Risk of Severe Infection in Patients With Biopsy-proven Nonalcoholic Fatty Liver Disease – A Population-based Cohort Study

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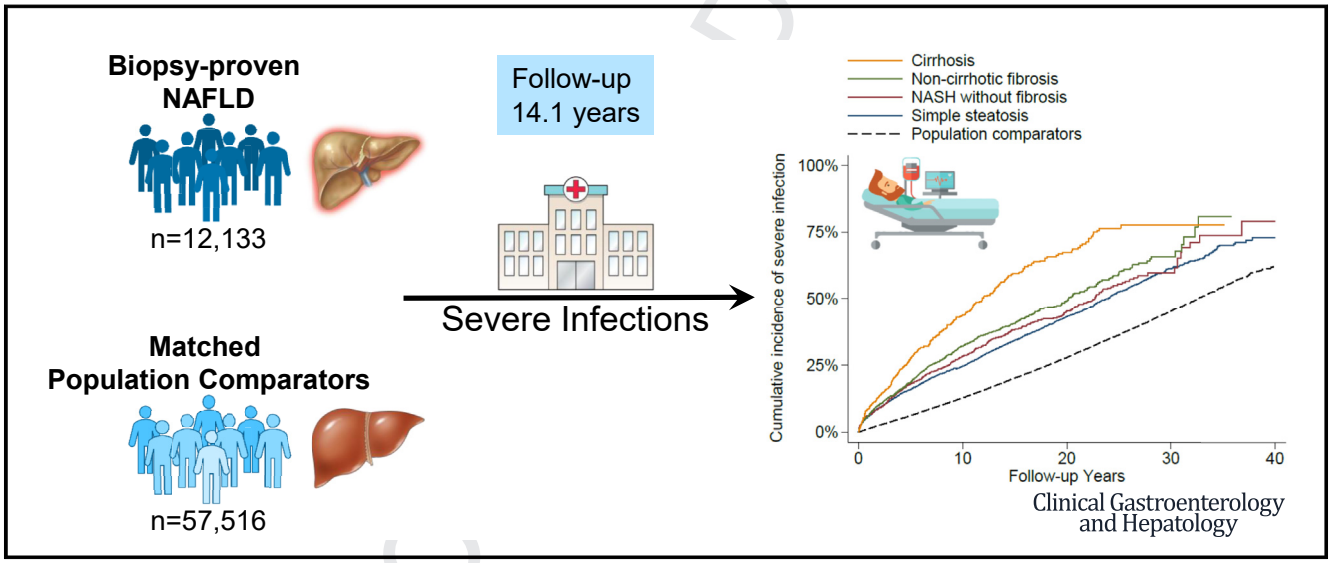

BACKGROUND & AIMS: **It has been suggested that patients with nonalcoholic fatty liver disease (NAFLD) might be at increased risk of severe infections, but large-scale data from cohorts with biopsy-proven NAFLD are lacking.**

METHODS: **Population-based cohort study including all Swedish adults with histologically confirmed NAFLD (n = 12,133) from 1969 to 2017. NAFLD was defined as simple steatosis (n = 8232), nonfibrotic steatohepatitis (n = 1378), noncirrhotic fibrosis (n = 1845), and cirrhosis (n = 678). Patients were matched to ≤5 population comparators (n = 57,516) by age, sex, calendar year, and county. Swedish national registers were used to ascertain incident severe infections requiring hospital admission. Multivariable adjusted Cox regression was used to estimate hazard ratios in NAFLD and histopathological subgroups.**

Abbreviations used in this paper: aHR, adjusted hazard ratio; CI, confidence interval; ESPRESSO, Epidemiology Strengthened by histoPathology Reports in Sweden; ICD, International Classification of Diseases; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPV, positive predictive value; PY, person-year.

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RESULTS: **Over a median of 14.1 years, 4517 (37.2%) patients with NAFLD vs 15,075 (26.2%) comparators were hospitalized for severe infections. Patients with NAFLD had higher incidence of severe infections than comparators (32.3 vs. 17.0/1000 person-years; adjusted hazard ratio [aHR], 1.71; 95% confidence interval, 1.63−1.79). The most frequent infections were respiratory (13.8/1000 person-years) and urinary tract infections (11.4/1000 person-years). The absolute risk difference at 20 years after NAFLD diagnosis was 17.3%, equal to one extra severe infection in every 6 patients with NAFLD. Risk of infection increased with worsening histological severity of NAFLD (simple steatosis [aHR, 1.64], nonfibrotic steatohepatitis [aHR, 1.84], noncirrhotic fibrosis [aHR, 1.77], and cirrhosis [aHR, 2.32]. Also compared with their full siblings, patients with NAFLD were at increased risk of severe infections (aHR, 1.54; 95% confidence interval, 1.40–1.70).**

CONCLUSIONS: **Patients with biopsy-proven NAFLD were at significantly higher risk of incident severe infection requiring hospitalization both compared with the general population and compared with siblings. Excess risk was evident across all stages of NAFLD and increased with worsening disease severity.**

Keywords: Hospitalization; Immune System; Infection; Metabolic Syndrome; Nonalcoholic Fatty Liver Disease.

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Nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent chronic liver disease worldwide, and in some countries, it is projected to become the leading cause for end-stage liver disease and liver transplantation.[1,2] Despite the increasing burden of the disease, there is still no approved pharmacological treatment for NAFLD.[3]

NAFLD is increasingly viewed as a multifaceted disease affecting multiple organ systems,[4] with increased risk of developing impaired metabolism,[5,6] cancer,[7,8] cardiovascular disease,[9,10] chronic kidney disease,[11,12] and there is increasing data suggesting a dysregulation of the immune system.[13] In NAFLD, it has been shown that the immune function is deranged at various levels,[14] resulting in impaired function of hepatic natural killer cells,[15] Kupffer cells,[16] neutrophils,[17] and their complex interactions, which taken together may result in an increased susceptibility towards various viral, bacterial, and fungal infections.

Although patients with NAFLD share metabolic risk factors that are known to increase the risk for infection,[18] it has been suggested that NAFLD itself may independently predispose the patient to severe infections.[19]

However, evidence on the interconnection of NAFLD with the risk of infections is scarce. Hence, in the current nationwide matched cohort study of patients with biopsy-confirmed NAFLD, we aimed to assess the risk of incident severe infections.

Material and Methods

This was a population-based matched cohort study using the Epidemiology Strengthened by histoPathology Reports in Sweden (ESPRESSO) cohort,[20] which encompasses all liver histopathology data from all 28 Swedish pathology departments from 1965 to 2016. Using the individual's personal identity number, which is unique to all Swedish residents, these data were linked to validated, nationwide registers including data on demographics, comorbidities, prescribed medications, incident cancers, and causes of death.[21-24] ESPRESSO was approved by the Stockholm Regional Ethics Committee, which waived informed consent due to its registry-based design. This study followed the Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) reporting guideline.[25]

Patient Population

We included all adult patients aged ≥18 years in whom liver biopsy was performed between 1969 and 2017, confirming the diagnosis of NAFLD without any other competing liver disease. Using a validated International Classification of Diseases (ICD) algorithm in accordance with international expert panel consensus recommendations,[26] we excluded patients with prior alcohol abuse/misuse, recorded other etiology of acute or chronic liver disease, liver transplantation, or emigration from Sweden before the liver biopsy date (ie, the index date) (Supplementary Table 1). This methodology has previously been shown to yield a positive predictive value (PPV) for NAFLD of 92%.[27] Detailed definitions on NAFLD ascertainment and histological subcategories can be found in the Supplementary Methods.

Each patient with NAFLD was matched to 5 general population comparators (direct matching with replacement) without recorded NAFLD, according to age at index date, sex, calendar year of index date, and county of residence.

Primary and Secondary Outcomes

The primary endpoint was incident severe infection requiring hospital admission. Secondary outcomes

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included 7 prespecified infection subgroups: sepsis; respiratory tract (including ear-nose-throat); gastrointestinal except for bacterial peritonitis; bacterial peritonitis (including spontaneous bacterial peritonitis); urogenital; musculoskeletal, skin, and soft tissue; and other infection outcomes. The definitions of all infection outcomes are summarized in Supplementary Table 3. We used the inpatient part of the National Patient Register to identify infections requiring hospitalization including both primary and contributing diagnoses.

Statistical Analysis

Using Cox proportional hazard models, we estimated multivariable adjusted hazard ratios (aHRs) for 2 models: Model 1 was conditioned on matching factors (age, sex, county of residence, and calendar year of biopsy). In the second model, we further adjusted for education, country of birth, and relevant baseline clinical comorbidities: diabetes, obesity, dyslipidemia, hypertension, number of hospitalizations in the year preceding the index date, and chronic obstructive pulmonary disease (Supplementary Table 4). Furthermore, we performed a competing risk regression, considering all-cause mortality and liver transplantation as competing risks.[28,29] Patients were followed from date of biopsy or index date until first incident severe infection, death, liver transplantation, emigration, or end of follow-up (Dec 31, 2019), whichever came first. We constructed Kaplan-Meier failure curves to present cumulative risk and to compute absolute risk differences with 95% confidence intervals (CIs) at 20 years of follow-up.

We conducted several sensitivity analyses to test the robustness of our results. First, we reanalyzed the data using both inpatient and specialized outpatient care diagnoses in the definition of severe infection. Second, in an attempt to increase the specificity of our primary outcome, we evaluated severe infections only as main diagnosis of the respective hospitalization. Third, we repeated the analyses restricting the cohort to patients with NAFLD and reference individuals without any parameters of the metabolic syndrome at baseline. Fourth, to account for incident diagnoses of diabetes mellitus or alcohol abuse/misuse during the long follow-up period, we additionally performed a sensitivity analysis adding these diagnoses as time-varying covariates. Fifth, because a major histological scoring system of NAFLD was introduced in 2005,[30] we conducted an analysis restricted to individuals diagnosed with NAFLD since that year. Sixth, we excluded any individual who experienced a severe infection in the last 3 years before the start of follow-up. Seventh, to minimize potential bias related to the primary indication for liver biopsy, we performed a sensitivity analysis restricting the cohort to patients with histologically defined NAFLD, with simple steatosis as the comparator. Eighth, we repeated the primary and secondary analyses after rematching the patients with NAFLD to their full siblings without NAFLD. Nineth, we calculated the "E-value,"[31] which estimates the effect an unmeasured confounder needs to have to reduce an observed risk ratio to 1.

Statistical analyses were conducted using SAS (version 9.4) and Stata (version 17.0). A 2-sided $P < .05$ was considered statistically significant.

What You Need to Know

Background

Nonalcoholic fatty liver disease (NAFLD) is a disorder affecting multiple organ systems. It has been suggested that NAFLD may lead to an impaired immune function and increase susceptibility towards infections.

Findings

In this nationwide matched cohort study including 12,133 individuals with biopsy-proven NAFLD and 57,516 general population comparators, NAFLD was associated with a higher risk for severe infections requiring hospitalization.

Implications for patient care

Our findings highlight that NAFLD is a multisystem disorder that warrants reversal at all stages. Prevention of infections should become a major public health effort to tackle NAFLD-associated morbidity.

