BMJ Open

Estimating the clinical and healthcare burden of metabolic dysfunction-associated steatohepatitis in England: a retrospective cohort study using routinely collected healthcare data from 2011 to 2020

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To cite: Davidson JA, Brewer HR, Rice CT, *et al*. Estimating the clinical and healthcare burden of metabolic dysfunction-associated steatohepatitis in England: a retrospective cohort study using routinely collected healthcare data from 2011 to 2020. *BMJ Open* 2025;**15**:e095761. doi:10.1136/bmjopen-2024-095761

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-095761).

Received 28 October 2024
Accepted 31 March 2025

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ABSTRACT

Objective To characterise patients with metabolic dysfunction-associated steatohepatitis (MASH) in England and to estimate its associated healthcare resource use (HCRU) and costs, both overall and by progression status and comorbidities.

Design This was a retrospective observational study of adults with a MASH-coded primary and/or secondary care recorded diagnosis in England (2011–2020). The analysis used data from the Clinical Practice Research Datalink linked to the Hospital Episode Statistics and death registrations. Annualised all-cause and MASH-related (ie, coded as MASH, end-stage liver disease or major adverse cardiovascular event) HCRU and costs were calculated for patients with incident MASH. Subgroup analyses were conducted for patients with type 2 diabetes, overweight/obesity, cardiovascular disease or progression to cirrhosis. Comparative cost analysis was conducted between those with progressed MASH and those who did not progress.

Results A total of 2696 patients were included (mean follow-up: 4 years). Incidence of MASH was estimated at 4.7 per 100 000 person-years overall and increased among patients with key comorbidities. Patients who had type 2 diabetes had greater HCRU and costs than those who did not (eg, mean 1.8 vs 1.0 all-cause inpatient admissions and £2227 vs £1151 all-cause inpatient costs per-patient per-year). Some patients with MASH progressed to compensated (8.6%) or decompensated cirrhosis (6.5%) during the study. HCRU and costs were substantially higher among patients who progressed than among those who did not (eg, mean 2.4 vs 1.1 all-cause inpatient admissions and £3620 vs £1290 all-cause inpatient costs per-patient per-year).

Conclusion HCRU and costs associated with MASH are higher among patients who have cardiometabolic comorbidities or who progress to advanced disease stages. Therefore, efforts to detect cases early and prevent disease progression could reduce healthcare burden.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study analysed large routinely collected healthcare datasets capturing information from both primary and secondary care settings across England from 2011 to 2020, equating to the inclusion of ~25% of the English population.
⇒ Multiple definitions for metabolic dysfunction-associated steatohepatitis (MASH) were used to mitigate potential under or late diagnosis, although the use of different definitions was exploratory and each definition relied on diagnosis codes.
⇒ As mean follow-up was only ~4 years, the overall proportion of patients who will progress to end-stage liver disease may have been underestimated.
⇒ As the aim of the study was to describe MASH progression and consider the impact of progression on healthcare resource use and costs, a non-MASH comparator to estimate the incremental clinical and economic burden associated with MASH was not included. Most analyses were descriptive, preventing adjustment for confounding factors.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as non-alcoholic fatty liver disease, is the most common chronic liver disease in Western populations.[1–3] About a quarter of individuals with MASLD will develop a progressive form called metabolic dysfunction-associated steatohepatitis (MASH), previously known as non-alcoholic steatohepatitis.[1 4–6] MASH is characterised by severe liver damage due to long-term inflammation in addition to fat accumulation.[3 5 6]

Over time, MASH increases the risk of end-stage liver disease (ESLD).[2 7 8] Many people with MASH develop fibrosis and

some progress to cirrhosis.[9 10] Compensated cirrhosis (CC) is an asymptomatic stage where hepatic function is preserved.[11 12] However, CC can progress to decompensated cirrhosis (DC) due to predisposing factors and precipitating events.[11] In turn, DC can lead to complications like hepatocellular carcinoma (HCC), liver failure and death.[8 12] Notably, a third of people waiting for liver transplants in the USA have MASH and this percentage has been increasing.[13]

Cardiovascular-related mortality is the leading cause of death among patients with MASH.[14 15] MASLD/MASH may be both a precursor and a complication of cardiometabolic conditions such as cardiovascular disease (CVD), diabetes and obesity, for which patients with MASLD/MASH have increased risk.[2 16–21] Conversely, patients with diabetes also have a higher prevalence of steatohepatitis.[18] Obesity and diabetes are key determinants of risk of progression to cirrhosis and HCC.[17]

Indirect estimates of MASH prevalence derived from histology, annual health checks, national health surveys and autopsy data suggest that this condition affects 3%–5% of the global population.[9] While biomarker-based and imaging-based non-invasive tests have been adopted,[22 23] liver biopsy remains the reference standard.[8 9 15] However, its use for screening the general population for MASH is not deemed acceptable due to its cost and risk of complications.[8 9 15 24] Therefore, existing estimates likely underestimate the true prevalence of MASH, with many patients remaining undiagnosed and most of those diagnosed presenting advanced fibrosis.[15 25]

MASH is associated with substantial costs, and the hospital length-of-stay per patient is longer than for other serious liver diseases.[26] Direct healthcare costs need to be estimated for each country as they vary considerably between them.[26 27] In the UK, the total economic costs of diagnosed MASH were estimated to range £2–£4 billion in 2018.[15] Advanced liver disease, particularly cirrhosis, presents the highest costs, highlighting the economic burden linked to MASH progression.[15 26 28]

The estimated incidence and prevalence of MASH have roughly doubled globally in the last three decades,[29] and the incidence of cirrhosis caused by MASH doubled between 1990 and 2017.[30] Further, the prevalence of associated risk factors like type 2 diabetes mellitus (T2DM) is expected to keep rising by 2030, so the corresponding rates of CC or DC, HCC and liver-related death are also expected to increase.[4 14 31] Therefore, costs associated with MASH are likely to rise, further stressing the importance of early diagnosis and management of MASH.[5 6]

While accurately estimating healthcare resource use (HCRU) and costs at a national level requires an adequate estimation of prevalence in each country,[26] there is limited knowledge of the prevalence of MASH in England[15] or of the prevalence of complications such as major adverse cardiovascular events (MACE) among patients with MASH.[9] Given the limited MASH and MASH-associated complication prevalence estimates, HCRU and costs of MASH in England remain unquantified[9 26]; thus, the economic burden of this condition is also believed to be underestimated.[28] This study used routinely collected primary and secondary care data from England to characterise patients with MASH (including complications and progression) and to estimate the HCRU and healthcare costs associated with this condition, both overall and by subgroups based on MASH progression and cardiometabolic comorbidities.

