies were published in 2019 or 2020, however, suggesting an increasing focus on understanding the economic impact of NASH.

The identified studies assessed a wide range of cost factors, presented data from a variety of cost perspectives, and used a variety of methods for their measurement. Furthermore, while many studies assessed similar outcomes, they reported varying measurement units for the analysis of the data. Therefore, while trends from the analyses could be assessed, it was generally not possible to make direct comparisons across studies.

There was a general trend for higher hospitalisation rates in patients with NASH versus the general population or patients with T2D [26], and the hospitalisation/LOS burden was greater among NASH populations with comorbid conditions or late-stage complications [27, 28, 31]. NASH-LT was a notable concern, with reported post-transplant LOS ranging from 10 to 46 days [21–23, 25]. Higher pre-transplant hospitalisation rates and longer LOS with NASH-LT versus non-NASH-LT patients [22, 25], coupled with a rapid increase in the proportion of LTs attributable to NASH versus non-NASH aetiology in recent years [22], demonstrate that NASH-LT will be a growing burden on healthcare services in years to come.

NASH was also associated with a high burden in terms of HCRU (drugs and devices, tests and procedures, and visits to healthcare providers). Differences in HCRU were seen between NASH subgroups, with a greater burden reported among biopsy-confirmed versus NASH-suspected

patients, and in patients with more advanced [F4] versus less advanced fibrosis. Variation was also seen at a national level in terms of diagnostic testing, which may reflect differences in healthcare systems, local management practices, accessibility of procedures and NASH management guidelines [29].

Although only a limited number of studies assessed the cost burden across subpopulations of NASH patients, identified evidence indicate high direct costs incurred by patients with advanced (F3–4) NASH and those with complications [27, 30, 31]. Variability in per person hospitalisation costs between NASH subpopulations is likely linked to LOS in part, with longer LOS reported for patients with higher costs [27, 31].

National-level, comparative data on per person medical costs was scarce, but available evidence indicate substantial between-countries differences. The highest direct costs per person were reported for the US. This is not unexpected, with the US spending 17.8% of its GDP on healthcare in 2016, compared with 9.6–12.4% in other high-income countries, driven by higher administrative costs of care, pharmaceutical costs and HCP salaries [35]. Non-medical direct costs also varied considerably between countries, driven by large differences in professional and informal caregiver costs between countries. This may reflect cultural differences, but also the relatively low number of patients that returned the questionnaires covering non-medical costs (5–41%) in each country [30].

Four studies assessed the national direct cost burden of NASH or NASH plus T2D, with stark variation seen between nations and predictions that were heavily reliant on the accuracy of NASH prevalence estimates [14, 30, 32, 33]. The studies indicate higher per person costs for patients with more severe disease, although the per person cost disparity between early (F0–2) and advanced (F3–4) fibrosis was variable in different countries, ranging from four-fold greater costs for advanced- versus early-stage fibrosis in Germany to only 1.2-fold greater in the US. In Hong Kong, the predicted direct medical cost burden for NASH alone appears to be much lower than that reported for the US and EU5 countries [32]; however, any comparisons between studies should be interpreted with caution, due to differences in methodologies and prevalence estimations in each study. Two other cost-of-illness studies in the literature evaluated the economic impact of NASH in 2018 [36, 37]. Morgan et al. [36] reported UK health system costs ranging from £200 million (low prevalence estimate) to £369 million (high prevalence estimate). Per person health system costs were estimated to range from £803–828. Schattenberg et al. [37] evaluated costs in the EU5 countries, reporting average health system costs across the countries of €619–1291 and per person costs of €1244–1470. In line with the GAIN study, most economic costs in these studies were experienced in late disease stages.