Results

Patient Characteristics

The baseline characteristics of all patients and comparators are summarized in Table 1. In total, 12,133 patients with histologically confirmed NAFLD and 57,516 matched population comparators were included (Figure 1). Among patients with NAFLD, the average age at index biopsy was 54 years, and 54.8% were male. The majority of patients had simple steatosis (n = 8232; 67.8%), whereas 1378 patients (11.4%) had nonalcoholic steatohepatitis (NASH) without fibrosis, 1845 patients (15.2%) had NASH with noncirrhotic fibrosis, and 678 (5.6%) were diagnosed with cirrhosis. Patients with NAFLD were more likely than comparators to have a diagnosis of diabetes mellitus, hypertension, and dyslipidemia (Table 1). Median follow-up was 9.7 years (interquartile range [IQR], 3.3–18.9 years) among patients with NAFLD, and 14.9 years (IQR, 7.7–22.3 years) among population comparators.

Overall Incidence of Severe Infections

Overall, we documented 4517 incident severe infections among patients with NAFLD (32.3 per 1000

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Table 1. Baseline Characteristics of Patients With NAFLD and Matched Population Comparators

Characteristic	Reference population (n = 57,516)	All NAFLD (n = 12,133)	Simple steatosis (n = 8232)	NASH without fibrosis (n = 1378)	Noncirrhotic fibrosis (n = 1845)	Cirrhosis (n = 678)
Sex						
Women	26,394 (45.9)	5484 (45.2)	3664 (44.5)	669 (48.5)	849 (46.0)	302 (44.5)
Men	31,122 (54.1)	6649 (54.8)	4568 (55.5)	709 (51.5)	996 (54.0)	376 (55.5)
Age, years						
Mean	54.0 (14.8)	54.2 (14.8)	53.2 (15.0)	54.2 (15.2)	56.1 (14.0)	60.2 (11.7)
Median	55.4 (43.5–65.2)	55.6 (43.7–65.4)	54.2 (42.2–64.6)	55.4 (43.5–65.6)	57.8 (47.4–66.5)	62.4 (53.7–68.2)
Range, min–max	18.0–92.5	18.1–91.9	18.1–91.8	18.2–91.8	18.1–91.9	18.7–85.0
Age categories, years						
18–<40	11,238 (19.5)	2344 (19.3)	1753 (21.3)	272 (19.7)	274 (14.9)	45 (6.6)
40–<60	24,531 (42.7)	5153 (42.5)	3558 (43.2)	581 (42.2)	769 (41.7)	245 (36.1)
≥60	21,747 (37.8)	4636 (38.2)	2921 (35.5)	525 (38.1)	802 (43.5)	388 (57.2)
Country of birth						
Nordic country	52,711 (91.6)	10,919 (90.0)	7469 (90.7)	1223 (88.8)	1611 (87.3)	616 (90.9)
Other	4801 (8.3)	1214 (10.0)	763 (9.3)	155 (11.2)	234 (12.7)	62 (9.1)
Missing	4 (0.0)	0	0	0	0	0
Level of education using highest level of education in parents when missing, years[a]						
≤9	19,182 (33.4)	4176 (34.4)	2819 (34.2)	467 (33.9)	610 (33.1)	280 (41.3)
10–12	22,651 (39.4)	5003 (41.2)	3334 (40.5)	596 (43.3)	807 (43.7)	266 (39.2)
>12	13,452 (23.4)	2302 (19.0)	1583 (19.2)	256 (18.6)	380 (20.6)	83 (12.2)
Missing	2231 (3.9)	652 (5.4)	496 (6.0)	59 (4.3)	48 (2.6)	49 (7.2)
Start year of follow-up						
1969–1980	1271 (2.2)	258 (2.1)	214 (2.6)	22 (1.6)	8 (0.4)	14 (2.1)
1981–1990	11,592 (20.2)	2388 (19.7)	1861 (22.6)	193 (14.0)	195 (10.6)	139 (20.5)
1991–2000	22,877 (39.8)	4767 (39.3)	3487 (42.4)	508 (36.9)	511 (27.7)	261 (38.5)
2001–2010	14,682 (25.5)	3151 (26.0)	1867 (22.7)	433 (31.4)	682 (37.0)	169 (24.9)
2011–2017	7094 (12.3)	1569 (12.9)	803 (9.8)	222 (16.1)	449 (24.3)	95 (14.0)
Disease history ever before start of follow-up						
Diabetes	1928 (3.4)	1524 (12.6)	795 (9.7)	187 (13.6)	358 (19.4)	184 (27.1)
Obesity	251 (0.4)	542 (4.5)	318 (3.9)	66 (4.8)	111 (6.0)	47 (6.9)
Dyslipidemia	2711 (4.7)	968 (8.0)	492 (6.0)	131 (9.5)	265 (14.4)	80 (11.8)
Hypertension	4468 (7.8)	2187 (18.0)	1224 (14.9)	273 (19.8)	497 (26.9)	193 (28.5)
Number of components of metabolic syndrome						
0	51,208 (89.0)	8726 (71.9)	6255 (76.0)	969 (70.3)	1107 (60.0)	395 (58.3)
1	3896 (6.8)	2119 (17.5)	1339 (16.3)	240 (17.4)	398 (21.6)	142 (20.9)
2	1818 (3.2)	840 (6.9)	449 (5.5)	101 (7.3)	213 (11.5)	77 (11.4)
3	550 (1.0)	370 (3.0)	164 (2.0)	57 (4.1)	101 (5.5)	48 (7.1)
4	44 (0.1)	78 (0.6)	25 (0.3)	11 (0.8)	26 (1.4)	16 (2.4)
COPD (age ≥40 years)	365 (0.6)	206 (1.7)	127 (1.5)	26 (1.9)	34 (1.8)	19 (2.8)
Any infection within 3 years prior to baseline	1421 (2.5)	1132 (9.3)	742 (9.0)	148 (10.7)	181 (9.8)	61 (9.0)
Any infection within 90 days prior to baseline	180 (0.3)	459 (3.8)	307 (3.7)	59 (4.3)	68 (3.7)	25 (3.7)

Note: All variables reported as mean (standard deviation), median (interquartile range), or number (%),
Note: For definitions of the NAFLD histological groups and all covariates, see the Supplementary Appendix.
COPD, Chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
[a]Education categories based on compulsory school, high school, and college (Supplementary Appendix). Education level was recorded beginning in 1990, thus data presented are for persons with index dates on or after January 1, 1990. For all other analyses, persons with index dates prior to 1990 had education level recorded as missing.

person-years [PYs]) and 15,075 incident severe infections among population comparators (17.0 per 1000 PYs) (Table 2 and Supplementary Table 5). The 20-year cumulative incidence rate for severe infection was 45.0% for patients with NAFLD compared with 27.8% among population comparators, resulting in an absolute risk

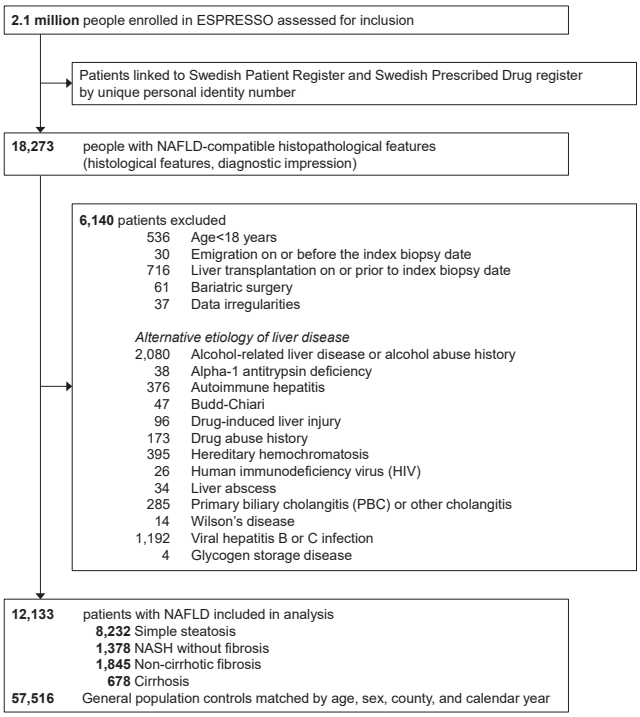

Figure 1. Study profile. ESPRESSO, Epidemiology strengthened by histopathology reports in Sweden; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

difference of 17.3% (95% CI, 16.8–17.7) (Supplementary Table 6), equal to one extra severe incident infection in every 6 patients with NAFLD.

After multivariable adjustment, the aHR for incident overall severe infections was 1.71 (95% CI, 1.63–1.79) in the fully adjusted model. This significant, positive association was slightly more pronounced among women (aHR, 1.84; 95% CI, 1.72–1.97) compared with men (aHR, 1.60; 95% CI, 1.51–1.71; $P_{\text{heterogeneity}} < .001$) (Table 2). The risk for severe infection was highest in the year after histologic NAFLD diagnosis (aHR, 2.77; 95% CI, 2.43–3.16) but remained statistically significantly increased even after ten years (aHR, 1.61; 95% CI, 1.49–1.73). Rates of incident severe infection increased progressively with worsening NAFLD histological severity ($P_{\text{trend}} < .001$) (Table 2). Compared with reference individuals, the incidence rate differences and corresponding aHRs with simple steatosis, NASH without fibrosis, non-cirrhotic fibrosis, and cirrhosis were 13.4 per 1,000 PYs (aHR, 1.64; 95% CI, 1.55–1.73), 15.6 per 1000 PYs (aHR, 1.84; 95% CI, 1.60–2.12), 20.9 per 1000 PYs (aHR, 1.77; 95% CI, 1.56–2.00), and 38.1 per 1000 PYs (aHR, 2.32; 95% CI, 1.92–2.82), respectively (Table 2; Figure 2; Supplementary Figure 1). When repeating the analyses using a competing risk regression with all-cause mortality and liver transplantation as competing risks, the finding of significantly increased risk of severe infection remained robust (aHR, 1.40 [95% CI, 1.35-1.45]). Although there was a stepwise increase in incidence rates with age, relative risks due to NAFLD were unchanged ($P_{\text{heterogeneity}} > .05$).

Incidence of Specific Infections

The overall distribution of specific severe infections leading to hospitalization were identical between patients with NAFLD and general population comparators. The most frequent cause of infection were respiratory tract infections with 13.8 per 1000 PYs among patients with NAFLD and 8.2 per 1000 PYs in reference individuals, yielding a rate difference of 5.6 per 1000 PYs (aHR, 1.52; 95% CI, 1.42–1.62) (Table 3). The second most common cause of severe infections was urogenital tract infections with 11.4 per 1000 PYs in patients with NAFLD compared with 6.7 per 1000 PYs in comparators, followed by infections classified as "other subtype" (definition in Supplementary Table 3). Sepsis was diagnosed as the fourth leading cause of severe infection, and the risk was more than doubled in patients with NAFLD (6.2 per 1000 PYs) compared with population comparators (2.5 per 1000 PYs), yielding an aHR of 2.16 (95% CI, 1.95–2.39) (Table 3).

Incidence of Severe Infections in NAFLD-only Subgroups

After restricting the cohort to patients with biopsy-confirmed NAFLD, and using simple steatosis as the comparator, we observed a similar, gradually increasing relationship between worsening NAFLD histological severity and increased overall incidence of severe infections (Table 4). Compared with simple steatosis, the overall risk for severe infections was comparable in patients with NASH without fibrosis (29.9 vs. 33.3 per 1000 PYs) with an aHR of 1.04 (95% CI, 0.94–1.15). However, patients with noncirrhotic fibrosis and cirrhosis were at significantly higher risk of severe infections with 37.9 events per 1000 PYs (aHR, 1.13; 95% CI, 1.04–1.23) and 59.5 per 1000 PYs (aHR, 1.37; 95% CI, 1.21–1.55), respectively.

