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Original article

Societal costs and survival of patients with biopsy-verified non-alcoholic steatohepatitis: Danish nationwide register-based study

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ABSTRACT

Introduction and Objectives: Studies on the societal burden of patients with biopsy-confirmed non-alcoholic fatty liver disease (NAFLD) are sparse. This study examined this question, comparing NAFLD with matched reference groups.

Materials and Methods: Nationwide Danish healthcare registers were used to include all patients (≥18 years) diagnosed with biopsy-verified NAFLD (1997–2021). Patients were classified as having simple steatosis or non-alcoholic steatohepatitis (NASH) with or without cirrhosis, and all matched with liver-disease free reference groups. Healthcare costs and labour market outcomes were compared from 5 years before to 11 years after diagnosis. Patients were followed for 25 years to analyse risk of disability insurance and death.

Results: 3,712 patients with biopsy-verified NASH (n = 1,030), simple steatosis (n = 1,540) or cirrhosis (n = 1,142) were identified. The average total costs in the year leading up to diagnosis was 4.1-fold higher for NASH patients than the reference group (EUR 6,318), 6.2-fold higher for cirrhosis patients and 3.1-fold higher for simple steatosis patients. In NASH, outpatient hospital contacts were responsible for 49 % of the excess costs (EUR 3,121). NASH patients had statistically significantly lower income than their reference group as early as five years before diagnosis until nine years after diagnosis, and markedly higher risk of becoming disability insurance recipients (HR: 4.37; 95 % CI: 3.17–6.02) and of death (HR: 2.42; 95 % CI: 1.80–3.25).

Conclusions: NASH, simple steatosis and cirrhosis are all associated with substantial costs for the individual and the society with excess healthcare costs and poorer labour market outcomes.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterised by hepatic steatosis (>5 % of liver cells containing fat vacuoles), diagnosed either by imaging or by histology, with no other causes for secondary hepatic fat accumulation [1]. NAFLD was recently redefined following international consensus and is now called metabolic dysfunction–associated steatotic liver disease (MASLD) [2]. This new MASLD definition covers individuals with steatotic liver disease who have at least one of five cardiometabolic risk factors. For the present study though, we have kept the NAFLD nomenclature because our data does not allow us to assess whether the patients we included have at least one of the cardiometabolic risk factors.

Non-alcoholic steatohepatitis (NASH) is a progressive form of NAFLD defined by the presence of histologically verified hepatic steatosis, inflammation, and ballooning with or without fibrosis [1]. The prevalence of NASH in the general population is believed to be 3–5 %, but it is underdiagnosed partly because there are no specific

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NPR, national patient register; T2D, type 2 diabetes; 95 % CI, 95 % confidence interval

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symptoms [3–5]. NASH entails an increased risk of cirrhosis, hepatocellular carcinoma (HCC), cardiovascular disease (CVD) and type 2 diabetes (T2D) [6,7].

The burden of disease associated with NASH may be substantial [5,8-17]. Two previous studies on the topic were based on survey data and health economic modelling [8,9] and one has included nationwide patient-level register data [18]. Other studies in France and Germany were based on patient databases, but both applied inclusion criteria based on ICD-10 codes without confirmation of the NASH diagnosis and applied a narrow healthcare sector perspective on costs, omitting labour market costs, and neither study estimated the excess (attributable) costs of NASH (i.e., added costs in the NASH patient population compared to a liver disease-free reference group) [10,11]. Furthermore, studies of patients with biopsy-confirmed NAFLD/NASH are sparse and include <700 subjects [12–14] or focused on a single outcome such as CVD [12,15]. A recent systematic literature review highlighted the need for more evidence on the excess costs of NASH to better understand the public health burden and healthcare planning needs [16].

The purpose of this population-based register study was to investigate the excess costs as well as labour market outcomes and survival in patients with biopsy-confirmed NASH diagnosed between 1997 and 2021 using routinely collected individual-level Danish register data. The Danish healthcare system is a single payer system, where all Danes have equal access to treatment and care, free at the point of consumption. To ensure a broad overview of the disease, the same outcomes were analysed for patients diagnosed with simple steatosis or cirrhosis as well as for matched reference groups without these diseases.

2. Materials and methods

2.1. Data sources

Since 1968, all Danish citizens have been assigned a unique personal identification number at birth or immigration, recorded in the Danish Civil Registration System [19]. The Civil Registration System records the date of birth, gender, vital status, region of residence and family relationships of all individuals. Moreover, it enables an identity-secure linkage of information across all the Danish national registers, which all cover the entire population. Patient-specific data were collected from the Danish National Patient Register (NPR), which contains information on all hospitalisations in Denmark since 1977 [20]. In addition, the NPR contains information on all outpatient activities, emergency room contacts and psychiatric ward contacts, including diagnoses and performed procedures, since 1995, and information on all tariffs and unit costs since 2002. The liver biopsy results of study participants were obtained from the Danish National Pathology Register, which contains information on all histological examinations conducted in Denmark since 1997 as well as subsets of examinations from most of the 26 Danish Pathology Departments since the 1970s [21]. Data on primary healthcare services and unit costs were retrieved from the Danish National Health Service Register for Primary Care [22]. Data on prescription medicine costs were collected from the Danish National Prescription Register [23]. Information regarding home care services was retrieved from the Register of Municipal Services. Data on income were retrieved from the Income Statistics Register [24]. Information regarding labour market affiliation was retrieved from the DREAM Database, which includes information on weekly labour market public transfer payments, i.e., unemployment benefits or disability payments, for all Danish citizens since 1991 [25]. Data on the highest attained education were retrieved from the Danish Education Register [26] and were defined by the highest attained education at the time of inclusion in the study. Information on death and migration was obtained from the Cause of Death Register and the Migration Register, respectively.

2.2. Study population

The study population was defined as patients ≥18 years diagnosed with biopsy confirmed NAFLD in the period between 1997 and 2021. First, all patients with one of the following ICD-10 codes (10th edition of the International Classification of Diseases) as primary diagnosis in the period between 1997 and 2021 were identified in the NPR: K74.0 (hepatic fibrosis), K74.6 (other or unspecified cirrhosis of liver), K75.8 (other specified inflammatory liver diseases), K76.0 (fatty change of liver, not elsewhere classified) or R74.0 (nonspecific elevation of levels of transaminase and lactic acid dehydrogenase).