Although not directly comparable, there were parallels between the national cost burden analyses, including high indirect costs in most countries. In the GAIN study, direct non-medical and indirect costs were high in all countries except France, while Younossi et al. found that the societal costs of NAFLD were consistently higher than direct medical costs in all countries evaluated [14, 30]. Similarly, the published UK and EU5 2018 cost-of-illness studies reported productivity (incurred through reduced workforce participation) and other economic costs (which included care costs, deadweight loss and other costs such as funeral costs due to premature mortality) to be 10-fold higher than health system costs in 2018, ranging from £1999–3707 million in the UK (£8285–8286 per person), and €7928–18,254 million in the EU5 (€15,083–15,212 per person) [36, 37]. There was a higher prevalence of absenteeism, presenteeism, overall work impairment and activity impairment with NASH versus the general population [26], particularly in symptomatic patients [29], indicating a high social burden. However, there was no difference between patients with NASH and those with T2D in terms of productivity, indicating similar impairment on work and daily activities [26].

Diagnosis of NASH is complex, with non-specific symptoms such as fatigue and upper abdominal pain often the only indicators of its presence. In many cases, NASH is not identified until advanced liver damage has already occurred, and despite the increasing prevalence of NASH globally, the disease remains underdiagnosed [38]. This makes it challenging to fully understand the economic and HCRU burden of the disease. In addition, in the absence of approved pharmacological therapies for NASH, current resource use is often directed at managing complications of the disease, meaning that the cost and HCRU burden associated with NASH may change in the coming years and decades as NASH-specific drugs become available. Understanding the resource utilisation and costs associated with NASH is critical to guide priorities and policy, and for society in general, especially when NASH is predicted to become the leading cause of LT in the future.

4.1 Limitations and Evidence Gaps

This SLR was limited to English language full-text publications from January 2010 to January 2021 to examine the most recent evidence. Conference abstracts were not included because there were enough full-text articles to provide a sufficient level of relevant information, but it is possible that some relevant preliminary trial results published as conference materials were omitted. Most of the studies were retrospective in nature and included heterogenous patient populations. In addition, some studies had small patient or response numbers, and some used extrapolation methodologies. Thirteen of 14 studies were conducted in Europe and/

Table 4 Direct per patient costs associated with NASH

Study	Country	Currency, ref year	Population	*N*	Total direct costs	Medical costs
Cirrhosis-related costs						
Axley et al. [27]	US	USD, NR	Hospital admissions for cirrhosis with ACLF (2006–2014)	112,174	NR	**Total hospital charges/patient:** • NASH-related: $151,196 • Alcohol-related: $97,492 • Viral hepatitis-related: $117,016 • Other aetiologies: $140,279 • Overall non-NASH-related: $134,597 ($p < 0.0001$ vs NASH-related)
			NASH-related	8903		
			Alcohol-related	27,890		
			Viral hepatitis-related	9491		
			Other aetiologies	65,890		
			Hospital admissions for CC (2006–2014)	1,358,275	NR	**Median total hospital charges/admission:** • NASH-related: $143,258 • Alcohol-related: $97,472 • Viral hepatitis-related: $117,016
			NASH-related	699,668		
			Alcohol-related	NR		
			Viral hepatitis-related	NR		

Table 4 (continued)