Sensitivity Analyses

The findings were robust across all sensitivity analyses. When analyzing both inpatient and specialized outpatient care, NAFLD remained significantly and positively associated with any infection (aHR, 1.65; 95% CI, 1.59–1.72) and for all cause-specific infection subtypes (Supplementary Table 12). This was also confirmed when only the main diagnosis of the inpatient cases was used to define the primary outcome (aHR 1.67; 95% CI, 1.58–1.77) (Supplementary Table 13). When we restricted the cohort to patients with NAFLD and reference individuals without any parameters of the metabolic syndrome at baseline, the aHR for severe infections was 1.76 (95% CI, 1.67−1.86), confirming that even among those without any baseline features of the metabolic syndrome, NAFLD was an independent risk factor for the development of severe infections. Furthermore,

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Table 2. Risk of Any Infection Overall and by Subgroups in Patients With NAFLD and Matched General Population Comparators

	N (%)		N events		Incidence rate (95% CI) per 1000 PY			
Group	NAFLD	Comparators	NAFLD	Comparators	NAFLD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Overall	12,133 (100)	57,516 (100)	4517 (37.2)	15,075 (26.2)	32.3 (31.3–33.2)	17.0 (16.7–17.2)	2.46 (2.37–2.56)	1.71 (1.63–1.79)
Follow–up, y								
<1	12,133 (100)	57,516 (100)	726 (6.0)	769 (1.3)	65.9 (61.1–70.7)	13.6 (12.6–14.5)	5.10 (4.58–5.67)	2.77 (2.43–3.16)
1–<5	10,449 (86.1)	56,050 (97.5)	1134 (10.9)	2671 (4.8)	30.7 (28.9–32.4)	12.6 (12.1–13.1)	2.85 (2.64–3.08)	1.81 (1.65–1.98)
5–<10	8135 (67.0)	48,964 (85.1)	892 (11.0)	3151 (6.4)	25.6 (23.9–27.2)	14.5 (14.0–15.0)	2.14 (1.97–2.32)	1.60 (1.44–1.76)
≥10	5953 (49.1)	38,264 (66.5)	1765 (29.6)	8484 (22.2)	31.0 (29.5–32.4)	21.1 (20.7–21.6)	1.92 (1.80–2.04)	1.61 (1.49–1.73)
≥1y	10,449 (86.1)	56,050 (97.5)	3791 (36.3)	14,306 (25.5)	29.4 (28.5–30.3)	17.2 (16.9–17.5)	2.21 (2.12–2.30)	1.62 (1.54–1.71)
Sex								
Women	5484 (45.2)	26,394 (45.9)	2253 (41.1)	7279 (27.6)	40.0 (38.3–41.6)	18.6 (18.1–19.0)	2.80 (2.65–2.96)	1.84 (1.72–1.97)
Men	6649 (54.8)	31,122 (54.1)	2264 (34.1)	7796 (25.0)	27.1 (26.0–28.2)	15.7 (15.4–16.1)	2.19 (2.07–2.31)	1.60 (1.51–1.71)
Age, y								
18–<40	2344 (19.3)	11,238 (19.5)	562 (24.0)	1110 (9.9)	14.3 (13.1–15.4)	5.1 (4.8–5.4)	3.03 (2.72–3.38)	2.02 (1.75–2.32)
40–<60	5153 (42.5)	24,531 (42.7)	1941 (37.7)	5665 (23.1)	27.7 (26.4–28.9)	13.0 (12.7–13.4)	2.47 (2.33–2.62)	1.72 (1.60–1.85)
≥60	4636 (38.2)	21,747 (37.8)	2014 (43.4)	8300 (38.2)	66.4 (63.5–69.3)	35.4 (34.6–36.1)	2.31 (2.18–2.45)	1.58 (1.48–1.70)
Year								
1969–1980	258 (2.1)	1271 (2.2)	121 (46.9)	571 (44.9)	35.9 (29.5–42.4)	21.3 (19.5–23.0)	2.52 (1.98–3.21)	1.95 (1.46–2.61)
1981–1990	2388 (19.7)	11,592 (20.2)	1147 (48.0)	4486 (38.7)	32.2 (30.4–34.1)	18.8 (18.2–19.3)	2.34 (2.16–2.52)	1.75 (1.59–1.92)
1991–2000	4767 (39.3)	22,877 (39.8)	1857 (39.0)	6687 (29.2)	28.2 (26.9–29.5)	16.4 (16.0–16.8)	2.17 (2.05–2.31)	1.51 (1.40–1.62)
2001–2010	3151 (26.0)	14,682 (25.5)	1018 (32.3)	2767 (18.8)	35.8 (33.6–38.0)	15.8 (15.2–16.4)	2.75 (2.54–2.99)	1.91 (1.74–2.10)
2011–2017	1569 (12.9)	7094 (12.3)	374 (23.8)	564 (8.0)	55.9 (50.3–61.6)	14.3 (13.2–15.5)	4.58 (3.95–5.30)	2.57 (2.13–3.10)
Year – infection during the first 5y of follow–up								
1969–1980	258 (2.1)	1271 (2.2)	31 (12.0)	53 (4.2)	30.9 (20.0–41.8)	8.8 (6.4–11.2)	3.78 (2.36–6.07)	1.94 (1.05–3.55)
1981–1990	2388 (19.7)	11,592 (20.2)	334 (14.0)	635 (5.5)	34.6 (30.9–38.4)	11.6 (10.7–12.6)	3.52 (3.05–4.06)	2.20 (1.85–2.62)
1991–2000	4767 (39.3)	22,877 (39.8)	608 (12.8)	1290 (5.6)	31.0 (28.5–33.5)	12.0 (11.3–12.6)	2.86 (2.58–3.17)	1.70 (1.50–1.93)
2001–2010	3151 (26.0)	14,682 (25.5)	544 (17.3)	1014 (6.9)	44.5 (40.7–48.2)	14.7 (13.8–15.6)	3.51 (3.13–3.94)	2.21 (1.93–2.53)
2011–2014	1051 (8.7)	4782 (8.3)	232 (22.1)	323 (6.8)	59.5 (51.8–67.1)	14.3 (12.8–15.9)	4.80 (3.97–5.79)	2.48 (1.94–3.16)
Country of birth								
Nordic	10,919 (90.0)	52,711 (91.6)	4168 (38.2)	14,217 (27.0)	33.2 (32.2–34.2)	17.3 (17.0–17.5)	2.47 (2.37–2.57)	1.72 (1.63–1.80)
Other	1214 (10.0)	4801 (8.3)	349 (28.7)	858 (17.9)	24.5 (21.9–27.0)	13.4 (12.5–14.3)	3.14 (2.24–4.39)	2.29 (1.50–3.51)
Education, y[c]								
≤9	4176 (34.4)	19,182 (33.4)	1878 (45.0)	7061 (36.8)	41.1 (39.2–43.0)	24.0 (23.5–24.6)	2.12 (1.96–2.29)	1.47 (1.35–1.61)
10–12	5003 (41.2)	22,651 (39.4)	1783 (35.6)	5083 (22.4)	28.3 (27.0–29.6)	13.8 (13.4–14.2)	2.72 (2.51–2.95)	1.96 (1.78–2.16)
>12	2302 (19.0)	13,452 (23.4)	660 (28.7)	2216 (16.5)	22.7 (20.9–24.4)	10.5 (10.1–11.0)	2.71 (2.31–3.19)	1.66 (1.36–2.02)
NAFLD subgroup								
Simple steatosis	8232 (67.8)	39,244 (68.2)	3086 (37.5)	10,576 (26.9)	29.9 (28.9–31.0)	16.5 (16.2–16.8)	2.33 (2.22–2.44)	1.64 (1.55–1.73)
NASH without fibrosis	1378 (11.4)	6476 (11.3)	483 (35.1)	1638 (25.3)	33.3 (30.3–36.3)	17.7 (16.8–18.5)	2.53 (2.25–2.84)	1.84 (1.60–2.12)
Noncirrhotic fibrosis	1845 (15.2)	8592 (14.9)	659 (35.7)	1859 (21.6)	37.9 (35.0–40.8)	17.0 (16.3–17.8)	2.71 (2.45–3.00)	1.77 (1.56–2.00)
Cirrhosis	678 (5.6)	3204 (5.6)	289 (42.6)	1002 (31.3)	59.5 (52.7–66.4)	21.8 (20.5–23.2)	3.67 (3.12–4.32)	2.32 (1.92–2.82)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-years.

[a]Conditioned on matching set (age, sex, county, and calendar period).

[b]Conditioned on matching set and further adjusted for education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

[c]Patients with missing data on education are not presented in this table.

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accounting for time-varying diagnoses of diabetes mellitus and/or alcohol abuse/misuse during the follow-up period, we found similarly increased risks for incident severe infections among patients with NAFLD (aHR, 1.44; 95% CI, 1.37–1.51). When the follow-up was restricted to infections occurring at least 1 year after NAFLD diagnosis, the risk was consistently increased (aHR, 1.62; 95% CI, 1.54–1.71) (Table 2). Furthermore, our results were again confirmed in 2 additional sensitivity analyses: after restriction of the cohort to NAFLD cases diagnosed since 2005 (aHR, 2.19; 95% CI, 1.96–2.44) and after exclusion of any individual with severe infection in the last 3 years before start of follow-up (aHR, 1.75; 95% CI, 1.66–1.84).

After restricting the cohort to patients with NAFLD with $\geq$1 full sibling without recorded NAFLD and then comparing each patient with NAFLD with his or her full sibling(s), our findings were consistent showing an increased risk of severe infections for patients with NAFLD (aHR, 1.54; 95% CI, 1.40–1.70) (Supplementary Tables 7–11 and Supplementary Figures 2–3).

Using the E-value approach,[31] we found that the minimum strength of an unmeasured confounder, to the observed aHR of 1.71 to be reduced to 1, would need to be 2.8-fold to both the exposure (NAFLD) and to the outcome (any infection).

Discussion

In this nationwide, population-based cohort study including more than 12,000 patients with biopsy-proven NAFLD, we found that NAFLD was associated with a 71% higher hazard and a 20-year absolute excess risk of 17.3% for severe infections requiring hospital admission compared with matched individuals from the general population. A significantly elevated risk of severe infection was already present among patients with simple steatosis, further increased with noncirrhotic fibrosis, and was highest in patients with cirrhosis.