Second, as the ICD-10 code R74.0 is a broad diagnosis, the mortality of patients identified with only R74.0 was compared with patients identified with any of the other ICD-10 codes in the inclusion criteria. This approach was made to ensure a homogeneous patient population, and that the R74.0 inclusion criterion did not bias the NASH population. As the mortality did not differ, patients with R74.0 were included in the study population.

Third, patients were excluded if they did not have a liver biopsy (Systemized Nomenclature of Medicine code (SNOMED) code T56) recorded in the Danish National Pathology Register within six months before or after the registration of any of the relevant ICD-10 codes. Then, individuals with possible alcohol-related liver disease were identified and excluded according to ICD-10 codes, procedure codes and ATC codes for prescription drugs suggesting alcohol-related diseases (see Supplementary Table 1).

Finally, NAFLD groups were identified based on liver biopsy findings. Patients with simple steatosis were identified with SNOMED code M50080 (fatty degeneration), M50084 (steatosis), M50085 (macrovesicular steatosis), M50086 (microvesicular steatosis), M55200 (fat deposition) or M55280 (fat infiltration). Patients with NASH were identified with SNOMED code M45400, indicating steatohepatitis. Cirrhosis patients were identified with the following SNOMED codes: M49500, M49501, M49503, M49504, M49505, M49506, M49510, M49514, M49516, M49520, M49524, M49526, M49527, M49528, M49530, or M49690 (see Supplementary Table 2). In case SNOMED codes for multiple groups were found in the same biopsy, patients were classified with the more severe disease (i.e., any form of cirrhosis > NASH > simple steatosis). The incidence date was defined as the latest of the following dates: the date of the first biopsy matching the inclusion criteria or the date of the first hospital visit with a relevant diagnosis code.

Each patient with NASH, simple steatosis or cirrhosis was matched with five suitable reference individuals from the Danish population with no history of liver disease or alcohol-induced disease at the time of case diagnosis. The reference individuals were matched exactly by sex, year of birth and region of residence in the incidence year, while education was matched by pairwise propensity score matching.

2.3. Outcome variables and unit costs

Outcomes for this study included the excess societal costs of patients with NASH compared to a reference group. Healthcare costs, lost wages, labour market exit through disability insurance, unemployment, long-term sick leave and survival were the included outcomes. Moreover, we included the excess use of healthcare services for the patients with NASH compared to the reference group. The same outcomes were analysed for patients diagnosed with simple steatosis or cirrhosis. The cost of illness was defined as the value of the resources that are expended or forgone as a result of a health problem or condition.

2.3.1. Healthcare costs

Healthcare costs comprised the costs in the primary healthcare sector, as well as the costs in the hospital care sector, including costs

of inpatient and outpatient visits at the hospital, estimated by fees and Diagnosis-Related Group tariffs, as well as Danish Outpatient Grouping System tariffs. Costs from both private and public clinics and hospitals were included. Furthermore, prescription medicine costs were included using pharmacy selling prices (including the Danish value-added tax of 25 %) and covering both the public reimbursement and the patient co-payment. Additionally, home care costs were estimated as the allocated hours of nursing and practical services multiplied by hourly wages of DKK 422 (2021 price level) [27]. Healthcare costs were calculated for all diseases in the patient groups (NASH, simple steatosis and cirrhosis) as well as in the corresponding liver-disease free reference populations. The difference in costs for the NASH group and the reference group was the excess costs associated with NASH.

2.3.2. Labour Market Outcomes

Labour market participation outcomes were defined as production loss, proxied by lost income, weeks spent unemployed and long-term sick-leave (sick leave lasting longer than four weeks) and labour market exit through disability insurance. In order to become a disability insurance recipient, a recommendation from a physician is required. The recommendation should only be made if the physician considers the individual to have a permanently reduced ability to work. Whether or not disability insurance is granted after such a recommendation is decided by the patient's municipality of residence.

Only individuals younger than 65 years were included in the analyses of labour market outcomes. The 65-year age limit corresponds to the normal retirement age at the beginning of the study period.

Income was defined as annual income observed in the Income Statistics Register. Weeks of long-term sick leave, unemployment, and disability insurance were extracted from the DREAM database.

The outcomes were calculated for all patient groups and the respective reference groups. The excess burden of disease was calculated as the difference between the patient group and the respective reference group.

All costs and earnings were inflated to the 2021 level according to the consumer price index and converted to euros (DKK 7.5 = EUR 1).

2.4. Survival

The start time of survival analyses was set at the index date, and the end date was the date of death from any cause. Participants were censored at emigration or at the end of follow-up (31 December 2021).

2.5. Statistical analyses

The study observed participants from five years before the first diagnosis of NASH, simple steatosis or cirrhosis (i.e., the index date) to 10 years after the index date. Outcomes described above were calculated for each period.

Continuous outcomes were estimated in a difference-in-difference model with variation in treatment timing setup [28]. The cost of primary care, prescription medicine, in- and outpatient hospital care, home care services or income was estimated by an ordinary least square regression model. In the model, time (defined as years in relation to the index date) interacted with group assignment (NASH, simple steatosis, cirrhosis and the respective reference groups) to estimate the mean of the outcome for each study period. Observations were weighted to balance the dataset in each period. Excess costs were calculated as the difference between patients and their respective reference groups for each year before and after the index date.

The mean excess costs and contacts per observed patient year were calculated for defined time intervals. The intervals started one year before the index date and included one, five and ten years of mean cost per observed patient year. The same outcomes were calculated for the number of inpatient hospital admissions, number of outpatient visits and hours of home care.

For the time-to-event outcomes (survival time and time to obtain disability insurance), hazard ratios (HR) were estimated using Cox proportional hazard regression models with NASH reference individuals as the reference group, adjusted for the following covariates: age, sex, region of residence and education. Furthermore, Kaplan −Meier survival curves were computed for all-cause mortality. Cumulative incidence curves were computed for disability insurance, considering death without disability insurance and reaching age 65 years as competing risks.

Data management and statistical analyses were carried out using R statistical software (version 3.4.4) [29] on Statistics Denmark's research computer via a remote server.

2.6. Ethical statement

According to Danish law, approval from the Danish Data Protection Agency, as well as ethical committee approval, is not required for registry-based studies and non-interventional studies.