Study	Country	Currency, ref year	Population	*N*	Total direct costs	Medical costs
NASH-related costs with or without comorbidities						
O'Hara et al. [30]	US and EU5[a]	Euros, 2019	NASH	Total: 3754 Early (F0–2): 2604 (69%) Advanced (F3–4): 1150 (31%) Germany: 540 Spain: 522 France: 508 UK: 423 Italy: 540 US: 1221	**Total annual costs PP, mean (SD):** • Overall: €4754 (22,117) • F0–2 vs F3–4: €3883 (20,634) vs €6727 (25,052) • **DE:** €3629 (8795); **ES:** €3323 (11,258); **FR:** €2440 (6241); **UK:** €3879 (3811); **IT:** €2739 (8296); **US:** €7258 (36,704) **NASH-related annual costs PP, mean (SD):** • Overall: €2763 (21,216) • F0–2 vs F3–4: €2224 (19,956) vs €3983 (23,788) • **DE:** €1917 (7715); **ES:** €2162 (10,220); **FR:** €1357 (5427); **UK:** €1851 (2406); **IT:** €1732 (7799); **US:** €4881 (42,077) **Non-NASH annual costs PP, mean (SD):** • Overall: €1991 (4840) • F0–2 vs F3–4: €1659 (4117) vs €2743 (6107) • **DE:** €1712 (3698); **ES:** €1161 (3200); **FR:** €1082 (2234); **UK:** €2027 (2897); **IT:** €1006 (2397); **US:** €2957 (7170)	**Test/procedure annual costs PP, mean (SD):** • Overall: 283 (486) • F0–2 vs F3–4: 265 (439) vs 323 (575) • **DE:** €183 (221); **ES:** €168 (180); **FR:** €124 (117); **UK:** €415 (668); **IT:** €220 (448); **US:** €435 (726) **NASH treatment annual costs PP, mean (SD):** • Overall: 1106 (3877) • F0–2 vs F3–4: 989 (3596) vs 1373 (4438) • **DE:** €655 (2218); **ES:** €739 (3047); **FR:** €502 (1292); **UK:** €624 (1550); **IT:** €431 (1718); **US:** €2241 (6743) **Surgery annual costs PP, mean (SD):** • Overall: 915 (20,512) • F0–2 vs F3–4: 653 (19,609) vs 1507 (22,420) • **DE:** €848 (6740); **ES:** €735 (8197); **FR:** €228 (4590); **UK:** €103 (1141); **IT:** €573 (7113); **US:** €1582 (34,825) **Consultation annual costs PP, mean (SD):** • Overall: 264 (314) • F0–2 vs F3–4: 259 (298) vs 274 (348) • **DE:** €89 (90); **ES:** €300 (312); **FR:** €203 (197); **UK:** €665 (487); **IT:** €275 (224); **US:** €210 (291)

Table 4 (continued)

Study	Country	Currency, ref year	Population	*N*	Total direct costs	Medical costs
						Hospitalisation annual costs PP, mean (SD): • Overall: 195 (2094) • F0–2 vs F3–4: 58 (815) vs 507 (3561) • **DE:** €143 (967); **ES:** €219 (2203); **FR:** €300 (1669); **UK:** €56 (443); **IT:** €233 (1232); **US:** €201 (3420) **Non-medical annual costs PPb, mean (SD):** • Overall (*n*=767): 2556 (7308) • F0–2 (*n*=546) vs F3–4 (*n*=221): 1704 (5785) vs 4661 (9839) • **DE (*n*=132):** €2695 (7273); **ES (*n*=169):** €4713 (10,828); **FR (*n*=130):** €213 (920); **UK (*n*=20):** €2063 (3707); **IT (*n*=219):** €1977 (5515); **US (*n*=97):** €3243 (7685)
Reja et al. [31]	US	USD, 2016 (Payer)	Hospitalised NASH patients with or without kidney failure, 2016	Total: 1196 With kidney failure: 598 Without kidney failure: 598	NR	**Total charge of hospitalisation, mean (SD):** • Overall: $58,023.7 (116,290.8) • With vs without kidney failure: $78,022.7 (158,580.8) vs $38,024.8 (33,476.0). β/OR = 37,045.9 (95% CI 31,756.18–42,335.62; $p < 0.0001$)

[a]EU5 includes France, Germany, Italy, Spain and the UK

[b]Professional (34%) and informal (48%) caregivers account for most non-medical costs. Other costs resulted from transport, disability allowances, alternative therapies, home alteration and OTC remedies

ACLF acute-on-chronic liver failure, *CC* compensated cirrhosis, *CI* confidence interval, *DE* German cohort, *ES* Spanish cohort, *F0–4* fibrosis stages 0–4, *FR* French cohort, *IT* Italian cohort, *NASH* non-alcoholic steatohepatitis, *NR* not reported, *OR* odds ratio, *OTC* over-the-counter, *PP* per patient, *SD* standard deviation, *UK* UK cohort, *US* US cohort, *USD* US dollars