METHODS

Data sources

Patient data were obtained from the Clinical Practice Research Datalink (CPRD) Aurum, which contains anonymised electronic healthcare records routinely collected from primary care providers (general practitioners, GPs) in the UK, mainly in England.[32] At time of data acquisition, CPRD Aurum captured records for more than 13 million currently registered patients, representing ~23% of the England population.[33 34]

Secondary care data were obtained from Hospital Episode Statistics (HES) datasets, which include inpatient admissions (Admitted Patient Care dataset), outpatient appointments (Outpatient dataset), emergency care attendances (Accident and Emergency dataset) and Diagnostic Imaging Dataset at National Health Service (NHS) hospitals in England.[35 36] Death registrations data were from the Office for National Statistics (ONS). Small area statistics allowed identification of socioeconomic deprivation levels among patients based on the Townsend deprivation score of their local area.[37]

CPRD data were linked to HES and ONS data by NHS Digital; the anonymised linked data were held and administered by CPRD. As these analyses involved anonymised structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients was not required.

Study design

This was a retrospective observational study comprising cross-sectional and open-cohort elements. The eligibility window was 1 January 2011 to 31 December 2020, and the study period was 1 January 2011 to 31 December 2021 (to allow at least 1 year of follow-up for each individual). Follow-up end was the date of ESLD diagnosis, date of death, administrative censoring (including patient transfer out of their GP practice or end of data collection at their GP practice), or 31 December 2021, whichever occurred first. The index date was 90 days after the date of earliest MASH diagnosis to account for late detection and ensure identification of incident cases. The study was conducted according to best practices, including the use of RECORD guidelines for reporting.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination of our research.

Study population

CPRD patients with ≥1 MASH-coded primary or secondary care record (see online supplemental methods for code details) during the eligibility window were included if they were eligible for HES linkage, were registered with their GP at least 12 months before index and were ≥18 years old at index. Patients were excluded if they had excess alcohol consumption; previous diagnosis of viral hepatitis B or C, Wilson's disease, Gaucher's disease, cholangitis, autoimmune hepatitis, primary biliary cirrhosis, haemochromatosis, HIV, heavy metal poisoning, or heart failure prior to index; an ESLD diagnosis (including CC, DC, HCC or liver transplant) before or ≤3 months after the index date; indeterminate gender; or a HES record matched to ≥2 CPRD patient records deemed to correspond to different people based on differences in year of birth and sex.

Due to the possible underdiagnosis and underreporting of MASH in the data sources, not all patients were expected to have a MASH-specific code; to account for this, additional MASH definitions were explored: a subset of patients with a MASH-coded diagnosis from an inpatient setting or ≥2 diagnoses from outpatient/primary care settings, and patients with MASLD-coded diagnosis and liver biopsy, which would be suggestive of patients likely to have progressed to MASH (see online supplemental methods and online supplemental tables S1–S3).

Patients who had T2DM prior to MASH, had CVD prior to MASH, or had a Body Mass Index (BMI) reading indicative of being overweight or obese (BMI≥25 kg/m^2) in the 2 years before MASH were included in analysis as additional comorbidity subgroup strata.

Epidemiological analysis

Prior to HCRU and cost analyses, descriptive epidemiological analyses were conducted. Baseline characteristics were summarised using descriptive statistics. Annual incidence of MASH among CPRD-recorded patients was calculated based on newly diagnosed patients occurring in each year of the study period; once a patient was diagnosed, they were censored from inclusion in incidence estimates for subsequent years. Overall incidence and incidence rate ratios (IRR) of MASH were calculated by comorbidity subgroup (presence vs absence of comorbidity).

Annual point prevalence of MASH was calculated for patients contributing to CPRD during the eligibility window, including those diagnosed before the study period; calculations used prevalence on 1 March of each year, with all patients diagnosed prior to the prevalence date as the numerator and all eligible patients contributing to the dataset on the same day of the year as the denominator.

Incidence and IRR for MACE (defined as myocardial infarction, stroke, acute heart failure or cardiovascular death) in patients with MASH were calculated overall and per MACE event type, and both for the overall population and for each comorbidity subgroup.

For analyses by progression status among patients with MASH, the incidence of ESLD (defined as CC, DC, HCC or liver transplant) during follow-up was calculated overall and per disease severity state (CC, DC or HCC). Progression to ESLD was identified by coded diagnoses and liver transplantation record (codes used are provided in online supplemental table S4). Median time to death was estimated using survival probability curves.

Health economic analysis

All-cause and MASH-related (coded with at least one of the following conditions: MASH, any ESLD, or MACE) HCRU and costs were calculated. HCRU and costs were annualised to account for variable follow-up across patients. For this, summary statistics were generated by dividing the total value per patient by the time the patient spent in the cohort during the study period, with adjustments made for patients with short (<12 months) follow-up or who died within 12 months. All costs were inflated to 2021–2022 Sterling (£) using the NHS Cost Inflation Index. Identification and costing of primary and secondary care HCRU are summarised below. Additional details are provided in online supplementary methods.

Primary care

Annualised primary care consultations and costs were calculated and reported per-patient per-year (PPPY), with additional stratification by staff type (GP (including partners and salaried GPs, doctors in training, and medical students) or nurse (practice or district nurse)). Only non-administrative consultation (ie, limited to patient contact time) was included.

Primary care was costed based on staff time spent consulting patients by staff type (exclusive of overheads and training fees). All doctors were costed as salaried GPs, practice and district nurses, and allied health professionals were costed at band 5. Unit costs were taken from the Unit Costs of Health and Social Care for the financial year in which the consultation occurred.[38]

Secondary care

Inpatient admissions (all-cause and MASH-related), outpatient appointments (all-cause and MASH-related), and all-cause emergency care attendances PPPY, as well as their associated costs, were calculated. Day case admissions (ie, admission events where patients were admitted and discharged on the same day with zero nights spent in hospital) were excluded from calculations of cumulative length of stay, but they were included in the analysis of number/cost of inpatient admissions.