3. Results

3.1. Study population

A flowchart of population identification is presented in Fig. 1. Between 1997 and 2021, after excluding people with diagnoses associated with alcohol use, 28,497 patients were identified with any of the relevant ICD-10 codes, and 7555 patients were identified in the pathology register with any of the relevant SNOMED codes. Of these patients, 4847 were identified with both a relevant diagnosis and biopsy results matching the inclusion criteria. However, 1068 patients were excluded because the ICD-10 diagnosis and the biopsy registration were not within six months, resulting in 3779 included patients. Among those, 1039 had NASH, 1559 had simple steatosis and 1181 had cirrhosis. After matching with respective reference populations, nine patients with NASH, 19 patients with simple steatosis and 39 patients with cirrhosis were excluded because of lack of reference individuals. Finally, 1030 patients with NASH, 1540 patients with simple steatosis and 1142 patients with cirrhosis were included in the analyses.

The median age at the index date in the NASH population and the simple steatosis population was 52 years and 50 years, respectively, while in the cirrhosis population, the median age was 63 years (Table 1). About 80 % of the patients with NASH were diagnosed in 2012 or later. Incidence for simple steatosis and cirrhosis was more evenly distributed over time. Approximately half of the NASH and simple steatosis populations were women, while women constituted 57 % of the cirrhosis population. NASH, non-alcoholic steatohepatitis; ICD-10 codes (10th edition of the International Classification of Diseases).

3.2. Healthcare resource use

Table 2 presents the resource utilisation relative to diagnosis date, both as nominal numbers, and as ratio relative to the reference population. Patients with NASH had 0.76 more inpatient hospital admissions on average than the reference group in the year before diagnosis, which is twice as many as the reference population. Patients with simple steatosis had 0.9 more admissions, while patients with cirrhosis had 2.96 more admissions.

For outpatient visits, patients with NASH or cirrhosis had comparable excess numbers of contacts, with 9.5 excess contacts, or 7.3 times as many as the reference population, for patients with NASH and 9.1 excess contacts, or 8.1 times as many contacts as the

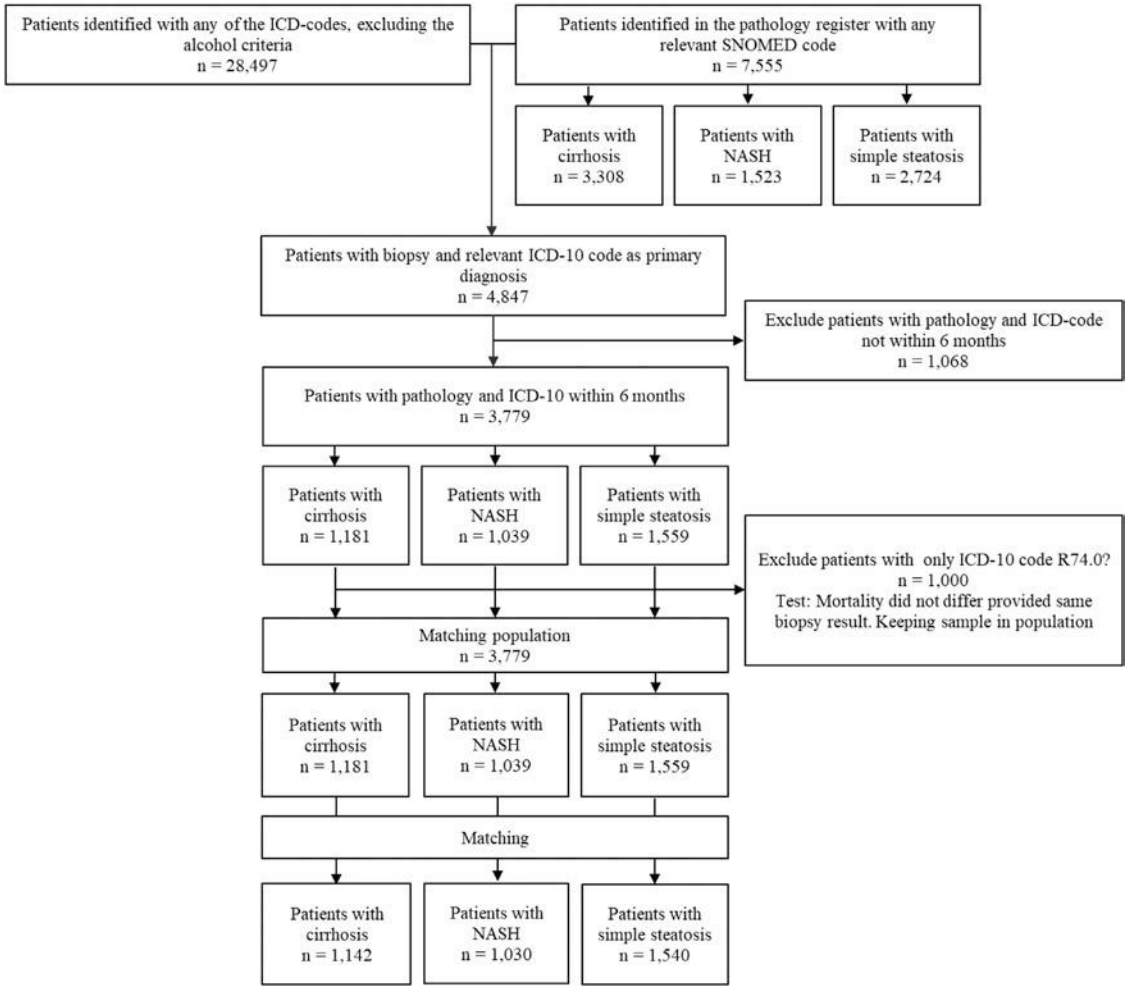

Fig. 1. Flowchart of study population.

reference groups for patients with cirrhosis. However, the mean excess visits per year over a 10-year period were lower for patients with NASH (6.44 NASH vs. 8.11 cirrhosis). Patients with simple steatosis had 7.06 excess contacts in the year leading up to the index date and 4.39 contacts per year over a 10-year period.