Table 5 Indirect costs associated with NASH

Study	Country	Population	*N*	Absenteeism	Presenteeism	Productivity impairment	Other
Balp et al. [26]	EU5[a]	Respondents to the National Health and Wellness Survey NASH Unmatched general population Unmatched T2D	 184 79,267 4783	Mean WPAI-GH (SD)[b]: • NASH versus matched gen. population: 28.48 vs 12.36 ($p = 0.003$) • NASH versus matched T2D: 28.33 vs 17.42 (p = ns)	Mean WPAI-GH (SD)[b]: • NASH versus matched gen. population: 33.71 vs 23.03 ($p = 0.006$) • NASH versus matched T2D: 37.15 vs 26.56 (p = ns)	Overall work impairment, mean WPAI-GH (SD)[b]: • NASH vs matched gen. population: 49.15 vs 30.77 ($p < 0.001$) • NASH vs matched T2D: 50.95 vs 37.06 (p = ns) Activity impairment, mean WPAI-GH (SD): • NASH vs matched gen. population: 48.02 vs 32.64 ($p < 0.001$) • NASH vs matched T2D: 47.23 vs 41.12 (p = ns)	
Geier et al. [29]	US, France and Germany	NASH patients who completed PROs (NASH-Atlas program July–November 2017)	Total: 299 Symptomatic: 206 Asymptomatic: 93	Mean WPAI:SHP (SD)[b]: • Overall: 9.0 (22.5) • Symptomatic: 10.4 • Asymptomatic: 5.6 (p = ns vs symptomatic)	Mean WPAI:SHP (SD)[b]: • Overall: 17.5 (19.9) • Symptomatic: 23.0 • Asymptomatic: 4.4 ($p < 0.05$ vs symptomatic)	Overall work impairment, mean WPAI:SHP (SD)[b]: • Overall: 24.7 (27.4) • Symptomatic: 30.7 Asymptomatic: 9.0 ($p < 0.05$ vs symptomatic) Activity impairment, mean WPAI:SHP (SD)[b]: •Overall: 30.7 (28.5) •Symptomatic: 38.2 •Asymptomatic: 14.2 ($p < 0.05$ vs symptomatic)	
			Biopsy-confirmed: 160 Symptomatic: 112 Asymptomatic: 48	Mean WPAI:SHP (SD)[b]: • Symptomatic: 7.4 • Asymptomatic: 6.8 (p = ns vs symptomatic)	Mean WPAI:SHP (SD)[b]: • Symptomatic: 22.4 • Asymptomatic: 4.4 ($p < 0.05$ vs symptomatic)	Overall work impairment, mean WPAI:SHP (SD)[b]: • Symptomatic: 27.7 • Asymptomatic: 10.1 ($p < 0.05$ vs symptomatic) Activity impairment, mean WPAI:SHP (SD)[b]: • Symptomatic: 40.6 • Asymptomatic: 8.5 ($p < 0.05$ vs symptomatic)	

Table 5 (continued)

Study	Country	Population	*N*	Absenteeism	Presenteeism	Productivity impairment	Other
O'Hara et al. [30]	US and EU5[b]	NASH	Total: 3754 Early (F0–2): 2604 (69%) Advanced (F3–4): 1150 (31%) Germany: 540 Spain: 522 France: 508 UK: 423 Italy: 540 US: 1221				Annual indirect costs PP, mean € (SD)[c]: • Overall: 7871 (18,104) • F0–F2: 5939 (15,989) • F3–4: 12,642 (21,813) • Germany: 2530 (9137) • France: 11,624 (24,003) • Spain: 5451 (12,175) • UK: 9541 (18,223) • Italy: 4994 (8166) • US: 13,435 (29,493)

[a]EU5 includes France, Germany, Italy, Spain and the UK

[b]Absenteeism, presenteeism and overall work impairment includes only employed respondents