Secondary care inpatient activity was costed based on health resource groups using the NHS payment grouper for the financial year in which the HCRU event occurred and corresponding to the diagnoses and procedures recorded during admission. Diagnoses were based on ICD-10 codes and procedures were based on OPCS-4 codes. Where costs were missing, these were imputed using the median cost for similar events with costs (see

Table 1 Baseline sociodemographic and clinical characteristics

Characteristic	N=2696
Months of follow-up, mean (SD)	52.0 (32.5)
Age in years, median (IQR)	57.1 (46.4, 66.7)
Gender, n (%)	
Female	1468 (54.5)
Male	1228 (45.5)
Ethnicity, n (%)	
White	2256 (83.7)
South Asian	255 (9.5)
Black	73 (2.7)
Mixed or other	88 (3.3)
Unknown	24 (0.9)
Comorbidities, n (%)	
Obesity*	1206 (44.7)
Hypertension	1274 (47.3)
T2DM	1104 (40.9)
CVD	517 (19.2)
Metabolic syndrome†	448 (16.6)
Chronic kidney disease, stages 3–5	290 (10.8)
Polycystic ovary syndrome	94 (3.5)
DCSI‡ score, mean (SD)	1.6 (1.7)
Smoking status, n (%)	
Non-smoker	1437 (53.3)
Current smoker	202 (7.5)
Ex-smoker	746 (27.7)
Current or ex-smoker§	290 (10.8)
Unknown	21 (0.8)
Townsend deprivation quintile, n (%)	
1 (least deprived)	521 (19.3)
2	509 (18.9)
3	500 (18.5)
4	545 (20.2)
5 (most deprived)	619 (23.0)
Charlson Comorbidity Index score, n (%)	
0	132 (4.9)
1–2	1511 (56.0)
3–4	848 (31.5)
≥5	205 (7.6)
Elixhauser Comorbidity Index score, n (%)	
0	573 (21.3)
1–2	1048 (38.9)
3–4	667 (24.7)
≥5	408 (15.1)
Number of all-cause hospital admissions per patient in the year before index, mean (SD)	2.6 (6.9)
All-cause healthcare costs per patient in the year before index, mean (SD)	£4786 (£5874)

*BMI≥30 kg/m^2; this differs from the overweight/obese group, which included BMI≥25 kg/m^2.
†Defined as the presence of at least three of the following conditions: obesity based on BMI, diagnosed hypertension, lowered HDL-cholesterol (<40 mg/dL in men or <50 mg/dL in women), elevated triglycerides (>150 mg/dL), and T2DM.
‡Among those with evidence of diabetes (coded diagnosis or ≥2 prescriptions of an antidiabetic treatment (oral glucose-lowering drugs or insulin)).
§Defined where the status was ambiguous; it does not reflect the sum of the current and ex-smoker categories.
BMI, Body Mass Index; CVD, cardiovascular disease; DCSI, Diabetes Complications Severity Index; HDL, high-density lipoprotein; T2DM, type 2 diabetes mellitus.

online supplemental methods). Outpatient costs were determined by the specialty consulted and whether the visit was consultant-led. Emergency care costs were determined by the number and premium of the investigations/treatments provided.

Comparative cost analysis

To compare all-cause and MASH-related costs for each progressed severity state against those who did not progress during the study period, a comparative cost analysis was conducted. Differences in total all-cause and total MASH-related costs in natural units were estimated using a generalised linear model with a gamma distribution and identity link; a residual value was added to entries with zero costs (10^{-6}) to allow model convergence. Estimates of the incremental cost for those who progressed were adjusted for comorbidity using Charlson Comorbidity Index score and continuous follow-up time. Individual p values were calculated using Wald tests.

RESULTS

Study population

Overall, 2696 individual patients with ≥1 MASH-coded primary or secondary care record MASH diagnosis were included (online supplemental figure S1), and the mean duration of follow-up was approximately 4 years. The mean age at baseline was 56 years (SD: 15 years), slightly over half of patients (55%) were female, and most (84%) were of white ethnicities. Over 40% of patients had obesity (BMI≥30 kg/m^2), hypertension, and/or T2DM, and 19% had CVD. About half of patients were current smokers or ex-smokers (table 1). Baseline characteristics using other MASH definitions are reported in online supplemental table S5.

The incidence of MASH increased between 2011 and 2020, peaking in 2019, with an overall incidence of 4.7 per 100 000 person-years. By the end of the study period (2020), the prevalence was 26.6 per 100 000 people (online supplemental figure S2). Incidence and prevalence with other MASH definitions are reported in online supplemental figure S2.

The incidence of MASH was nine times higher among patients with T2DM (IRR: 9.46), twice higher among patients with CVD (IRR: 2.34) and five times higher among patients who were overweight or obese (IRR: 5.20), compared with patients without the corresponding comorbidity in each case (online supplemental table S6).

Clinical outcomes

Among patients with incident MASH between 2011 and 2020, the overall incidence of MACE was 165 per 1000 person-years (online supplemental table S7). Acute heart failure was the most frequent type of MACE.

In patients with MASH, the IRR for MACE was higher among patients with T2DM (1.85), overweight/obesity (1.10) or CVD (1.86) than among those without each condition (online supplemental table S8).

Approximately 13% of patients with MASH progressed to ESLD during follow-up. The median time to ESLD progression among those who progressed was 1.4 years. MASH progression to CC was the most frequent progression observed (8.6%), followed by DC (6.5%); less than 1% of patients progressed to HCC. Percentages do not add up to 13% because some patients had multiple progression events recorded (online supplemental table S9).

Primary care HCRU and costs

The mean number of all-cause primary care consultations was 16.8 PPPY. The mean number of consultations coded as MASH-related was 0.1 PPPY, all of which were GP consultations (table 2).