3.3. Cost of healthcare services

Figure 2 presents the average excess costs of in- and outpatient hospital care, primary care, prescription medicine and home care per individual per year in relation to index date for NASH, simple steatosis, and cirrhosis. The year leading up to the index date (year −1) was the year with the highest costs. In year −1, the excess costs of hospital admissions were EUR 2527, or 5.3 times higher than the reference population for patients with NASH, and EUR 2460 and EUR 8790 for patients with simple steatosis and cirrhosis, respectively (Fig. 2A and Table 2). The excess costs of outpatient visits were EUR 3121 in year −1 for patients with NASH, EUR 1646 and EUR 3584 for patients with simple steatosis and cirrhosis, respectively (Fig. 2B and Table 2). The excess costs of primary care were EUR 345 in year −1 for patients with NASH, and EUR 339 and EUR 223 for patients with simple steatosis and cirrhosis, respectively (Fig. 2C and Table 2). The excess cost of prescription medicine was highest for all groups in the year following the index date (year 0), and summed to EUR 333 for patients with NASH, and EUR 362 and EUR 467 for patients with simple steatosis and cirrhosis, respectively (Fig. 2D and Table 2). There were negligible differences (<EUR 150) in excess costs of home care in year −1 or year 0 (Fig. 2E and Table 2). Summing up the excess costs due to NASH, the average patient with NASH generated additional total healthcare costs of EUR 6318, or 4.1 times higher than the reference group, in the year leading up to the index date. The corresponding excess costs for patients with simple steatosis and cirrhosis were EUR 4716 and EUR 12,949, respectively (Table 2).

Table 2 also presents the costs referred to above and the mean excess costs per observed patient year for NASH, simple steatosis and cirrhosis in five- ("−1 to 3", i.e., from 1 year before to 3 years after the index date) and 10-year ("−1 to 8") windows starting the year before diagnosis. The mean annual excess cost of a NASH patient was EUR 4419 in the five-year perspective, and EUR 4325 in a ten-year perspective. The corresponding numbers for patients with simple steatosis were EUR 3162 and 3011, and for cirrhosis, EUR 10,220 and EUR 9183. Outpatient visit costs constituted 49% of the total costs for patients with NASH, hospital admission costs constituted 40%, while primary healthcare costs and prescription medicine costs each constituted 5% of the total costs. As the time perspective increased, prescription medicine costs constituted a larger share of the total costs.

3.4. Income loss

Patients with NASH, simple steatosis and cirrhosis had lower income than their respective reference groups throughout the entire study period (Fig. 3). The difference was significant in each year from year −5 to 8 ($p < 0.05$).

Table 1
Characteristics of the study population.

	Cirrhosis		NASH		Simple steatosis	
	Patient	Reference	Patient	Reference	Patient	Reference
N	1142	5682	1030	5119	1540	7650
Incidence						
Before 2002	217		33		354	
2002–2006	185		85		301	
2007–2011	171		92		181	
2012–2016	198		224		290	
2017–2021	371		596		414	
Age, median (IQR)	63 (54, 70)	63 (54, 70)	52 (39, 62)	52 (39, 62)	50 (37, 59)	50 (37, 59)
Sex						
Male	490 (43%)	2440 (43%)	500 (49%)	2481 (48%)	775 (50%)	3836 (50%)
Female	652 (57%)	3242 (57%)	530 (51%)	2638 (52%)	765 (50%)	3814 (50%)
Education						
Primary	427 (39%)	1796 (33%)	295 (29%)	1159 (23%)	446 (30%)	1931 (26%)
Higher primary	459 (42%)	2316 (42%	490 (46%)	2255 (45%)	677 (45%)	3398 (45%)
Bachelor	156 (14%)	1090 (20%)	181 (18%)	1220 (24%)	288 (19%)	1642 (22%)
Master or higher	48 (4.4%)	302 (5.5%)	68 (6.7%)	410 (8.1%)	91 (6.1%)	570 (7.6%)
Unknown	52	178	16	75	38	109
Region of residence						
North Denmark Region	104 (9.1%)	509 (9.0%)	88 (8.5%)	434 (8.5%)	127 (8.2%)	629 (8.2%)
Central Denmark Region	268 (23%)	1339 (24%)	243 (24%)	1206 (24%)	419 (27%)	2081 (27%)
Region of Southern Denmark	265 (23%)	1321 (23 %)	213 (21 %)	1062 (21 %)	370 (24 %)	1821 (24 %)
The Capital Region	363 (32%)	1806 (32 %)	396 (38 %)	1979 (39 %)	420 (27 %)	2100 (27 %)
Region Zealand	142 (12%)	707 (12%)	90 (8.7%)	438 (8.6%)	204 (13%)	1019 (13%)
Laboratory test						
ALAT - Abnormal	179 (15.67%)	68 (1.51%)	254 (24.66%)	116 (2.26%)	234 (15.19%)	88 (1.15%)
ALAT - Normal	513 (44.92%)	1280 (22.53%)	517 (50.19%)	1402 (27.39%)	447 (29.02%)	1206 (15.76%)
HbA1c - Abnormal	58 (5.08%)	137 (2.41%)	68 (6.60%)	112 (2.18%)	40 (2.6%)	118 (1.54%)
HbA1c - Normal	99 (8.67%)	802 (14.11%)	188 (18.25%)	933 (18.23%)	145 (9.42%)	796 (10.4%)
Comorbidity at baseline						
CKD (%)	31 (2.7%)	22 (7.4%)	10 (1%)	30 (0.9%)	16 (1%)	31 (0.7%)
CVD (%)	501 (43.9%)	612 (20.5%)	331 (32.1%)	522 (15.3%)	382 (24.8%)	608 (14.4%)
HCC (%)	33 (2.9 %)	0	<5	0	<5	0
Sleep apnoea (%)	34 (3%)	127 (4.3%)	117 (11.4%)	108 (3.2%)	100 (6.5%)	129 (3%)
T2D (%)	401 (35.1%)	113 (3.8%)	258 (25.1%)	136 (4%)	137 (11.2%)	122 (2.9%)

IQR, interquartile range; ALAT, alanine aminotransferase; CKD, chronic kidney disease ; CVD, cardiovascular disease; HCC, hepatocellular carcinoma, T2D, type 2 diabetes.

In year 0, the attributable average individual difference in income was EUR −8737 in patients with NASH, and EUR −10,160 and EUR −6757 in patients with cirrhosis and simple steatosis, respectively (Table 2) (Fig. 3).