Previous studies have shown that advanced fibrosis is the most important histologic determinant of adverse clinical outcomes in patients with NASH, especially for survival.[27,32-35] In our study, even simple steatosis without the existence of neither steatohepatitis nor fibrosis already significantly increased the risk of incident severe infection, independent from age. While the existence of NASH did not additionally increase the risk, the development of fibrosis and ultimately cirrhosis led to a further increase in the risk of severe infection. In fact, there is strong evidence that patients with cirrhosis encounter a significantly higher risk of infections and that infections are often the reason for decompensation, acute-on-chronic liver failure, intensive care unit admission, and eventually liver-related mortality.[36,37] Paradoxically, although patients with cirrhosis exhibit a hyperinflammatory state, they experience at the same time a profound immunoparesis and increased susceptibility to bacterial infection.[38] In cirrhosis, spontaneous bacterial peritonitis due to bacterial translocation is traditionally believed to be the predominant site of infection, due to intestinal dysmotility, increased gastric pH, and increased intestinal permeability, as well as dysbiosis of the gut microbiome.[39] However, recent studies have challenged this view.[40,41] In our study, patients with NAFLD exhibited the same spectrum of infection sites as compared with the general population – with respiratory and urogenital tract infections being the 2 most common sites of infection. Therefore, NAFLD may be linked either to an increased susceptibility to infections in general, without changing the spectrum, or to a more severe course of infections. Nevertheless, the proportion of patients with cirrhosis was very low (5.6%) and despite low absolute risks, HRs were highest for bacterial peritonitis.

Our data are in line with a previous small retrospective study by Nseir and colleagues which demonstrated that among 247 patients with NAFLD the risk for recurrent bacterial infections was increased independent of the metabolic syndrome.[42] In their study, urinary tract infections were more common than respiratory tract infections; however, upper and lower respiratory tract infections were recorded separately. In another retrospective study, NAFLD was associated with a higher risk of hospitalization for community-acquired pneumonia with an odds ratio of 2.5 (95% CI, 2.0–3.2; $P = .02$),[43] being further associated with a more severe course of infection and higher mortality,[44] when compared with reference individuals without NAFLD.

We can only speculate on the underlying mechanisms that lead to this observed increased risk of infections in patients with NAFLD. Infection is actually a rather frequent reason for hospitalization or primary care visit in patients with the metabolic syndrome, specifically in diabetes. In fact, it has been shown that each year around 40% of all patients with diabetes mellitus have at least 1 outpatient visit, and nearly 6% have at least 1 hospitalization for an infectious disease.[45] Experimental research has unveiled numerous defects in host immune defense mechanisms in patients with diabetes. For instance, neutrophils have been shown to have impaired phagocytic capabilities, migration, phagocytosis, and chemotaxis.[46] However, we adjusted for parameters of the metabolic syndrome and performed multiple sensitivity analyses and therefore show an increased risk of infection with NAFLD independent of parameters of the metabolic syndrome. Future mechanistic studies are required to unveil the underlying cellular and molecular causes of that observed infection risk.

Our study has several strengths. It was based on a nationwide population-based cohort of more than 12,000 patients with biopsy-proven NAFLD of all severities experiencing more than 4500 severe infection events over a long study period, altogether yielding substantial statistical power and external validity. Using histopathology data, we were able to separate the different histological stages of NAFLD disease severity on a

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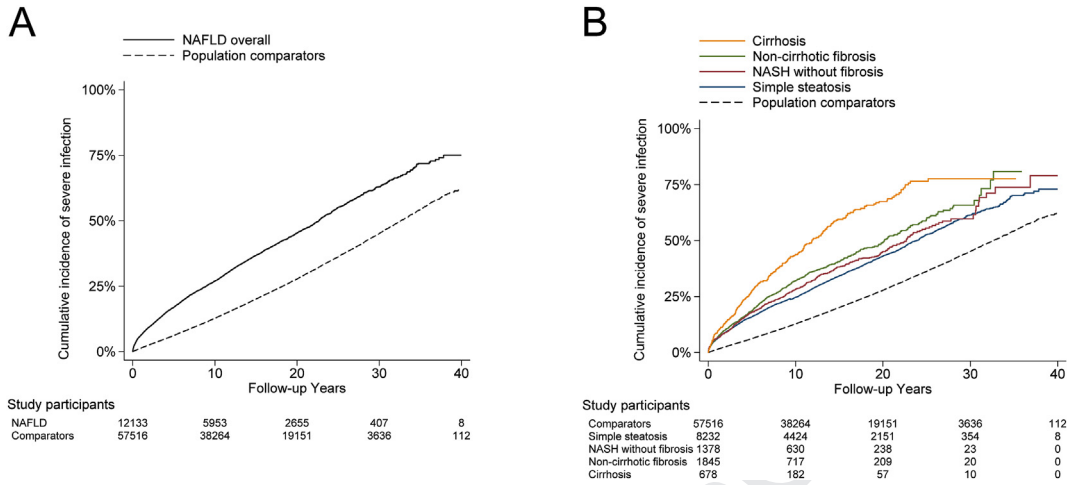

Figure 2. Increased risk of severe infection among all histological subgroups of NAFLD. Cumulative incidence curves of time to any severe infection in all patients with biopsy-proven NAFLD (*A*) and among histological subgroups* of NAFLD severity compared to matched population comparators (*B*). NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. *Histological severity of NAFLD was defined in 4 categories: simple steatosis, NASH without fibrosis, non-cirrhotic fibrosis and cirrhosis (see Supplementary Methods).

population-based level, which is unique worldwide. Furthermore, our results were highly robust in several sensitivity analyses even after rematching patients with NAFLD with full siblings and within the patient population of biopsy-proven NAFLD using patients with simple steatosis as comparators.

Our data must be interpreted in the context of the study design. Because data on primary care visits are not registered in Sweden, our results apply to infections that require in-hospital or emergency department care, and therefore cannot be extrapolated to milder infections. Second, use of administrative data for the definition of infection outcomes has demonstrated suboptimal specificity and accuracy for some of the infectious sub-entities – especially for respiratory tract infections – however, such inaccuracy likely applies to both patients with NAFLD and comparators, reducing the risk for differential misclassification bias. Third, in patients with cirrhosis, we cannot determine whether infection led to decompensation or vice versa. Fourth, despite careful matching and multivariable adjustment for various demographic and clinical confounders, residual confounding cannot be fully excluded, especially because we lacked detailed data on smoking status, alcohol consumption, frailty, vaccination status, body mass index, and laboratory values. Another key limitation is the lack of an external validation cohort. Finally, consistent with other administrative data sets, the recorded prevalence of parameters of the metabolic syndrome were underestimated, which could lead to unmeasured confounding. Nevertheless, our findings remained similar in patients with and

Table 3. Risk of Specific Infection Sub-entities in Patients With NAFLD and Matched General Population Comparators

	N events		Incidence rate (95% CI) per 1000 PY			
Infection	NAFLD	Comparators	NAFLD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Sepsis	1012 (8.3)	2 426 (4.2)	6.2 (5.8–6.6)	2.5 (2.4–2.6)	3.16 (2.91–3.44)	2.16 (1.95–2.39)
Respiratory tract	2147 (17.7)	7630 (13.3)	13.8 (13.2–14.4)	8.2 (8.0–8.3)	2.14 (2.03–2.26)	1.52 (1.42–1.62)
Gastrointestinal	681 (5.6)	1594 (2.8)	4.2 (3.9–4.5)	1.7 (1.6–1.7)	3.11 (2.81–3.44)	1.97 (1.74–2.23)
Bacterial peritonitis including SBP	221 (1.8)	286 (0.5)	1.3 (1.2–1.5)	0.3 (0.3–0.3)	5.45 (4.46–6.66)	3.71 (2.89–4.75)
Urinary tract	1797 (14.8)	6329 (11.0)	11.4 (10.8–11.9)	6.7 (6.5–6.9)	2.40 (2.26–2.55)	1.63 (1.51–1.75)
Musculoskeletal, skin, and soft tissue	828 (6.8)	2196 (3.8)	5.1 (4.7–5.4)	2.3 (2.2–2.4)	2.69 (2.46–2.94)	1.83 (1.64–2.04)
Other	1574 (13.0)	4424 (7.7)	9.8 (9.3–10.3)	4.6 (4.5–4.8)	2.79 (2.61–2.98)	1.91 (1.76–2.07)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-years; SBP, spontaneous bacterial peritonitis.
[a]Conditioned on matching set (age, sex, county, and calendar period).
[b]Conditioned on matching set and further adjusted for education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

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Table 4. Risk of Infections in the NAFLD-only Subgroup

	Simple steatosis (ref.) (n = 8232)	NASH without fibrosis (n = 1378)	Noncirrhotic fibrosis (n = 1845)	Cirrhosis (n = 678)
N events (%)	3086 (37.5)	483 (35.1)	659 (35.7)	289 (42.6)
Incidence rate (95% CI) per 1,000 PY	29.9 (28.9–31.0)	33.3 (30.3–36.3)	37.9 (35.0–40.8)	59.5 (52.7–66.4)
Incidence rate difference (95% CI)	0 (ref.)	3.4 (0.2–0.7)	8.0 (4.9–11.0)	29.6 (22.7–36.6)
HR[a] (95% CI)	1.00 (ref.)	1.06 (0.97–1.17)	1.10 (1.01–1.20)	1.46 (1.30–1.65)
HR[b] (95% CI)	1.00 (ref.)	1.04 (0.94–1.15)	1.13 (1.04–1.23)	1.37 (1.21–1.55)
Cumulative incidence (95% CI) at 20 years of follow-up	42.8 (41.5–44.1)	45.1 (41.7–48.6)	49.1 (45.8–52.4)	67.4 (62.0–72.8)
20-year absolute risk difference (95% CI)	0 (ref.)	2.3 (0.9–3.8)	6.3 (4.8–7.7)	24.7 (23.3–26.0)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-years; ref, reference.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

without metabolic diagnoses, when compared with comparators with the same comorbidities. Moreover, our sensitivity analysis demonstrated that our results are robust to unmeasured confounding; specifically, a confounder would need to have both an aHR $\geq$2.8 for NAFLD and severe infections to fully attenuate our results. Thus, the excess risk of incident severe infections in patients with NAFLD appears to exceed that which could be explained by the metabolic syndrome alone.

Our findings identifying patients with NAFLD at risk for severe infections have clinical implications: clinicians need to be aware of the increased risk among patients with NAFLD and should have an increased clinical vigilance for infections and consider preventive measures such as regular check of the vaccination status (eg, pneumococcal, influenza, and herpes zoster vaccines). Furthermore, known modifiable risk factors such as diabetes mellitus need to be well-controlled.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.05.013.

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Fahim Ebrahimi, MD, MSc (Conceptualization: Equal; Formal analysis: Equal; Funding acquisition: Equal; Methodology: Equal; Writing – original draft: Lead; Writing – review & editing: Equal)

Tracey G. Simon, MD (Methodology: Supporting; Writing – review & editing: Supporting)

Hannes Hagström, MD (Writing – review & editing: Equal)

Jonas Söderling, PhD (Formal analysis: Lead; Methodology: Equal; Writing – review & editing: Equal)

Axel Wester, MD, PhD (Writing – review & editing: Supporting)

Bjorn Roelstraete, PhD (Methodology: Supporting; Writing – review & editing: Supporting)

Jonas F. Ludvigsson, MD, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Equal; Funding acquisition: Lead; Methodology: Lead; Resources: Lead; Supervision: Lead; Writing – original draft: Equal; Writing – review & editing: Equal)

Conflicts of interest Q3

These authors disclose the following: Jonas F. Ludvigsson has coordinated a study on behalf of the Swedish IBD quality register (SWIBREG). That study received funding from Janssen Corporation. Jonas F. Ludvigsson has also received financial support from MSD developing a paper reviewing national healthcare registers in China. Hannas Hagström's institutions have received research grants from Astra Zeneca, EchoSens, Gilead, Intercept, MSD and Pfizer. The remaining authors disclose no conflicts.