Mean annualised costs for all-cause consultations were £602 PPPY, including £354 for GP consultations and £101 for nurse appointments. Mean annualised costs for consultations coded as MASH-related were £3 PPPY,

Table 2 Primary care HCRU among patients with incident MASH in England (2011–2020)

	Total (n=2696)	T2DM		Overweight /obese* (n=1667)	CVD (n=517)	Progressed to cirrhosis	
		No (n=1592)	Yes (n=1104)			No (n=2347)	Yes (n=349)
Consultations PPP							
All-cause							
Mean (SD)	16.8 (13.1)	13.6 (11.2)	21.4 (14.3)	18.1 (13.3)	22.0 (15.3)	16.0 (12.6)	21.9 (15.2)
Median (IQR)	13.6 (8.0–21.9)	10.9 (6.3–18.2)	18.0 (11.8–27.0)	14.6 (9.1–23.4)	19.3 (11.5–28.5)	13.0 (7.4–21.2)	17.8 (12.0–26.9)
MASH-related†							
Mean (SD)	0.1 (0.6)	0.1 (0.4)	0.1 (0.8)	0.1 (0.7)	0.2 (1.3)	0.1 (0.3)	0.2 (1.4)
Median (IQR)	0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.1)
GP consultations PPPY							
All-cause							
Mean (SD)	10.3 (8.8)	8.6 (7.8)	12.6 (9.7)	10.7 (8.9)	13.6 (10.5)	9.7 (8.4)	13.7 (10.8)
Median (IQR)	8.0 (4.4–13.6)	6.7 (3.5–11.4)	10.2 (6.0–16.4)	8.6 (4.9–14.2)	11.4 (6.0–17.4)	7.5 (4.1–13.0)	10.8 (6.9–17.0)
MASH-related*							
Mean (SD)	0.1 (0.6)	0.1 (0.4)	0.1 (0.7)	0.1 (0.6)	0.2 (1.2)	0.0 (0.3)	0.2 (1.3)
Median (IQR)	0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.1)
Nurse appointments PPPY							
All-cause							
Mean (SD)	2.0 (3.6)	1.5 (2.8)	2.8 (4.3)	2.3 (3.8)	2.6 (4.8)	1.9 (3.5)	2.5 (3.8)
Median (IQR)	0.8 (0.0–2.5)	0.5 (0.0–1.8)	1.3 (0.0–3.8)	0.9 (0.0–2.9)	0.9 (0.0–3.3)	0.7 (0.0–2.4)	1.2 (0.1–3.1)
MASH-related*							
Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)
Median (IQR)	0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)

*Included overweight (BMI≥25 kg/m^2) and obese (BMI≥30 kg/m^2).
†Included a MACE, MASH or ESLD diagnosis.
BMI, Body Mass Index; CVD, cardiovascular disease; ESLD, end-stage liver disease; GP, general practitioner; HCRU, healthcare resource use; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; PPPY, per-patient per-year; T2DM, type 2 diabetes mellitus.

Table 3 Primary care costs among patients with incident MASH in England (2011–2020)

		T2DM		Overweight /obese*		Progressed to cirrhosis	
	Total (n=2696)	No (n=1592)	Yes (n=1104)	(n=1667)	CVD (n=517)	No (n=2347)	Yes (n=349)
Cost of consultations PPPY							
All-cause							
Mean (SD)	£602 (£475)	£487 (£406)	£768 (£517)	£649 (£482)	£785 (£549)	£575 (£459)	£779 (£539)
Median (IQR)	£488 (£280–£781)	£392 (£219–£652)	£642 (£415–£982)	£524 (£324–£831)	£670 (£404–£1031)	£465 (£262–£755)	£635 (£433–£966)
MASH-related*							
Mean (SD)	£3 (£20)	£2 (£14)	£3 (£26)	£3 (£23)	£7 (£43)	£2 (£11)	£8 (£47)
Median (IQR)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£5)
Cost of GP consultations PPPY							
All-cause							
Mean (SD)	£354 (£304)	£298 (£267)	£434 (£335)	£370 (£305)	£466 (£360)	£336 (£289)	£472 (£371)
Median (IQR)	£273 (£152–£469)	£233 (£120–£393)	£353 (£207–£562)	£296 (£168–£489)	£391 (£206–£601)	£258 (£140–£449)	£375 (£243–£590)
MASH-related*							
Mean (SD)	£2 (£19)	£2 (£13)	£3 (£24)	£2 (£21)	£6 (£40)	£2 (£10)	£7 (£44)
Median (IQR)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£4)
Cost of nurse appointments PPPY							
All-cause							
Mean (SD)	£101 (£181)	£74 (£146)	£139 (£216)	£114 (£194)	£131 (£240)	£97 (£181)	£122 (£182)
Median (IQR)	£37 (£0–£127)	£26 (£0–£93)	£61 (£0–£192)	£45 (£0–£144)	£46 (£0–£164)	£35 (£0–£120)	£60 (£6–£155)
MASH-related†							
Mean (SD)	£0 (£2)	£0 (£2)	£0 (£2)	£0 (£2)	£0 (£3)	£0 (£2)	£0 (£2)
Median (IQR)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)	£0 (£0–£0)

*Included overweight (BMI≥25 kg/m^2) and obese (BMI≥30 kg/m^2).
†Included a MACE, MASH or ESLD diagnosis.
BMI, Body Mass Index; CVD, cardiovascular disease; ESLD, end-stage liver disease; GP, general practitioner; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; PPPY, per-patient per-year; T2DM, type 2 diabetes mellitus.

including £2 for GP appointments and zero for nurse appointments (table 3).

Patients with MASH and T2DM had more all-cause consultations PPPY (mean: 21.4 vs 13.6 visits) and higher costs (£768 vs £487) than those who did not have T2DM. Patients who progressed to cirrhosis had more all-cause consultations PPPY (mean: 21.9 vs 16.0 visits) and higher costs (£779 vs £575) than those who did not progress. HCRU is summarised in table 2 and costs are summarised in table 3. Results with other MASH definitions are reported in online supplemental tables S10 and S11.

Secondary care HCRU and costs

On average, there were 1.3 all-cause and 0.2 MASH-related inpatient admissions PPPY. 74.9% were day case admissions, and the mean cumulative all-cause length of stay PPPY (excluding day case admissions) was 3.2 days. On average, there were 5.8 (all-cause) and 1.1 (MASH-related) outpatient appointments PPPY. The mean number of all-cause emergency care attendances was 0.5 PPPY (table 4).

Mean annualised costs for inpatient admissions PPPY were £1592 (all-cause) and £477 (MASH-related). Mean annualised costs for outpatient appointments were £702 (all-cause) and £152 (MASH-related). Emergency care attendances cost a mean of £78 PPPY (table 5).