3.5. Disability insurance

Patients with NASH had 4.37 (CI: 3.17–6.02) times higher hazard of receiving disability insurance compared to their reference group. Patients with simple steatosis had a 3.18 (CI: 2.3–3.89) times higher hazard of receiving disability insurance, while patients with cirrhosis had 7.21 (CI: 5.43–9.58) times higher hazard compared to their reference group. The 10-year risk of early retirement to receive disability insurance was 24% for patients with NASH vs. 4% for their reference group. For patients with simple steatosis, the corresponding risks were 15 % vs. 3.8%, while the risks were 20 % vs. 4.5% for patients with cirrhosis (Fig. 4).

3.6. Survival

Patients with NASH had 2.42 times higher mortality compared to their reference group (95 % CI: 1.80–3.25). Patients with simple steatosis had 1.84 times higher mortality compared to their reference group (95 % CI: 1.58–2.14). Patients with cirrhosis had the highest mortality, 7.49 times higher than their reference group (95 % CI: 3.45 −5.78). Fig. 5 presents the Kaplan–Meier survival curves for the NASH reference group and patients with NASH, simple steatosis cirrhosis.

4. Discussion

This study makes use of Danish high-quality individual-level national register-based data spanning 25 years. Our main findings were average excess costs of EUR 6318 among patients with NASH, or four times the costs of a matched reference group in the year leading up to the diagnosis. The five- and ten-year mean annual excess cost was EUR 4419 and EUR 4325, respectively. The primary cost driver was hospital care. Furthermore, patients with NASH had lower income than their reference individuals both before and after diagnosis, and they also had higher risks of early retirement and death. Thus, the burden of disease for the individual and for the national healthcare systems is substantial and the latter may increase in the future.

The findings are consistent with the natural history of NAFLD. As the disease progresses from simple steatosis to NASH to cirrhosis, mortality increases. Risk of early retirement increased from simple steatosis to NASH, while it is likely that the cirrhosis patients did not survive long enough or qualified for age related retirement before needing disability insurance. The progression of the disease is also reflected in the costs generated in the patient groups, and the resource utilization in the form of hospital contacts.

Table 2
Mean healthcare costs and utilisation per observed patient year in period year −1 to year 0, year −1 to year 3 and year −1 to year 8, in Euro.

	Cirrhosis				NASH				Simple steatosis			
	Patient	Reference	Excess	Ratio:Patient/ Reference	Patient	Reference	Excess	Ratio: Patient/ Reference	Patient	Reference	Excess	Ratio: Patient/ Reference
Mean cost per observed patient year in period												
Inpatient contacts												
−1 to 0	9463	673	8790	14.07	3111	585	2527	5.32	3244	783	2460	4.14
−1 to 3	7659	840	6819	9.12	1946	580	1367	3.36	1830	673	1158	2.72
−1 to 8	7092	1020	6070	6.95	2035	624	1411	3.26	1706	720	987	2.37
Outpatient contacts												
−1 to 0	4355	771	3584	5.65	3931	811	3121	4.85	2461	815	1646	3.02
−1 to 3	3480	783	2697	4.45	3139	834	2305	3.76	1957	672	1284	2.91
−1 to 8	3258	852	2405	3.82	2943	841	2102	3.50	1936	714	1222	2.71
GP cost												
−1 to 0	582	359	223	1.62	646	301	345	2.15	629	289	339	2.17
−1 to 3	544	379	165	1.44	547	302	244	1.81	549	300	250	1.83
−1 to 8	537	400	137	1.34	556	314	241	1.77	570	318	252	1.79
Drug cost												
−1 to 0	860	393	467	2.19	613	280	333	2.19	636	274	362	2.32
−1 to 3	1022	424	598	2.41	759	293	467	2.59	719	274	444	2.62
−1 to 8	1010	444	566	2.28	797	296	501	2.69	770	297	473	2.59
Home care												
−1 to 0	171	282	−115	0.61	83	66	−7	1.26	212	128	−90	1.65
−1 to 3	258	268	−59	0.96	103	55	36	1.88	145	93	26	1.57
−1 to 8	321	293	5	1.09	132	65	69	2.04	193	87	77	2.23
Total healthcare cost												
−1 to 0	15,431	2478	12,949	6.23	8384	2042	6318	4.11	7181	2291	4716	3.13
−1 to 3	12,962	2693	10,220	4.81	6495	2064	4419	3.15	5200	2012	3162	2.58
−1 to 8	12,217	3009	9183	4.06	6463	2140	4325	3.02	5176	2136	3011	2.42
Income												
−1 to 0	24,387	34,547	−10,160	0.71	29,630	38,367	−8737	0.77	29,561	36,319	−6757	0.81
−1 to 3	21,470	34,287	−12,817	0.63	28,516	38,908	−10,392	0.73	29,496	37,416	−7919	0.79
−1 to 8	20,704	34,272	−13,568	0.60	29,008	39,152	−10,143	0.74	30,555	38,374	−7818	0.80
Mean utilisation per observed patient year in period												
Inpatient contacts												
−1 to 0	3.09	0.84	2.96	3.68	1.53	0.77	0.76	1.99	1.77	0.84	0.93	2.11
−1 to 3	2.23	0.89	1.92	2.49	0.87	0.66	0.21	1.32	1.03	0.75	0.27	1.36
−1 to 8	2.03	0.98	1.64	2.08	0.85	0.68	0.17	1.25	0.92	0.80	0.12	1.15
Outpatient contacts												
−1 to 0	10.37	1.29	9.08	8.04	11.00	1.50	9.50	7.33	8.17	1.11	7.06	7.36
−1 to 3	10.23	1.24	8.98	8.23	8.82	1.76	7.06	5.00	6.03	1.03	5.01	5.87
−1 to 8	9.43	1.31	8.11	7.17	8.20	1.76	6.44	4.67	5.44	1.05	4.39	5.18
Hours of home care												
−1 to 0	3.04	5.01	−1.97	0.61	1.47	1.17	0.30	1.26	3.77	2.28	1.49	1.65
−1 to 3	4.59	4.77	−0.18	0.96	1.83	0.98	0.86	1.88	2.58	1.65	0.93	1.57
−1 to 8	5.71	5.21	0.49	1.09	2.35	1.15	1.20	2.04	3.43	1.54	1.89	2.23

In this study, the index date was set in association with a liver biopsy. However, most patients may have been followed for elevated liver enzymes or suffered from chronic comorbidities, sometimes for years, before a biopsy is conducted. This effect is evident in Figs. 2B, C and 3, where patients have more frequent contacts in both the primary and hospital sector and reduced income compared to the reference group in the years before diagnosis.