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Supplementary Methods

Definition of Nonalcoholic Fatty Liver Disease and Nonalcoholic Fatty Liver Disease Histological Categories

Nonalcoholic fatty liver disease (NAFLD) was defined using an established algorithm of SNOMED topography and morphology codes for histopathology,[1] after excluding other etiologies of liver disease.[2] In brief, patients were identified through liver biopsy histopathology reports that included a topography code for liver (T56), and a morphology code for steatosis (M5008x or M5520x). In Sweden, clinically indicated liver biopsies are generally conducted with a single pass of the liver, unless a satisfactory specimen could not be obtained. According to Swedish liver histopathology reporting recommendations, it is documented if any biopsy is too short in length (ie, <15 mm in length), has fewer than 5 portal tracts, or is fragmented, respectively.[1]

To perform analyses on the different stages of NAFLD disease severity, patients meeting criteria for NAFLD were subsequently categorized into 4 histological subgroups using SNOMED definitions[1] for coherent nationwide histopathology reporting in Sweden: simple steatosis, nonalcoholic steatohepatitis (NASH) without fibrosis, noncirrhotic fibrosis, and cirrhosis (Supplementary Table 2).[2] Histological subgroups have the following positive predictive values (PPVs): 90% for simple steatosis, 87% for NASH without fibrosis, 93% for NASH with noncirrhotic fibrosis, and 97% for cirrhosis.

Comparators

Reference individuals from the general population were systematically sampled by the central authority "Statistics Sweden" that holds detailed census-level data on all Swedish citizens leveraging the Total Population Register.[3] Identical exclusion criteria were applied to controls, ensuring that reference individuals did neither have a diagnosis of any other liver disease at or before baseline (Supplementary Table 1), whereby some patients with NAFLD may have ended up with less than 5 comparators.

Definitions of Secondary Outcomes

The primary outcome was any severe infection leading to inpatient care. The International Classification of Diseases codes for the definition of severe infections are summarized in Supplementary Table 3. Secondary outcomes included each category (n = 7) of severe infections: sepsis; respiratory tract (including ear-nose-throat disease); gastrointestinal except for peritonitis; bacterial peritonitis (including spontaneous bacterial peritonitis and other forms of peritonitis); urogenital; musculoskeletal, skin, and soft tissue; and "other infection" outcomes (Supplementary Table 3).

Definitions of Covariates

Definitions of clinical and demographic covariates are outlined in the Methods section and in Supplementary Table 4. We ascertained demographic data (eg, age, sex, emigration from Sweden) using the Total Population Register.[3] Data on education level were collected from the prospective LISA (longitudinal integrated database for health insurance and labour market studies) database.[4] Clinical comorbidities were obtained from the National Patient Register, which prospectively includes all data from hospitalizations since 1964 and specialized outpatient care visits from 2001.[5] Previous validation studies confirmed PPVs for clinical diagnoses of 85% to 95%.[5] Follow-up time was ascertained using the Total Population Register, the National Patient Register, and the Cause of Death Register[6] with end of follow-up on December 31, 2019.

Proportional Hazard Assumption

The proportional hazard assumption was tested by including an interaction term of the exposure and follow-up time in the model. The proportional hazard assumption was violated for the overall follow-up period as well as for <1 year and ≥1 year of follow-up, but we found no evidence that the proportional hazard assumption was violated for 1 to <5 years, 5 to <10 years, or ≥10 years of follow-up.

Follow-up time	*P*-value for interaction term
Overall	< .001
<1 y	< .001
1–<5 y	.23
5–<10 y	.11
≥10 y	.32
≥1 y	< .001

Any Infection

Using the E-value approach[7], we found that the minimum strength of an unmeasured confounder (such as smoking), to the observed adjusted risk ratio of 1.71 to be reduced to 1, would need to be 2.8 fold to both the exposure (NAFLD) and to infection. The lower limit of the confidence interval could be shifted below 1 by an unmeasured confounder that was associated with both NAFLD and infection by a risk ratio of 2.6-fold.

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Supplementary References

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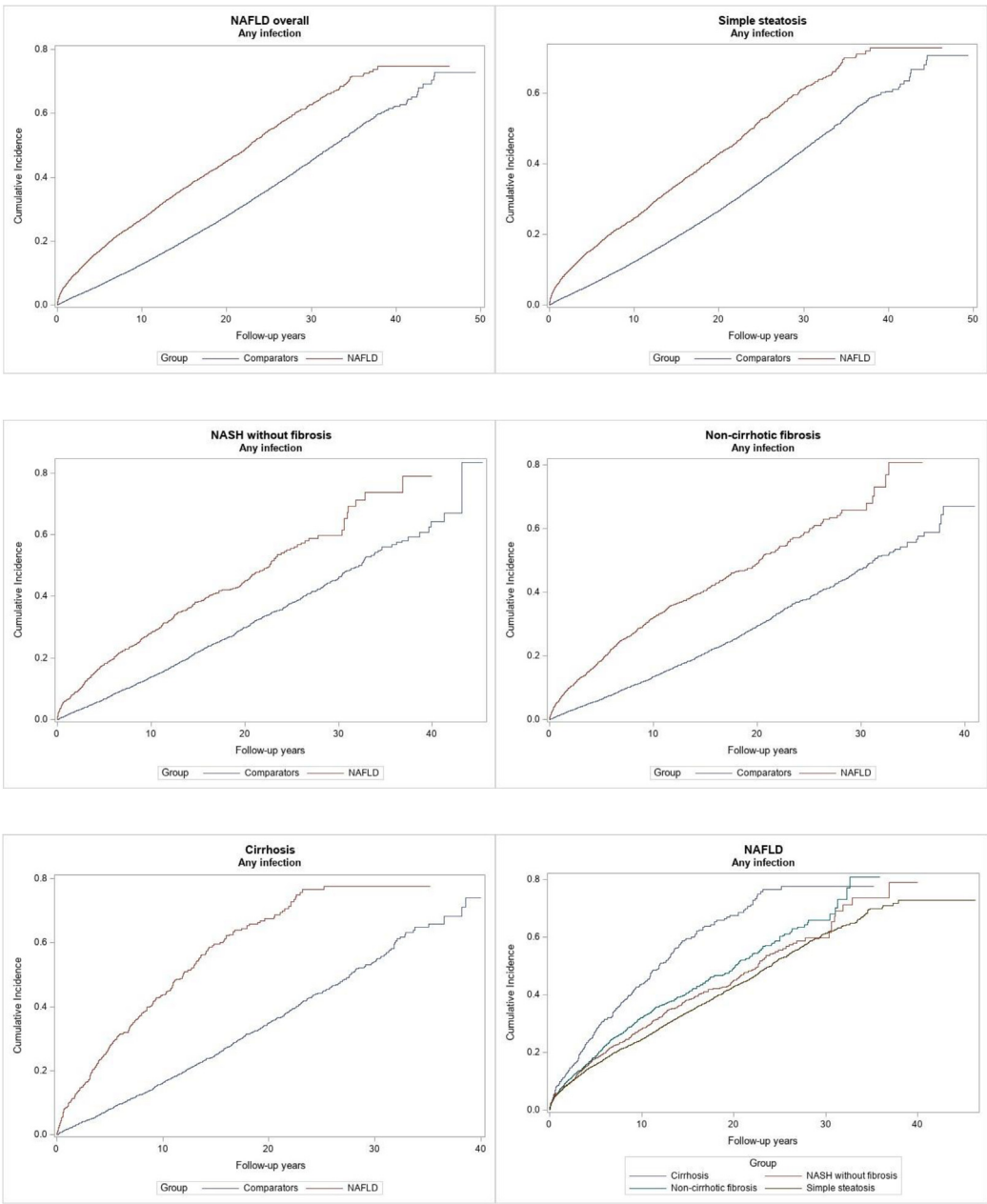

Supplementary Figure 1. Cumulative incidence curves of time to any severe infection in patients with NAFLD and matched population comparators.

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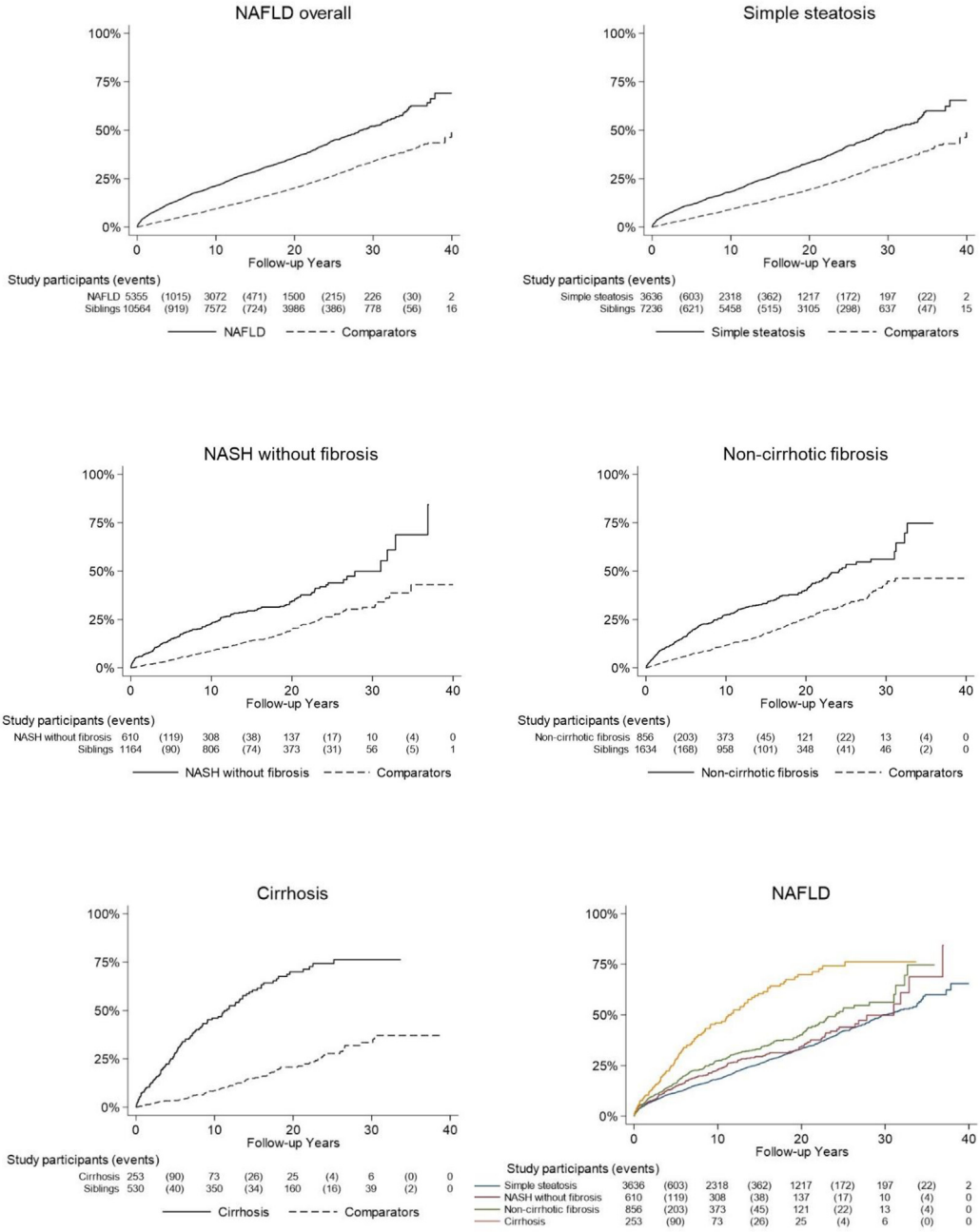

Supplementary Figure 2. Kaplan-Meier failure curves of time to any infection in patients with NAFLD and sibling comparators.