There were more all-cause inpatient admissions and outpatient appointments for those with T2DM (1.8 and 7.3 PPPY, respectively) than for those without T2DM (1.0 and 4.8 PPPY, respectively). Similarly, patients who progressed to cirrhosis had approximately twice as many all-cause inpatient admissions and outpatient appointments (2.4 and 9.9 PPPY, respectively) than those who did not progress (1.1 and 5.2 PPPY, respectively) (table 4). Mean all-cause inpatient costs PPPY were higher in patients who had T2DM than in those who did not (£2227 vs £1151) and in patients who progressed to cirrhosis than in those who did not (£3620 vs £1290) (table 5). Emergency care costs showed the same pattern (tables 4–5). Secondary HCRU and cost results with other MASH definitions are reported in online supplemental tables S12 and S13.

Table 4 Secondary care HCRU among patients with incident MASH in England (2011–2020)

	Total (n=2696)	T2DM		Overweight /obese* (n=1667)	CVD (n=517)	Progressed to cirrhosis	
		No (n=1592)	Yes (n=1104)			No (n=2347)	Yes (n=349)
Total admissions PPPY							
All-cause							
Mean (SD)	1.3 (6.2)	1.0 (4.3)	1.8 (8.1)	1.3 (6.8)	2.4 (11.1)	1.1 (6.2)	2.4 (6.1)
Median (IQR)	0.3 (0.0–1.0)	0.2 (0.0–0.8)	0.4 (0.0–1.2)	0.3 (0.0–1.0)	0.7 (0.0–1.8)	0.2 (0.0–0.8)	1.0 (0.4–2.0)
MASH-related†							
Mean (SD)	0.2 (1.6)	0.1 (0.6)	0.4 (2.4)	0.2 (0.6)	0.4 (1.0)	0.1 (0.7)	1.0 (4.0)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.2)	0.0 (0.0–0.0)	0.0 (0.0–0.4)	0.0 (0.0–0.0)	0.3 (0.1–0.8)
Day case admissions, n (%)	9071 (74.9)	4252 (75.4)	4819 (74.4)	5779 (75.5)	2773 (73.0)	6697 (76.0)	2374 (71.8)
All-cause length of stay, days PPPY, mean (SD)	3.2 (14.9)	2.2 (12.4)	4.6 (17.9)	2.8 (13.1)	7.3 (24.4)	2.6 (14.3)	6.8 (18.4)
Outpatient appointments PPPY							
All-cause							
Mean (SD)	5.8 (7.8)	4.8 (6.4)	7.3 (9.3)	5.9 (7.3)	7.4 (9.6)	5.2 (7.2)	9.9 (10.3)
Median (IQR)	3.4 (1.1–7.6)	2.7 (0.7–6.2)	4.4 (1.7–9.3)	3.6 (1.2–8.0)	4.7 (1.6–10.0)	2.9 (0.9–6.6)	7.0 (3.9–12.2)
MASH-related‡							
Mean (SD)	1.1 (2.2)	1.0 (1.7)	1.3 (2.7)	1.1 (1.8)	1.4 (2.1)	0.9 (1.7)	2.2 (4.1)
Median (IQR)	0.4 (0.0–1.5)	0.3 (0.0–1.3)	0.6 (0.0–1.7)	0.5 (0.0–1.5)	0.6 (0.0–2.0)	0.3 (0.0–1.2)	1.5 (0.6–2.6)
Emergency care attendances PPPY							
Mean (SD)	0.5 (1.3)	0.4 (1.0)	0.7 (1.6)	0.5 (1.3)	0.9 (1.9)	0.5 (1.1)	1.0 (1.8)
Median (IQR)	0.0 (0.0–0.5)	0.0 (0.0–0.4)	0.1 (0.0–0.7)	0.0 (0.0–0.5)	0.2 (0.0–1.0)	0.0 (0.0–0.5)	0.4 (0.0–1.0)

*Included overweight (BMI≥25 kg/m^2) and obese (BMI≥30 kg/m^2).
†Included a MACE, MASH or ESLD diagnosis.
‡Outpatient appointments with gastroenterology, hepatology or cardiology.
BMI, Body Mass Index; CVD, cardiovascular disease; ESLD, end-stage liver disease; HCRU, healthcare resource use; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; PPPY, per-patient per-year; T2DM, type 2 diabetes mellitus.

Comparative cost analysis

Over the study follow-up period (mean: 4 years), all-cause and MASH-related costs were significantly higher for patients with MASH who progressed to CC or DC than for those who did not progress. Using those who did not progress as the reference, the estimated incremental all-cause adjusted costs were greater for those who progressed from MASH to DC (mean (95% CI): £18 376 (£12 874, £25 706)) than for those who progressed to CC (£7500 (£4075, £10 924)) (online supplemental table S14).

DISCUSSION

This study used routinely collected data from primary and secondary care settings in England to assess the characteristics of MASH as well as to describe MASH progression. Furthermore, the analysis described HCRU and healthcare costs among patients with incident MASH, both overall and based on progression and the presence or absence of key comorbidities.

We provide the first direct estimates of MASH incidence and prevalence in England. We found a sustained increase in MASH incidence over time (with the reduction in 2020 likely to be related to COVID-19). Notably, MASH prevalence in our study (equivalent to 0.02%–0.03%) was much lower than estimates (3%–5%) previously derived for the UK and other countries.[9] However, most prior estimates were based on Markov modelling[4 14] or feedback from clinical panels.[15] By contrast, our analysis was based on real-world data sources including the general population. Given the diagnostic challenges of MASH (particularly at early stages, where symptoms may be few or non-specific),[2] true MASH incidence and prevalence may have been underestimated in our study.