Most patients with NAFLD are diagnosed incidentally through screening tests or routine medical examinations in patients with obesity, type 2 diabetes or other cardiometabolic risk factors. General screening for NAFLD has not been implemented and a large proportion of patients remain undiagnosed, reflecting lack of awareness as well as the lack of specific tests. However, with the emergence of validated tests and the recognition that, in at least a subgroup of patients with NAFLD, progression may be prevented through lifestyle interventions, screening of at-risk patients should reduce the number who remain undiagnosed. The emergence of effective treatments may also increase incentives to ensure an early and accurate diagnosis. After NAFLD diagnosis, some patients are offered outpatient visits while others are sent back to their general practitioner. Patients with fibrosis or cirrhosis are the most likely to be offered follow-up outpatient visits, and those visits will be free of charge to the patient, like all other patient care in Danish hospitals.

The excess healthcare costs of NASH in the year before diagnosis (EUR 6318) correspond well with previous findings and with the observed higher comorbidity burden in the patient groups. A systematic review of the economic burden of NASH was recently published [16]. The authors highlighted the general scarcity of NASH-specific economic outcome data, yet they conclude that the annual direct costs of NASH in the year of diagnosis were EUR 4754, or EUR 7349 −9379 for patients with NASH and type 2 diabetes (2019 price level). Note that since there is no targeted treatment for NASH, all excess costs are due to treating associated comorbidities, including those that may be directly influenced by NASH (e.g., CVD and T2D). It is, therefore, reasonable that the estimates presented here are somewhere in between the cost estimates found in the review. Moreover, the EASL Lancet Liver Commission recently concluded that the largest potential savings due to liver disease-targeted policy changes would come from increased labour supply [17]. This aligns well with our finding that patients with NASH had significantly lower income as early as 5 years before and 8 years after the formal diagnosis, constituting a loss of about EUR 10,000 per patient (Table 2 and Fig. 3).

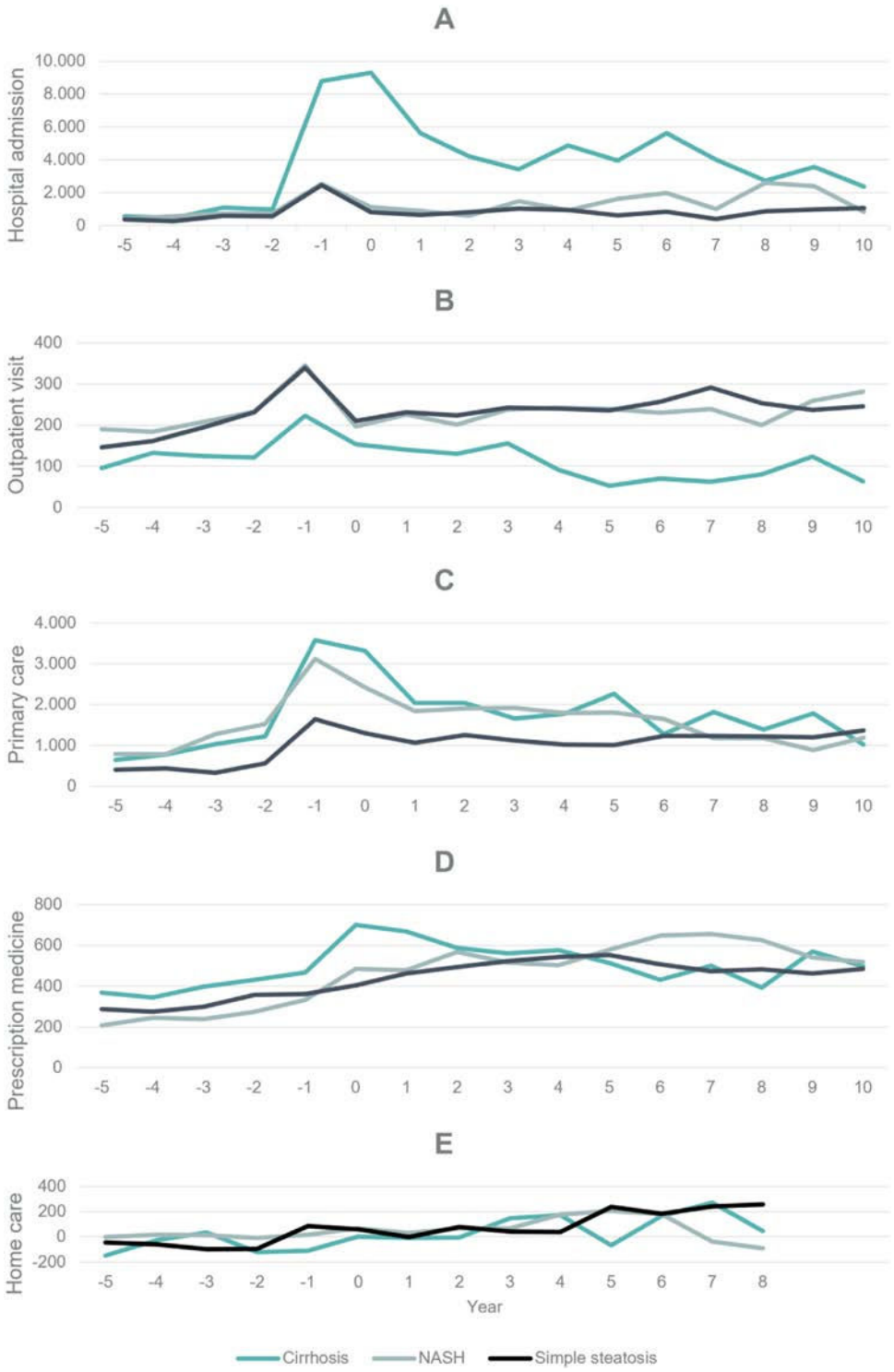

Fig. 2. Average annual individual healthcare costs before and after index date to cirrhosis, NASH and simple steatosis (excess costs), in Euro.
A Hospital admission costs, B Outpatient visit costs, C Primary healthcare costs, D Prescription medicine costs, E Home care costs.
Note: years on x-axis for all graphs in figure. Patient diagnosed at start of year 0.