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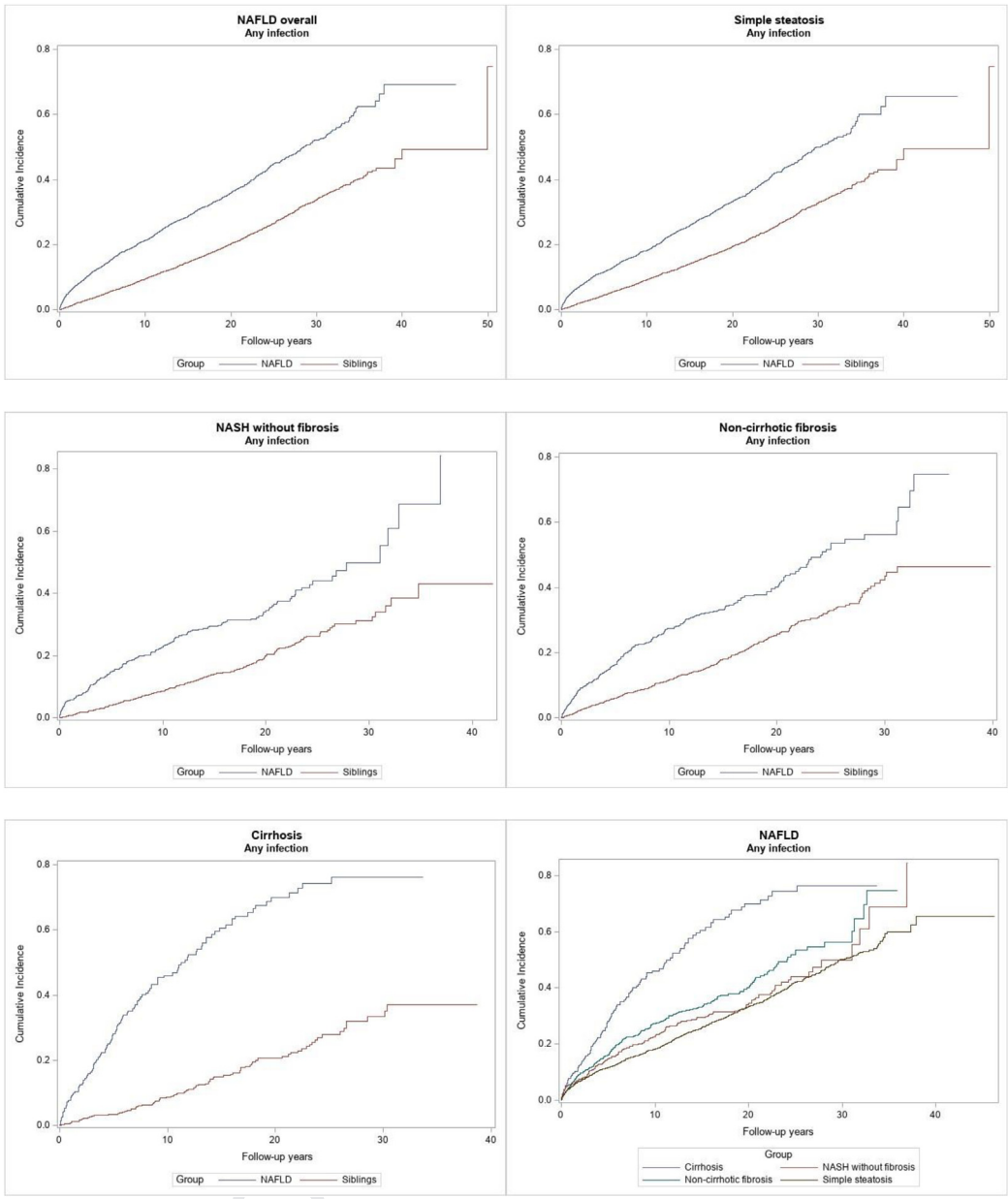

Supplementary Figure 3. Cumulative incidence curves of time to any infection in patients with NAFLD and sibling comparators.

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Supplementary Table 1. Study Exclusion Criteria

Excluded conditions[a]	ICD-7 / ICD-8	ICD-9	ICD-10
Alcohol abuse / misuse, or Alcohol-related liver disease	280,00; 281,00; 307,00; 307,10; 307,99; 322; 581,10; 583,10; 261,00; 262,00; 291; 291,1; 303; 571,00; 571,01; 979; 980,00; 980,01; 980,98; 980,99	291; 294A; 303; 305A; 357F; 425F; 535D; 571A-D; 760W; 790D; 977D; 980A; 980X; V97B	E24.4; F10; G31.2; G62.1; G72.1; I42.6; K29.2; K70; K86.0; Q35.4; R78.0; T51.0; T51.8; T51.9; X65; Y15; Y57.3; Y90; Y91; Z50.2; Z71.4; Z71.2
Other abuse- and drug-related diagnoses	571,0; E860; N980	571A-D	F11-F19
Drug-induced liver disease	–	573D	K71
Viral hepatitis (eg, hepatitis B, C)	070; 999,20	070	B15-19; B00.8; B25.1
Budd-Chiari	–	453A	I82
Liver abscess	572	572A	K75.0; A06.4
HIV	079,83; Y40,49; Y41,49	279K	B20-B24
Hemochromatosis	273,2	275A	E83.1
Wilson's disease	273,3	275B	E83.0
Autoimmune hepatitis	–	573D; 571E	K75.4
Primary biliary cholangitis	–	571G	K74.3; K74.4
Other cholangitis	574,06	576B	K83; K83.0A
Alpha-1 antitrypsin deficiency	–	277G	E88.0
Glycogen storage disease	–	271	E74
Liver transplantation[b]	–	V42H	Z94.4 JJC, DJ005; DJ006[b]
Gastric bypass surgery	–	–	JDF[b]

HIV, Human immunodeficiency virus; ICD, International Classification of Disease.

[a]We excluded any person with a diagnosis for another etiology of liver disease, or alcohol abuse/misuse or alcohol-related liver disease, defined on or prior to the index date.

[b]Liver transplantation and Bariatric surgery were further defined via procedure codes.

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Supplementary Table 2. Definition of NAFLD Subgroups According to Histology

#	Subgroup	SNOMED and ICD codes	
		Inclusion	Exclusion
1	Cirrhosis	M495 [exactly] or M4950x	
2	Noncirrhotic fibrosis (note that this may or may not include NASH)	Steatosis: either M5008x or M5520x, PLUS at least 1 fibrosis code: M49 [exactly], M4900x or M49060.	Cirrhosis codes: M495 [exactly] or M4950x.
3	NASH without fibrosis	Steatosis: either M5008x or M5520x, PLUS at least one of the following: 1. any M4- code, or 2. M5400x	M4 defines a very broad category of inflammation, both acute and chronic. Cannot have any of: Fibrosis codes (M49 [exactly], M4900x or M49060) OR Cirrhosis: M495 [exactly] or M4950x.
4	Simple steatosis	M5008x or M5520x	Cannot have any: Inflammation codes: M4- or M5400x OR Fibrosis: M49 [exactly], M4900x or M49060 OR Cirrhosis: M495 [exactly] or M4950x

ICD, International Classification of Diseases; SNOMED, Systematized Nomenclature of Medicine.

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Supplementary Table 3. Definition of Primary Endpoint Any Severe Infection and Infection Subcategories

Infection	ICD-8 code	ICD-9 code	ICD-10 code
Sepsis			
Sepsis	038	038	A 39.2, A40-41, R65.1
Septic shock		785F	R57.2
Anaerobic sepsis		038D	A41.4
Gram negative sepsis	038.80	038E	A41.5
Haemophilus influencae sepsis			A41.3
Listeria sepsis			A32.7
Candida sepsis		112F	B37.7
Meningococcal sepsis	036.10,80, 97,99	036C-X	A39.2-9
Pneumococcal sepsis	038.20	038C	
Salmonella sepsis/ (para) typhoid fever	001-002	002, 003B	A02.1
Staphylococcal sepsis (including TSS)	038.10	038B	A41.0-2, A48.3
Streptococcal sepsis	038.00	038A	A40
Respiratory tract infections (including ENT)			
Bronchitis and bronchiolitis	466,99	466	J20, J21
Tuberculosis	011-019	010-018, 320E	A15-A19, K23.0, K93.0
Chronic obstructive lung disease with infection			J44.0
Inflammation and abscesses in salivary glands, mouth, tongue	527.30, 528.30, 529.00	527C,D, 528D, 529A	K11.2-3, K12.2, K14.0
Laryngitis, tracheitis and epiglottitis	464, 508.03	464	J04, J05
Mastoiditis, petrositis	382.00,99 383.00,99	383A,C,X	H70.0, H70.2, H70.9, H75.0
Nasal abscess	508.01	478B	J34.0
Other lower respiratory tract infection			J22
Otitis (including external)	380, 381.00,99, 382.00,99	380B, 382A,E,X	H60.0-3 H62.0-4, H66, H67.0-1
Parotitis	072	072	B26
Peritonsillar, pharyngeal and retropharyngeal abscess	501.99, 508.02	475, 478C	J36, J39.0-1
Pertussis	033	033	A37
Pharyngitis	074.00-01, 462	074A, 462, 034A	B08.5, J02
Pleural empyema	510	510	J86
Pleuritis	511.10-20	511A,B, X	
Pneumonia (all: viral, bacterial, fungal)	480.99 (virus) 481-484, 485.09, 486	480 (virus), 481, 482, 483, 484, 485, 486	J12 (Virus), J13, J14, J15, J16, J17, J18
Pulmonary abscess	513.99	006E, 513	A06.5, J85
Sinusitis including ethmoiditis	461	461	J01
Tonsillitis	034.00, 463	034A, 463	J03
Unspecified respiratory tract infection			J98.7
Upper respiratory tract infection	465.99	465	J06
Gastrointestinal/abdominal infections excluding SBP			
Gastroenteritis –bacterial/protozoal	001-004, 006-007 (excl 006.00), 008.00-008.30	001-004, 006A-C, W,X, 007, 008A-F	A00-04 A06-07 (excl A06.4-6)
Gastroenteritis – unspecified	009	008W, 009	A09
Intestinal abscess	569.00	569F	K63.0
Liver abscess (including amoeba) /liver infection	006.00, 572.99	006D, 572A	A06.4, K75.0(?), K77.0
Perianal/anal abscess	566	566	K61
Bacterial peritonitis including SBP			
Peritonitis including SBP	567	567A,B,C,X	K65.0,9, K67
Urogenital infections			
Cystitis/urethritis	595.00,09 597.00,09	595A,W,X, 597	N30.0, N30.8-9, N33, N34.0-1
Glomerular, tubulointerstitial , disease (from infection) including pyelonephritis	590.10-14	078G, 590B,D,W,X	N08.0, N10, N12, N13.6, N16.0, A98.5
Hydrocele (infected)		603B	N43.1
Pelvic infection	567.00 616.00, 02		N74

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Supplementary Table 3. Continued