CVD was among the most prevalent comorbidities in this study population, in line with existing literature indicating a CVD prevalence of up to 20% among patients with MASH.[9] The percentage of patients with MASH and CVD in this study was much lower than in a previous report from the USA, where almost 70% of patients with MASH had CVD.[39] This difference may be explained by the different patient populations of both studies (USA vs England) in addition to the fact that patients with incident MASH in our study (as opposed to a prevalent MASH population) may not have had sufficient time to

Table 5 Secondary care costs among patients with incident MASH in England (2011–2020)

		T2DM		Overweight /obese*		Progressed to cirrhosis	
	Total (n=2696)	No (n=1592)	Yes (n=1104)	(n=1667)	CVD (n=517)	No (n=2347)	Yes (n=349)
Total admission† cost PPPY							
All-cause							
Mean (SD)	£1592 (£4420)	£1151 (£3058)	£2227 (£5793)	£1536 (£4112)	£3236 (£7323)	£1290 (£3934)	£3620 (£6497)
Median (IQR)	£217 (£0–£1255)	£154 (£0–£950)	£381 (£0–£1850)	£228 (£0–£1406)	£813 (£0–£3509)	£153 (£0–£1012)	£1153 (£314–£4063)
MASH-related‡							
Mean (SD)	£477 (£2394)	£278 (£1466)	£765 (£3281)	£477 (£2255)	£1199 (£4097)	£246 (£1630)	£2036 (£4867)
Median (IQR)	£0 (£0– £0)	£0 (£0–£0)	£0 (£0–£160)	£0 (£0–£0)	£0 (£0–£454)	£0 (£0–£0)	£327 (£80–£1871)
Outpatient appointment§ cost PPPY							
All-cause							
Mean (SD)	£702 (£986)	£583 (£837)	£872 (£1147)	£716 (£922)	£899 (£1165)	£625 (£897)	£1215 (£1343)
Median (IQR)	£399 (£128–£906)	£329 (£88–£740)	£520 (£205–£1140)	£425 (£154–£957)	£558 (£200–£1241)	£349 (£102–£785)	£841 (£445–£1522)
MASH-related¶							
Mean (SD)	£152 (£307)	£130 (£243)	£184 (£378)	£151 (£247)	£189 (£302)	£128 (£237)	£313 (£564)
Median (IQR)	£60 (£0–£200)	£40 (£0–£174)	£91 (£0–£238)	£65 (£0–£208)	£79 (£0–£270)	£40 (£0–£171)	£195 (£87–£390)
Emergency care attendance** cost PPPY							
Mean (SD)	£78 (£192)	£59 (£143)	£106 (£244)	£77 (£192)	£144 (£307)	£68 (£174)	£149 (£278)
Median (IQR)	£0 (£0–£74)	£0 (£0–£60)	£15 (£0–£103)	£0 (£0–£75)	£28 (£0–£142)	£0 (£0–£64)	£56 (£0–£158)

*Included overweight (BMI≥25 kg/m^2) and obese (BMI≥30 kg/m^2).
†The proportion of inpatient admissions with imputed costs was 10.2% (total), 9.8% (without T2DM), 10.5% (with T2DM), 8.6% (overweight/obese), 13.2% (CVD), 10.7% (not progressed to cirrhosis) and 8.7% (progressed to cirrhosis).
‡Included a MACE, MASH or ESLD diagnosis.
§The proportion of outpatient appointments with imputed costs was 27.0% (total), 28.5% (without T2DM), 25.3% (with T2DM), 26.7% (overweight/obese), 26.0% (CVD), 27.4% (not progressed to cirrhosis) and 25.6% (progressed to cirrhosis).
¶Outpatient appointments with gastroenterology, hepatology or cardiology.
**The proportion of emergency care attendances with imputed costs was 16.2% (total), 17.7% (without T2DM), 14.7% (with T2DM), 15.5% (overweight/obese), 14.8% (CVD), 16.8% (not progressed to cirrhosis) and 14.2% (progressed to cirrhosis).
BMI, Body Mass Index; CVD, cardiovascular disease; ESLD, end-stage liver disease; HCRU, healthcare resource use; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; PPPY, per-patient per-year; T2DM, type 2 diabetes mellitus.

develop CVD. Acute heart failure was the main incident MACE during the study period, which is consistent with recent evidence indicating a strong association between MASLD and the risk of developing heart failure.[40]

While most patients with MASH in our study were not observed to progress during their follow-up period, those who did progress (13%) did so with a median time to progression of 1.4 years. Our observed rates of progression to CC and DC did differ from previous analyses. In this study, about 8% of patients with MASH progressed to CC or DC over 4 years of study follow-up, which contrasts with a USA real-world study that first observed 1.4% of patients with MASLD/MASH to progress to CC and 27.6% to progress to DC over 8 years of study follow-up.[39] This discrepancy might be due to the different follow-up, methodology, and analysis population (USA vs England), but the fact that more patients were first observed with DC than with CC in the USA study is unsurprising given that CC is often asymptomatic.[11 12] Further, patients who progressed who only had the progression event recorded (and not MASH) would have been excluded from the current analysis. Rates of progression to HCC (0.4%–0.7%) in this analysis were consistent with the ~0.2% reported in the USA study.[39]

A key objective was to analyse HCRU and costs in primary and secondary care settings. Patients with MASH had an average of ~13 all-cause primary care consultations PPPY. This is over two times greater than the average number of all-staff consultations in primary care per patient in the UK in 2018–2019,[41] highlighting the substantial healthcare burden of MASH.[25] Primary care providers in England are funded on a per-capita basis; their funding was £160 per patient for 2020–2021,[42] but our estimates show that costs for primary care use in

MASH more than double this PPPY. Of note, all-cause costs PPPY were much higher than MASH-related costs; this likely reflects the fact that most events are not coded as related to MASH, even though they might be, due to multimorbidity. As cardiometabolic comorbidities may be both a cause and consequence of MASH,[2 16–21] all-cause costs provide a more comprehensive assessment.

Importantly, patients with MASH who also had T2DM had greater HCRU and costs than those who did not have diabetes, both in primary and secondary care settings. This finding is consistent with a recent literature review that found that costs were higher among patients with MASH who had comorbidities than among those who did not.[26] Specifically, our results suggest that concomitance of MASH and T2DM might result in more complications and require increased care, consistent with a recent US report that dual diagnosis with MASH and T2DM is associated with incremental costs.[43] Further, the subgroup of patients with both MASH and CVD had more appointments in primary care and admissions/attendances in secondary care than the overall sample of patients with MASH. This could be explained by the increased risk of cardiac complications in MASH, which has been shown to be independent of traditional cardiovascular risk factors and related to liver inflammation.[44] Together, these results stress the substantial HCRU and cost burden of cardiometabolic comorbidities. In line with this, current clinical guidelines for MASLD indicate that non-invasive tests (such as the fibrosis-4 index (FIB-4)) should be offered to individuals with cardiometabolic risk factors, and that screening of subpopulations with increased risk may be justified to enhance early diagnosis and management, which could prevent progression.[17]