[c]Most indirect costs resulted from early retirement or stopping working (74%), followed by time off work in the previous 12 months (26%)

F0–4 fibrosis stages 0–4, *Gen*. general, *GH* general health; *NASH* non-alcoholic steatohepatitis, *NASH-Atlas* Growth from Knowledge (currently Ipsos) Disease Atlas Real-World Evidence program, *ns* non-significant, *PP* per patient, *PROs* patient-reported outcomes, *SD* standard deviation, *SHP* specific health problem, *T2D* type 2 diabetes, *WPAI* Work Productivity and Activity Impairment

or North America, and over half were conducted in the US. Additional studies that assess costs in the rest of the world, including developing countries, are warranted to better understand the global economic burden of NASH. In many of the studies, patients had advanced fibrosis stage (including populations with cirrhosis or LT recipients), and thus average per patient costs are likely to be higher than in the overall NASH population. The burden of NASH was stratified by patient sex in only one of 14 studies, in which male patients with or without comorbid diabetes had a higher rate of hospital admissions compared with female patients [28]. Future studies may wish to consider the impact of sex on other aspects of costs and HCRU.

There was wide variation across the included studies regarding the type of cost and resource use burden reported, making it difficult to draw conclusions about specific costs and resource use associated with NASH, and, consistent with the findings of a recent appraisal of NASH health economic models [34], we found limited data on NASH-specific costs for different NASH disease stages and/or late-stage complications. Several studies included patient-reported data [26, 29, 30], which are susceptible to potential inaccuracies resulting from differences in health literacy, memory and patient condition (e.g. level of fatigue). Furthermore, some patient surveys were completed by only a small proportion of patients, which could contribute to variability seen in some outcomes.

More national-level NASH prevalence data is needed to generate accurate forecasts of HCRU and costs in the coming decades. In addition, available evidence on indirect or societal costs and caregiver burden is scarce and further research is justified to fully appreciate their impact on the economic burden of NASH. Finally, several of the included studies did not report data from patients with NASH alone but reported data from those with NASH with complications or comorbidities (e.g. T2D, kidney disease, ACLF), making it difficult to determine the cost burden driven purely by NASH and limiting the comparability of data across studies. It would be beneficial for future studies to separate costs and resource use based on comorbid conditions (e.g. cost of hospitalisation in patients with NASH only; NASH plus obesity; NASH plus obesity and T2D) to understand if HCRU increases alongside the number of comorbid conditions.

5 Conclusions

There is a scarcity of NASH-specific economic outcomes data, and a lack of consistency amongst available data leads to difficulties in estimating the true economic burden

associated with NASH. Despite this, the studies identified in this SLR show that NASH is associated with a significant economic burden in terms of increased HCRU, direct medical costs and societal burden, that increases with disease severity or when patients have complications or comorbidity. Increasing incidence rates of NASH coupled with the propensity for disease progression, duration of hospitalisation and associated amount of resource use are major factors in the economic burden of NASH to be absorbed by healthcare providers and patients alike. This burden, in parallel with the increasing obesity and T2D epidemics, is only likely to increase over time.

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Code Availability Not applicable to this article.

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Authors' Contributions PJ provided the study concept and design. JF, PA and SN performed the data extraction. All authors contributed to the analysis and interpretation of the data and contributed to the drafting of the paper, critically revised the paper for intellectual content, were involved in the final approval of the version to be published and agreed to be accountable for all aspects of the work. PJ is the overall guarantor.

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Authors and Affiliations

Michal Witkowski[1] · Søren Ilsøe Moreno[2] · João Fernandes[2] · Pierre Johansen[3] · Margarida Augusto[2] · Sunita Nair[4]

1 DRG Abacus (Clarivate), Bicester, UK

2 Novo Nordisk A/S, Søborg, Denmark

3 Novo Nordisk Denmark A/S, Region North & West Europe, Ørestad, Denmark

4 DRG Abacus (Clarivate), Mumbai, India