Infection	ICD-8 code	ICD-9 code	ICD-10 code
Renal abscess	590.20	590C	N15.1
Urinary tract infection, unspecified	590.98-99, 599.02	599A	N15.9, N39.0, N29.1
Musculoskeletal, skin, and soft-tissue (and connective tissue) infections			
Fasciitis			M72.6
Myositis	732.99, 074	728A	M60.0, M63.0-2
Osteomyelitis/osteitis	720.00,29,30,39	730A,C,X	M86.0-2, M86.9, M90.0-2
Septic/infectious arthritis	710	711A	M00, M01
Spondylodiscitis			M46.2-3,5, M49.0-3
Synovitis			M65.0-1, M68.0
Cellulitis, lymphangitis and abscesses	680, 681.0-01,08-09, 682		L02, L03
Dermatitis, infectious	692.82		L30.3
Erysipelas	035.99	035	A46
Impetigo	684	684	L01
Lymphadenitis	683	683	L04
Other local infections of skin and subcutaneous tissue	686	006G, 686	A06.7, L08
Pilonidal cyst w. abscess		685A	L05.0
Exfoliative dermatitis			L00
Other infections			
Aspergillosis	117.3	117D,E	B44
Candida	112,99	112	B37
Coccidoides	007,20	007.C	A07.3
Coccidioidomycosis	114.99	114	B38
Cryptococcosis			B45
Histoplasmosis	115.99	115	B39
legionellosis		482.J	A48.1
Listeriosis	027.01-09	027A	A32
Mycobacteria (non-tuberculosis)	031	031	A31
Nocardiosis		039B	A43
Pneumocystosis	136.01	136D	B59
Salmonellosis	003	003	A02
Toxoplasmosis	130	130	B58, K77.0
Intracranial abscess	322	006F, 324A	A06.6 G06.0, G07
Intraspinal abscess	322.03	324B	G06.1-2
Meningitis - bacterial	320, 036.00	036A,B, 320A-D, H, W, X	A32.1, A39.0, G00-01
Mycosis	110-117	110-118, 321A	B35-49, G02.1
Aspergillosis	117.3	117D,E	B44
Coccidioidomycosis	114.99	114	B38
Candida	112	112	B37
Dermatophytosis and other superficial mycoses	110, 111	110,111	B35
Protozoal diseases (including malaria, toxoplasmosis)	084-087, 130, 136.02,08	084, 085, 086, 130, 136C	(A06-7) B50-64, G02.8
Helminths	120-129	120-129	B65-B83
Zoonoses	020-27, 039.00, 039.91-93, 060-064, 067-068, 089, 100, 079.30, 073.99	020-027, 060-066, 088, 100W,X, 078D, 073	A20-28, A32, A44, A70, A83-84, A92-99
Other infections (specified and unspecified)			
Actinomycosis, nokardios	113.99	039	A42, A43
Bacterial infection (specified and unspecified)	039.90, 039.98	040, 041	A48 (excl A48.3), A49, B95-96
Diphteria	032	032	A36
Infection of the eye	054.05, 076.99, 078, 362, 366.00-01, 368.00, 03,369.00-01	054E, 076, 077, 360A, 373B,C, 376A	A71, B00.5, B30, H00, H03, H05.0, H06.1, H10.0, H13.0-1, H19.0-2, H22.0, H32.0, H44.0
Infection, unspecified	136.09	136W,X	B99
Leprosy	030	030	A30
Listeriosis	027.01-09	027A	A32
Mammary infection	611.00-01	611A, 680C	N61

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Supplementary Table 3. Continued

Infection	ICD-8 code	ICD-9 code	ICD-10 code
Mycobacterial infections (other – non-tuberculosis)	031	031	A31
Peri-/myo and endocarditis	074.20-21, 421.00	421A,B, 074C, 036E, 017W, 112W, 002A	I30.1, I32.0-1, I33.0, I40.0, I41.0-2, I43.0, I52.0-1 B37.6, A39.5, A18.8, A01.0
Rheumatic fever (not chorea)	390-391	390-391	I00-01
Rickettsiosis	080-083	080-083	A75-79
Scarlatina	034.10-19	034B	A38
Spirochetal disease, including borreliosis	088, 100, 101,102-103	087,101-104	A65-69
Splenic abscess	289.40		D73.3
Thymal abscess		254B	E06.0
Thyroid abscess		245A	E06.0

ENT, Ear-nose-throat; ICD, International Classification of Diseases; SBP, spontaneous bacterial peritonitis.

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Supplementary Table 4. Definition of Covariates

Comorbidity	ICD-7 / ICD-8	ICD-9	ICD-10	ATC-codes
Diabetes	250	250	E10-E14	A10A, A10B
Obesity	278, 649,1	278	E65-E67	
Dyslipidemia	272	272	E75, E77, E78	C10AA, C10BA, C10BX
Hypertension	400-404	401-405	I10-I13, I15	C09
COPD (age ≥40 years)	N/A	491-492, 496	J41-J44	

ATC, Anatomic therapeutic chemical classification; COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases.

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Supplementary Table 5. Incident Infection Among Patients With NAFLD and Population Comparators

Characteristic	Overall	Simple steatosis	NASH without fibrosis	Noncirrhotic fibrosis	Cirrhosis
Patients with NAFLD					
N	12,133	8232	1378	1845	678
Follow-up, y					
Mean (SD)	11.5 (9.3)	12.5 (9.8)	10.5 (8.6)	9.4 (7.6)	7.2 (7.3)
Median (IQR)	9.7 (3.3–18.9)	11.4 (3.5–20.4)	8.8 (3.1–16.8)	7.7 (3.5–13.9)	4.7 (1.6–10.8)
Range, min-max	0.0–46.2	0.0–46.2	0.0–40.0	0.0–35.9	0.0–35.2
Any infection					
Within 1 year after index date	726 (6.0)	471 (5.7)	85 (6.2)	115 (6.2)	55 (8.1)
Within 5 years after index date	1860 (15.3)	1169 (14.2)	221 (16.0)	317 (17.2)	153 (22.6)
Within 10 years after index date	2752 (22.7)	1729 (21.0)	320 (23.2)	489 (26.5)	214 (31.6)
All follow-up time	4517 (37.2)	3086 (37.5)	483 (35.1)	659 (35.7)	289 (42.6)
Incidence rate by 1000 PY	32.3 (31.3–33.2)	29.9 (28.9–31.0)	33.3 (30.3–36.3)	37.9 (35.0–40.8)	59.5 (52.7–66.4)
Reason for end of follow-up					
Infection	4517 (37.2)	3086 (37.5)	483 (35.1)	659 (35.7)	289 (42.6)
Liver transplantation	35 (0.3)	10 (0.1)	7 (0.5)	6 (0.3)	12 (1.8)
Death	2984 (24.6)	1991 (24.2)	347 (25.2)	388 (21.0)	258 (38.1)
Emigration	187 (1.5)	133 (1.6)	21 (1.5)	24 (1.3)	9 (1.3)
End of follow-up (December 31, 2019)	4410 (36.3)	3012 (36.6)	520 (37.7)	768 (41.6)	110 (16.2)
Comparators					
N	57,516	39,244	6476	8592	3204
Follow-up, y					
Mean (SD)	15.4 (9.1)	16.3 (9.3)	14.3 (8.7)	12.7 (8.1)	14.3 (8.9)
Median (IQR)	14.9 (7.7–22.3)	16.4 (8.4–23.3)	13.4 (6.9–20.8)	11.2 (6.2–18.1)	13.0 (6.7–21.3)
Range, min-max	0.0–49.3	0.0–49.3	0.0–45.4	0.0–40.9	0.0–40.0
Any infection					
Within 1 year after index date	769 (1.3)	498 (1.3)	96 (1.5)	119 (1.4)	56 (1.7)
Within 5 years after index date	3 440 (6.0)	2 249 (5.7)	415 (6.4)	530 (6.2)	246 (7.7)
Within 10 years after index date	6591 (11.5)	4354 (11.1)	789 (12.2)	988 (11.5)	460 (14.4)
All follow-up time	15,075 (26.2)	10,576 (26.9)	1638 (25.3)	1859 (21.6)	1002 (31.3)
Incidence rate by 1000 PY	17.0 (16.7–17.2)	16.5 (16.2–16.8)	17.7 (16.8–18.5)	17.0 (16.3–17.8)	21.8 (20.5–23.2)
Reason for end of follow-up					
Infection	15,075 (26.2)	10,576 (26.9)	1638 (25.3)	1859 (21.6)	1002 (31.3)
Liver transplantation	11 (0.0)	10 (0.0)	0	1 (0.0)	0
NAFLD	74 (0.1)	58 (0.1)	6 (0.1)	6 (0.1)	4 (0.1)
Death	9466 (16.5)	6763 (17.2)	955 (14.7)	1112 (12.9)	636 (19.9)
Emigration	1370 (2.4)	985 (2.5)	155 (2.4)	180 (2.1)	50 (1.6)
End of follow-up (December 31, 2019)	31,520 (54.8)	20,852 (53.1)	3722 (57.5)	5434 (63.2)	1512 (47.2)

IQR, Interquartile range; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-years; SD, standard deviation.

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Supplementary Table 6. Cumulative Incidence and Absolute Risk Difference for Severe Infection in Patients with NAFLD and Matched General Population Comparators

	1-year follow-up			10-year follow-up			20-year follow-up		
Infection	NAFLD	Comparators	Risk difference (95% CI)	NAFLD	Comparators	Risk difference (95% CI)	NAFLD	Comparators	Risk difference (95% CI)
Any infection	6.3 (5.8–6.7)	1.3 (1.3–1.4)	4.9 (4.7–5.1)	26.9 (26.0–27.8)	12.8 (12.5–13.1)	14.1 (13.7–14.6)	45.0 (43.9–46.1)	27.8 (27.3–28.2)	17.3 (16.8–17.7)
Sepsis	1.2 (1.0–1.4)	0.1 (0.1–0.2)	1.0 (0.9–1.1)	5.7 (5.2–6.2)	1.7 (1.6–1.8)	4.0 (3.8–4.2)	11.0 (10.3–11.8)	4.5 (4.3–4.8)	6.5 (6.2–6.8)
Respiratory tract	2.2 (1.9–2.5)	0.6 (0.6–0.7)	1.6 (1.4–1.7)	12.1 (11.4–12.7)	6.2 (6.0–6.5)	5.8 (5.5–6.1)	22.7 (21.7–23.7)	14.4 (14.1–14.8)	8.3 (7.9–8.7)
Gastrointestinal	0.8 (0.7–1.0)	0.1 (0.1–0.2)	0.7 (0.6–0.8)	4.0 (3.6–4.4)	1.4 (1.3–1.5)	2.6 (2.4–2.8)	7.6 (7.0–8.2)	3.1 (3.0–3.3)	4.4 (4.2–4.7)
SBP	0.4 (0.3–0.6)	0.0 (0.0–0.0)	0.4 (0.4–0.5)	1.3 (1.1–1.6)	0.2 (0.2–0.3)	1.1 (1.0–1.2)	2.3 (2.0–2.7)	0.5 (0.5–0.6)	1.8 (1.6–1.9)
Urogenital	1.5 (1.3–1.8)	0.4 (0.3–0.4)	1.1 (1.0–1.3)	9.6 (9.0–10.2)	4.7 (4.5–4.9)	4.9 (4.6–5.1)	19.2 (18.2–20.1)	11.8 (11.5–12.1)	7.4 (7.0–7.8)
Musculoskeletal, skin, and soft tissue	0.5 (0.4–0.7)	0.2 (0.1–0.2)	0.4 (0.3–0.5)	4.5 (4.1–4.9)	1.7 (1.6–1.8)	2.8 (2.6–2.9)	9.4 (8.8–10.2)	4.2 (4.0–4.4)	5.2 (5.0–5.5)
Other	1.5 (1.3–1.8)	0.2 (0.2–0.2)	1.3 (1.2–1.4)	7.9 (7.3–8.4)	2.7 (2.6–2.9)	5.1 (4.9–5.4)	16.9 (16.0–17.8)	7.9 (7.6–8.2)	9.0 (8.6–9.3)

CI, Confidence interval; ENT, otolaryngology; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; SBP, spontaneous bacterial peritonitis.