Healthcare use for MASH focuses on managing complications of the disease,[26] and most associated costs are incurred in secondary care.[15 25] Notably, we quantified HCRU and costs among patients with MASH who progressed to cirrhosis, which were significantly higher than among those who did not. Our quantitative findings support previous suggestions that early-stage MASH may progress to more costly ESLD if left untreated,[15] and that healthcare costs are generally higher for patients with MASH/MASLD in advanced stages, including cirrhosis, than for those in earlier stages.[27 45 46] Our comparative cost analysis demonstrated a significant incremental cost for patients who progressed to CC or DC, which is consistent with a recent US cohort study where costs PPPY were also significantly higher for patients with MASH who progressed or developed cirrhosis during follow-up compared with those who did not.[47] Overall, this study highlights the need for improved diagnosis and management of early-stage MASH to reduce the economic burden of this disease. Therapies that slow progression may help alleviate this burden,[47] and non-invasive diagnostic tests may improve detection of cases and reduce healthcare costs.[48]

Strengths and limitations

This study analysed patients obtained from a large primary care dataset which captures data from practices across England and used longitudinal data from 2011 to 2020. CPRD Aurum is widely regarded as broadly representative of the UK population.[32] However, this analysis also had some limitations. MASH diagnosis is limited by the non-specificity of symptoms at early stages (if patients show any symptoms at all[15]), and incidence and prevalence were likely to be underestimated due to under-reporting in routinely collected healthcare datasets. Indeed, 80% of the population with MASH in the UK in 2018 was estimated to be undiagnosed.[15] To mitigate this issue, we explored multiple definitions for MASH that had limited overlap (such that the patients included in each definition differed); results were generally consistent across definitions. However, the use of different definitions was exploratory; each definition relied on coded diagnosis of MASH/MASLD; patients without a coded diagnosis were not included in the study. We cannot assess the level of missing diagnoses/patients or know the reasons for missing diagnoses, but those patients may have either mild disease presentation (missing diagnosis) or have rapidly progressed disease (resulting in end-ESLD diagnosis only).[15]

The follow-up period (mean ~4 years) might have been insufficient to derive true rates of progression, as the study population consisted of patients with incident MASH, some of whom may have progressed after the study period. Disease burden should be analysed further in a cohort of patients with MASH with sufficient time to observe progression.

The study did not include the use of a non-MASH comparator, and most analyses were descriptive so confounding factors could not be accounted for. Prescription costs (excluding high-cost drugs that would be categorised under OPCS-4 codes) could not be determined for secondary care. High healthcare use and costs may be accrued largely by patients with late-stage, progressed MASH. Productivity loss or economic inactivity due to illness and other economic costs were not estimated in this analysis; previous work suggests that, in patients with MASH, these are substantially higher than direct healthcare costs.[26 27]

Conclusion

This study provides an up-to-date descriptive epidemiological and health economic summary of the burden of MASH in England. MASH places a significant demand on healthcare resources. As its prevalence continues to grow, the economic burden of MASH will become increasingly important. Patients who had comorbidities like T2DM or who progressed to cirrhosis showed higher HCRU and costs than those who did not. While rates of progression to CC and DC were relatively low in the study population, those who progressed did so with a median time to progression of 1.4 years. Notably, HCRU and costs were significantly higher among patients with MASH

who progressed to these advanced disease stages. Therefore, efforts towards preventing disease progression by improving early-stage diagnosis and management, particularly in high-risk populations, could reduce healthcare burden.

Acknowledgements The authors thank Pablo Izquierdo, PhD, of PPD (a Thermo Fisher company) for providing medical writing support, which was funded by Madrigal Pharmaceuticals Inc. and conducted in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The authors thank Jesse Fishman, PhD, and Ivan Quetier, PhD, for their contributions to the manuscript.

Contributors JAD, HRB, CTR and SJC contributed to conceptualisation. JAD, HRB, CTR, SJC and YK contributed to methodology. HRB, CTR and SJC contributed to investigation. JAD and YK contributed to supervision, and JAD and HRB contributed to project administration. SJC contributed to formal analysis, software and data curation. All authors reviewed and edited the manuscript. YK (guarantor).

Funding This study was funded by Madrigal Pharmaceuticals Inc.

Competing interests JAD, HRB, CTR and SJC are employed by CorEvitas (part of Thermo Fisher Scientific), which was funded by Madrigal Pharmaceuticals Inc. to conduct this research. YK is an employee and holds stocks of Madrigal Pharmaceuticals Inc.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval CPRD has ethics approval from the Health Research Authority to support research using anonymised patient data. The CPRD Research Data Governance body approved the study protocol (23_002615) and authorised use of patient data for the study. Separate ethics approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. This study was conducted using data obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (MHRA) following study protocol approval by the CPRD Research Data Governance process. Access to CPRD and linked datasets must be requested by application via the CPRD RDG process. Therefore, the dataset cannot be made publicly available. Code lists used to define variables in the datasets and analysis scripts are available upon request.