Upon further investigation, we found that patients with NASH had comparable income to their reference group in year −24 to year −13, but significantly lower income in all periods from year −12 to year 8 ($p < 0.05$, Supplementary Fig. 1 present wage development for the two groups). This finding was outside the study scope and protocol but relevant for further research.

NAFLD is linked with an excessive calorie intake, high levels of refined carbohydrates, added sugars, and unhealthy fats. A nutritional pattern with increased consumption of processed foods and sugary drinks combined with a high intake of fructose increases the risk of NAFLD as well as obesity and insulin resistance. Conversely, a balanced and healthy diet plays a protective role against NAFLD.

Fig. 3. Average annual individual difference in income between cirrhosis, NASH and simple steatosis, in Euro.
Note: Patient diagnosed at start of year 0.

There is a well-known inverse relationship between obesity and income, indicating that people with a low income are more likely to develop obesity. Contributing factors include the fact that individuals with lower incomes may have to rely on inexpensive, calorie-dense, and less nutritious foods. Limited access to recreational facilities and outdoor spaces may be a contributing factor.

4.1. Strengths and limitations

This study was based on prospectively collected national register data. The Danish national register data is of high completeness and validity. Potential bias may include social reforms and changes in treatment recommendations that might have influenced the results. Further, there is possible bias related to time, as 80 % of patients with NASH were diagnosed in 2012 or later, and temporal changes in the diagnostic strategy (such as introduction of fibroscan in 2014) are likely to have occurred, reflecting the availability of diagnostic biomarkers, imaging techniques as well as increased awareness.

A limitation of this study is that the specific SNOMED code used to identify patients with NASH was only included in the Danish National Pathology Register from 2015 onwards. However, it is not uncommon to add new SNOMED codes to previously conducted biopsies. Note that this addition of codes to previous biopsies are usually only done for individuals who are still alive. Therefore, a possible bias is that only the healthiest patients were identified from the earliest years of the study. Such coding issues are common in register studies, and the authors are unable to conduct further validation of the register. However, Danish health and administrative registers are frequently used for research purposes and are highly reliable [30].

It was a limitation of our work that patients did not have follow-up liver biopsies or other examinations that would help us assess fibrosis progression or regression. Access to prospective individual patient data and serial data could have made it possible to account for increasing disease severity with time and allowed for the incorporation of the dynamic nature of NAFLD into the modelling framework. This could have included incorporation of Markov models or dynamic models using information about the natural disease progression. Our analyses, therefore, provide information about the prediction of the disease trajectory and consequences of NAFLD without clear identification of specific subgroups that subsequently improved or progressed. When considering the group of patients with NASH, it is likely that the costs would have been higher for patients who progressed to advanced fibrosis and cirrhosis, whereas costs would have been lower for patients who improved, e.g., after lifestyle interventions. Nevertheless, our data provide important information about a large group of patients with biopsy verified NAFLD and clearly show that the condition is associated with increased costs, both at the individual and societal level.

We did not have access to detailed information about the increased costs associated with NAFLD. Once the diagnosis is made, costs may reflect the need for continued medical monitoring and management including follow-up visits with laboratory tests and diagnostic imaging studies to evaluate disease progression as well as possible complications. Increased costs may also reflect the development of cardiovascular disease and type 2 diabetes, as both conditions occur with an increased frequency in NAFLD. Once NAFLD advances to cirrhosis or hepatocellular carcinoma, close follow-up and the use of expensive medical and surgical interventions, including liver transplantation, are necessary. Overall, the economic burden is likely to be associated with a multifaceted impact of NAFLD on the use of healthcare resources as well as loss of productivity due to long-term illness.

It should further be noted that for a metabolic disease with no distinct treatment recommendations, regional or medical practice variation might influence which patients receive biopsies. Adding to this, many patients with NASH are asymptomatic. All in all, we cannot rule out the possibility of bias in patient selection.

It is a limitation of our study that we cannot disentangle the effect of NAFLD from the effects of other diseases, conditions, and lifestyle factors that are more prevalent among patients with NAFLD than among the general population. Our reference individuals were matched on demographic variables, and we were unable to match diabetes, obesity, or other clinical characteristics. As it is, confounding persists, and we do not know the healthcare costs of patients with NAFLD without diabetes versus the costs of patients with NAFLD in addition to diabetes.

The consumption of alcohol is crucial in NAFLD. Although the primary drivers of NAFLD are obesity and insulin resistance, even a limited or moderate alcohol intake may worsen the progression of the disease, reflecting the central role of the liver in the metabolization of alcohol and the excess calories associated with alcohol consumption. Chronic alcohol intake can contribute to inflammation and oxidative stress, which are important drivers of NAFLD progression. Although we excluded patients with alcohol related co-morbidities and hospital contacts, the lack of detailed information means that we are unable to adjust for this important confounding variable. People with NAFLD are advised to abstain from alcohol consumption to mitigate the potential adverse effects on the liver, but not all will follow this advice. On the other hand, we compared the NAFLD patients with matched reference groups of citizens not having NAFLD, and one could argue that these may have the same alcohol consumption —at least, there is no reason to expect a higher alcohol consumption

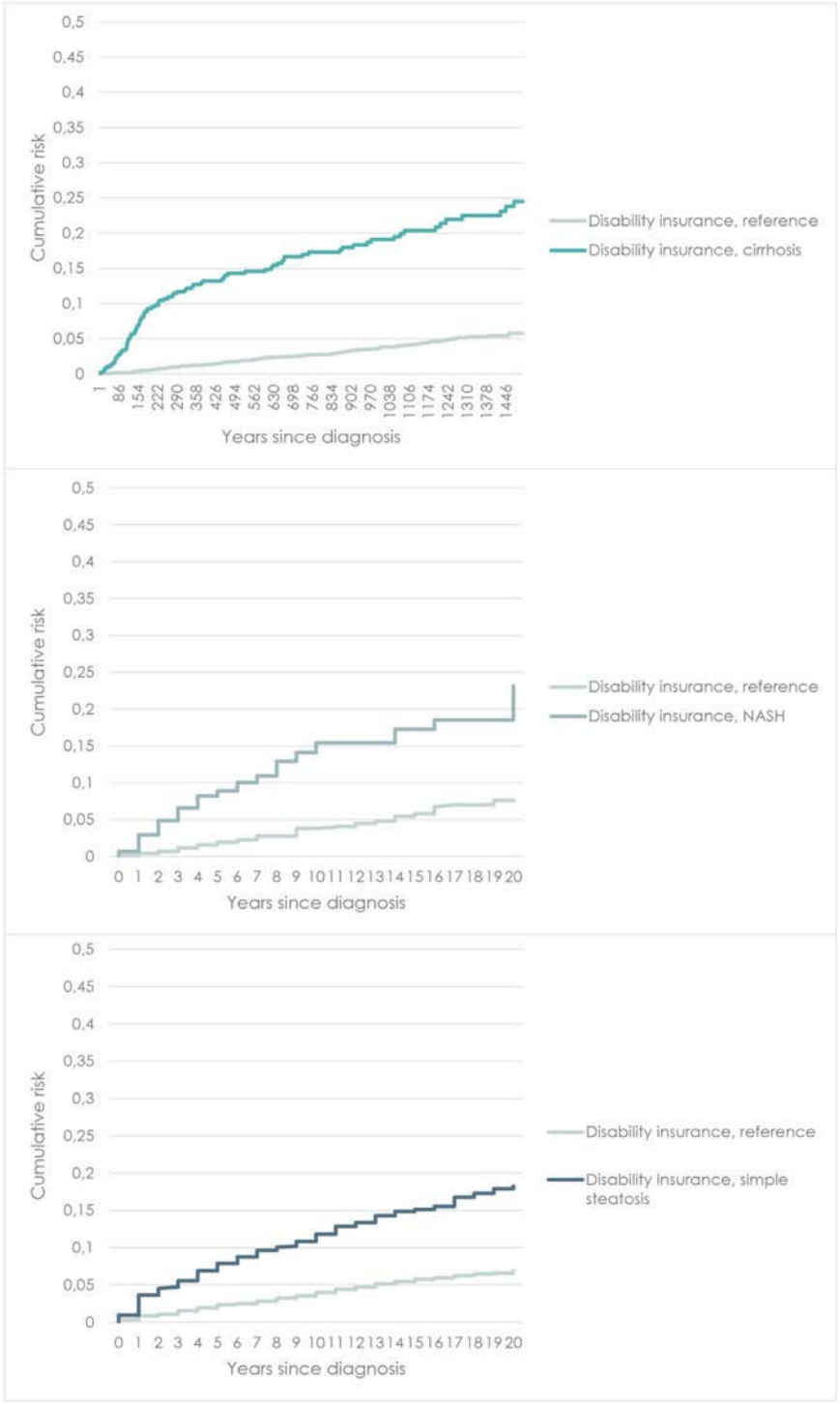

Fig. 4. Competing risk plots, demonstrating cumulative risk of death, disability insurance, and retirement. Censoring at emigration or end of study.

among the NAFLD patients. In the end, though, it is a limitation that we were unable to adjust for intake of alcohol in the study.

Lifestyle factors such as smoking, diet and physical activity were not accounted for in the analysis. Individuals observed with an alcohol-related diagnosis, prescription or procedure were excluded, yet that is not necessarily a complete exclusion criterion, and the alcohol intake of included patients is not known. In addition, it should be noted that patients with cirrhosis were included regardless of aetiology and the excess mortality and costs in this group could therefore be influenced by alcohol overuse.

5. Conclusions

The excess direct and indirect costs due to NAFLD diseases, i.e., simple steatosis and NASH with or without cirrhosis, were substantial, and the risk of death was significantly increased compared to the general population. In the case of NASH, the average patient-generated excess healthcare costs were EUR 6318 in the year leading up to diagnosis, and the primary cost driver was hospital care costs. Similar results were found for cirrhosis and simple steatosis, with the highest excess healthcare costs found for cirrhosis. Moreover, patients with NAFLD had significantly lower income compared to the general

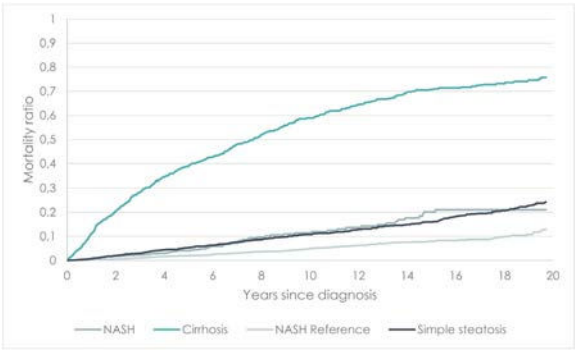

Fig. 5. Kaplan–Meier curves for survival among patients with cirrhosis, NASH, simple steatosis, and references for the NASH population.

population, both before and after the diagnosis, and significantly higher risk of receiving disability insurance.

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Authors contributions

All co-authors contributed equally and substantially to the conceptualization, methodology and validation of results in the study. Jan Håkon Rudolfsen were responsible for the data curation and conducted the formal analysis of the data. Peter Jepsen, Lise Lotte Gluud, Henning Grønbæk, Majken K. Jensen, and Mogens Vyberg were all responsible for supervision in the study in their roles as experts in the field of NAFLD/ MASLD. Anne Bloch Thomsen and Pfizer secured the funding acquisition for the study, and Peter Bo Poulsen were responsible for the project administration. Jan Håkon Rudolfsen and Jens Olsen were both responsible for the writing of the original manuscript, whereas the rest of the co-authors reviewed and edited the original manuscript. All co-authors have approved the final manuscript.

Conflicts of interest

Jan Håkon Rudolfsen and Jens Olsen are employees at EY, which is a paid vendor of Pfizer Denmark Aps. Lise Lotte Gluud, Henning Grønbæk, Majken K. Jensen, Mogens Vyberg and Peter Jepsen were paid by Pfizer Denmark Aps. for their work as members of the Study Steering Committee. Peter Bo Poulsen, Nanna Hovelsø, Nikolaj Ture Gregersen and Anne Bloch Thomsen are employees of Pfizer Denmark Aps. Peter Bo Poulsen, Nanna Hovelsø, and Anne Bloch Thomsen owns shares from Pfizer Inc. The authors report no other conflicts of interest in this work. Full ICMJE Disclosure forms are submitted for each co-author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2024.101285.

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