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REFERENCES

1 Rinella ME. Examining the nomenclature change from NAFLD and NASH to MASLD and MASH. *Gastroenterol Hepatol (NY)* 2023;19:697–9.
2 Fraile JM, Palliyil S, Barelle C, *et al*. Non-Alcoholic Steatohepatitis (NASH) - a review of a crowded clinical landscape, driven by a complex disease. *Drug Des Devel Ther* 2021;15:3997–4009.
3 Yang Z, Wang L. Current, emerging, and potential therapies for non-alcoholic steatohepatitis. *Front Pharmacol* 2023;14.
4 Estes C, Razavi H, Loomba R, *et al*. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018;67:123–33.
5 Peng C, Stewart AG, Woodman OL, *et al*. Non-alcoholic steatohepatitis: a review of its mechanism, models and medical treatments. *Front Pharmacol* 2020;11:603926.
6 Zhu B, Chan S-L, Li J, *et al*. Non-alcoholic steatohepatitis pathogenesis, diagnosis, and treatment. *Front Cardiovasc Med* 2021;8:742382.
7 Alexander M, Loomis AK, Fairburn-Beech J, *et al*. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. *BMC Med* 2018;16:130.
8 Chalasani N, Younossi Z, Lavine JE, *et al*. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328–57.
9 Povsic M, Wong OY, Perry R, *et al*. A structured literature review of the epidemiology and disease burden of non-alcoholic steatohepatitis (NASH). *Adv Ther* 2019;36:1574–94.
10 Sheka AC, Adeyi O, Thompson J, *et al*. Nonalcoholic steatohepatitis: a review. *JAMA* 2020;323:1175–83.
11 Kumar R, Kumar S, Prakash SS. Compensated liver cirrhosis: Natural course and disease-modifying strategies. *World J Methodol* 2023;13:179–93.
12 Liu YB, Chen MK. Epidemiology of liver cirrhosis and associated complications: Current knowledge and future directions. *World J Gastroenterol* 2022;28:5910–30.
13 Wong RJ, Singal AK. Trends in liver disease etiology among adults awaiting liver transplantation in the United States, 2014-2019. *JAMA Netw Open* 2020;3:e1920294.
14 Estes C, Anstee QM, Arias-Loste MT, *et al*. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol* 2018;69:896–904.
15 Morgan A, Hartmanis S, Tsochatzis E, *et al*. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis (NASH) in the United Kingdom (UK) in 2018. *Eur J Health Econ* 2021;22:505–18.
16 Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. *Gastroenterology* 2012;142:711–25.
17 European Association for the Study of the Liver. EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024.
18 Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. *JHEP Rep* 2019;1:312–28.
19 Labenz C, Prochaska JH, Huber Y, *et al*. Cardiovascular risk categories in patients with nonalcoholic fatty liver disease and the role of low-density lipoprotein cholesterol. *Hepatol Commun* 2019;3:1472–81.
20 Le MH, Devaki P, Ha NB, *et al*. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. *PLoS One* 2017;12:e0173499.
21 Mantovani A, Petracca G, Beatrice G, *et al*. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut* 2021;70:962–9.
22 Day JW, Rosenberg WM. The enhanced liver fibrosis (ELF) test in diagnosis and management of liver fibrosis. *Br J Hosp Med (Lond)* 2018;79:694–9.
23 Fishman J, O'Connell T, Parrinello CM, *et al*. Prevalence of nonalcoholic steatohepatitis and associated fibrosis stages among us adults using imaging-based vs biomarker-based noninvasive tests. *J Health Econ Outcomes Res* 2024;11:32–43.
24 UK National Screening Committee. Guidance criteria for a population screening programme, 2022. Available: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme
25 Schattenberg JM, Lazarus JV, Newsome PN, *et al*. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: A cost-of-illness analysis. *Liver Int* 2021;41:1227–42.
26 Witkowski M, Moreno SI, Fernandes J, *et al*. The economic burden of non-alcoholic steatohepatitis: a systematic review. *Pharmacoeconomics* 2022;40:751–76.
27 O'Hara J, Finnegan A, Dhillon H, *et al*. Cost of non-alcoholic steatohepatitis in Europe and the USA: The GAIN study. *JHEP Rep* 2020;2:100142.

28 Younossi Z, Mangla KK, Chandramouli AS, *et al*. Total healthcare cost and characteristics associated with higher change in cost in patients with non-alcoholic steatohepatitis. *J Hepatol* 2022;77:S150–1.
29 Chen H, Zhan Y, Zhang J, *et al*. The global, regional, and national burden and trends of NAFLD in 204 countries and territories: an analysis from global burden of disease 2019. *JMIR Public Health Surveill* 2022;8:e34809.
30 Zhai M, Liu Z, Long J, *et al*. The incidence trends of liver cirrhosis caused by nonalcoholic steatohepatitis via the GBD study 2017. *Sci Rep* 2021;11:5195.
31 Khan MAB, Hashim MJ, King JK, *et al*. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. *J Epidemiol Glob Health* 2020;10:107–11.
32 Wolf A, Dedman D, Campbell J, *et al*. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol* 2019;48:1740–1740g.
33 CPRD Aurum. Clinical practice research datalink, Available: https://www.cprd.com/cprd-aurum-may-2022-dataset
34 Office for National Statistics. England population mid-year estimate 2024, Available: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/enpop/pop
35 NHS England Digital. Hospital Episode Statistics (HES), Available: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics
36 Herbert A, Wijlaars L, Zylbersztejn A, *et al*. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017;46:1093–1093i.
37 Adams J, Ryan V, White M. How accurate are townsend deprivation Scores as predictors of self-reported health? A comparison with individual level data. *J Public Health (Oxf)* 2005;27:101–6.
38 Jones KC, Weatherly H, Birch S, *et al*. Unit costs of health and social care 2022 manual. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2023.
39 Loomba R, Wong R, Fraysse J, *et al*. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. *Aliment Pharmacol Ther* 2020;51:1149–59.
40 Mantovani A, Byrne CD, Benfari G, *et al*. Risk of heart failure in patients with nonalcoholic fatty liver disease: JACC review topic of the week. *J Am Coll Cardiol* 2022;79:180–91.
41 Kontopantelis E, Panagioti M, Farragher T, *et al*. Consultation patterns and frequent attenders in UK primary care from 2000 to 2019: a retrospective cohort analysis of consultation events across 845 general practices. *BMJ Open* 2021;11:e054666.
42 NHS England Digital. NHS Payments to General Practice England, 2020/21, Available: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-payments-to-general-practice/england-2020-21
43 Fishman J, Tapper EB, Dodge S, *et al*. The incremental cost of non-alcoholic steatohepatitis and type 2 diabetes in the United States using real-world data. *Curr Med Res Opin* 2023;39:1425–9.
44 Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut* 2020;69:1691–705.
45 Tapper EB, Bonafede M, Fishman J, *et al*. Healthcare resource utilization and costs of care in the United States for patients with non-alcoholic steatohepatitis. *J Med Econ* 2023;26:348–56.
46 Wong RJ, Kachru N, Martinez DJ, *et al*. Real-world comorbidity burden, health care utilization, and costs of nonalcoholic steatohepatitis patients with advanced liver diseases. *J Clin Gastroenterol* 2021;55:891–902.
47 Fishman JC, Qian C, Kim Y, *et al*. Cost burden of cirrhosis and liver disease progression in metabolic dysfunction–associated steatohepatitis: A US cohort study. *JMCP* 2024;30:929–41.
48 Srivastava A, Jong S, Gola A, *et al*. Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease. *BMC Gastroenterol* 2019;19:122.