Supplementary Table 7. Baseline Characteristics of Patients with NAFLD and their Siblings

Characteristic	Siblings (n = 10,564)	All NAFLD (n = 5355)	Simple steatosis (n = 3636)	NASH without fibrosis (n = 610)	Noncirrhotic fibrosis (n = 856)	Cirrhosis (n = 253)
Sex						
Women	5299 (50.2)	2155 (40.2)	1409 (38.8)	271 (44.4)	373 (43.6)	102 (40.3)
Men	5265 (49.8)	3200 (59.8)	2227 (61.2)	339 (55.6)	483 (56.4)	151 (59.7)
Age, y						
Mean	48.1 (12.8)	48.3 (13.0)	47.0 (12.7)	48.4 (13.0)	51.7 (13.3)	55.6 (12.0)
Median	48.6 (38.9–57.4)	49.1 (38.6–57.8)	47.3 (37.5–56.0)	50.1 (38.5–58.4)	53.8 (42.9–61.7)	57.5 (49.1–64.1)
Range, min–max	18.0–82.4	18.2–82.8	18.2–82.8	18.2–78.1	18.2–80.0	19.3–78.3
Categories						
18–<40	2878 (27.2)	1503 (28.1)	1125 (30.9)	170 (27.9)	176 (20.6)	32 (12.6)
40–<60	5673 (53.7)	2780 (51.9)	1931 (53.1)	314 (51.5)	423 (49.4)	112 (44.3)
≥60	2013 (19.1)	1072 (20.0)	580 (16.0)	126 (20.7)	257 (30.0)	109 (43.1)
Country of birth						
Nordic country	10,386 (98.3)	5269 (98.4)	3575 (98.3)	601 (98.5)	842 (98.4)	251 (99.2)
Other	178 (1.7)	86 (1.6)	61 (1.7)	9 (1.5)	14 (1.6)	2 (0.8)
Level of education using highest level of education in parents when missing, y						
≤9	3085 (29.2)	1453 (27.1)	992 (27.3)	157 (25.7)	223 (26.1)	81 (32.0)
10–12	5193 (49.2)	2635 (49.2)	1760 (48.4)	320 (52.5)	426 (49.8)	129 (51.0)
>12	2265 (21.4)	1263 (23.6)	880 (24.2)	133 (21.8)	207 (24.2)	43 (17.0)
Missing	21 (0.2)	4 (0.1)	4 (0.1)	0	0	0
Start year of follow–up						
1966–1980	44 (0.4)	25 (0.5)	22 (0.6)	1 (0.2)	2 (0.2)	(0.0)
1981–1990	1467 (13.9)	671 (12.5)	539 (14.8)	43 (7.0)	62 (7.2)	27 (10.7)
1991–2000	4213 (39.9)	2110 (39.4)	1599 (44.0)	218 (35.7)	204 (23.8)	89 (35.2)
2001–2010	3295 (31.2)	1688 (31.5)	1024 (28.2)	222 (36.4)	354 (41.4)	88 (34.8)
2011–2017	1545 (14.6)	861 (16.1)	452 (12.4)	126 (20.7)	234 (27.3)	49 (19.4)
Disease history ever before start of follow–up						
Diabetes	414 (3.9)	610 (11.4)	311 (8.6)	81 (13.3)	141 (16.5)	77 (30.4)
Obesity	86 (0.8)	306 (5.7)	191 (5.3)	35 (5.7)	53 (6.2)	27 (10.7)
Dyslipidemia	659 (6.2)	499 (9.3)	253 (7.0)	76 (12.5)	121 (14.1)	49 (19.4)
Hypertension	906 (8.6)	966 (18.0)	519 (14.3)	133 (21.8)	222 (25.9)	92 (36.4)
Metabolic syndrome						
0	9225 (87.3)	3840 (71.7)	2761 (75.9)	416 (68.2)	529 (61.8)	134 (53.0)
1	794 (7.5)	914 (17.1)	589 (16.2)	104 (17.0)	177 (20.7)	44 (17.4)
2	376 (3.6)	373 (7.0)	188 (5.2)	51 (8.4)	98 (11.4)	36 (14.2)
3	157 (1.5)	191 (3.6)	83 (2.3)	37 (6.1)	44 (5.1)	27 (10.7)
4	12 (0.1)	37 (0.7)	15 (0.4)	2 (0.3)	8 (0.9)	12 (4.7)
COPD (age ≥40 years)	64 (0.6)	64 (1.2)	39 (1.1)	8 (1.3)	8 (0.9)	9 (3.6)
Any infection within 3 years prior to baseline	255 (2.4)	437 (8.2)	271 (7.5)	67 (11.0)	76 (8.9)	23 (9.1)
Any infection within 90 days prior to baseline	31 (0.3)	167 (3.1)	106 (2.9)	26 (4.3)	26 (3.0)	9 (3.6)

Note: Data are presented as number (%), median (interquartile range) or mean (standard deviation).
COPD, Chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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Supplementary Table 8. Incident Infection Outcomes During Follow-up in Patients With NAFLD and Their Siblings

Characteristic	Overall	Simple steatosis	NASH without fibrosis	Noncirrhotic fibrosis	Cirrhosis
Patients with NAFLD					
N	5 355	3 636	610	856	253
Follow-up, y					
Mean	13.4 (9.5)	14.7 (9.7)	11.8 (8.8)	10.5 (7.9)	7.9 (7.8)
Median	12.4 (5.0-20.9)	14.9 (6.1-22.2)	10.1 (4.0-19.0)	9.0 (4.3-15.5)	5.2 (2.0-11.2)
Range, min-max	0.0-46.2	0.0-46.2	0.0-37.0	0.0-35.9	0.0-33.7
Any infection					
Within 1 year after index date	265 (4.9%)	165 (4.5%)	35 (5.7%)	46 (5.4%)	19 (7.5%)
Within 5 years after index date	679 (12.7%)	401 (11.0%)	84 (13.8%)	133 (15.5%)	61 (24.1%)
Within 10 years after index date	1 015 (19.0%)	603 (16.6%)	119 (19.5%)	203 (23.7%)	90 (35.6%)
All follow-up time	1 731 (32.3%)	1 159 (31.9%)	178 (29.2%)	274 (32.0%)	120 (47.4%)
Incidence rate by 1000 PY	24.2 (23.0-25.3)	21.7 (20.4-22.9)	24.8 (21.1-28.4)	30.5 (26.9-34.1)	60.0 (49.3-70.7)
Reason for end of follow-up					
Infection	1 731 (32.3%)	1 159 (31.9%)	178 (29.2%)	274 (32.0%)	120 (47.4%)
Liver transplantation	26 (0.5%)	6 (0.2%)	5 (0.8%)	5 (0.6%)	10 (4.0%)
Death	805 (15.0%)	519 (14.3%)	99 (16.2%)	125 (14.6%)	62 (24.5%)
Emigration	71 (1.3%)	53 (1.5%)	8 (1.3%)	8 (0.9%)	2 (0.8%)
End of follow-up (December 31, 2019)	2 722 (50.8%)	1 899 (52.2%)	320 (52.5%)	444 (51.9%)	59 (23.3%)
Siblings					
N	10 564	7 236	1 164	1 634	530
Follow-up, y					
Mean	16.6 (9.0)	17.7 (9.0)	15.4 (8.3)	13.2 (8.1)	15.0 (8.9)
Median	16.6 (9.2-23.3)	18.1 (10.2-24.5)	15.2 (8.6-21.6)	12.0 (6.7-18.3)	12.9 (7.5-22.1)
Range, min-max	0.0-50.6	0.0-50.6	0.0-42.0	0.0-39.8	0.2-38.7
Any infection					
Within 1 year after index date	97 (0.9%)	66 (0.9%)	9 (0.8%)	18 (1.1%)	4 (0.8%)
Within 5 years after index date	479 (4.5%)	320 (4.4%)	46 (4.0%)	95 (5.8%)	18 (3.4%)
Within 10 years after index date	919 (8.7%)	621 (8.6%)	90 (7.7%)	168 (10.3%)	40 (7.5%)
All follow-up time	2 086 (19.7%)	1 482 (20.5%)	200 (17.2%)	312 (19.1%)	92 (17.4%)
Incidence rate by 1000 PY	11.9 (11.4-12.4)	11.6 (11.0-12.2)	11.2 (9.6-12.7)	14.4 (12.8-16.0)	11.6 (9.2-14.0)
Reason for end of follow-up					
Infection	2 086 (19.7%)	1 482 (20.5%)	200 (17.2%)	312 (19.1%)	92 (17.4%)
Liver transplantation	2 (0.0%)	2 (0.0%)	(0.0%)	(0.0%)	(0.0%)
NAFLD	25 (0.2%)	17 (0.2%)	3 (0.3%)	4 (0.2%)	1 (0.2%)
Death	785 (7.4%)	578 (8.0%)	68 (5.8%)	92 (5.6%)	47 (8.9%)
Emigration	138 (1.3%)	106 (1.5%)	14 (1.2%)	11 (0.7%)	7 (1.3%)
End of follow-up (December 31, 2019)	7 528 (71.3%)	5 051 (69.8%)	879 (75.5%)	1 215 (74.4%)	383 (72.3%)

Note: Data are presented as number (%), median (interquartile range) or mean (standard deviation).
NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-years.

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Supplementary Table 9. Risk of Any Infection Overall and by Subgroups in Patients With NAFLD and their Siblings

	N (%)		N events		Incidence rate (95% CI) per 1000 PY			
Group	NAFLD	Siblings	NAFLD	Siblings	NAFLD	Siblings	HR[a] (95% CI)	HR[b] (95% CI)
Overall	5355 (100)	10,564 (100)	1731 (32.3)	2086 (19.7)	24.2 (23.0–25.3)	11.9 (11.4–12.4)	2.23 (2.07–2.41)	1.54 (1.40–1.70)
Follow–up, y								
<1	5355 (100)	10,564 (100)	265 (4.9)	97 (0.9)	52.5 (46.2–58.8)	9.2 (7.4–11.1)	5.71 (4.45–7.35)	2.66 (1.92–3.68)
1–<5	4870 (90.9)	10,423 (98.7)	414 (8.5)	382 (3.7)	23.3 (21.1–25.6)	9.5 (8.6–10.5)	2.36 (2.02–2.76)	1.58 (1.30–1.93)
5–<10	4009 (74.9)	9406 (89.0)	336 (8.4)	440 (4.7)	19.1 (17.0–21.1)	10.4 (9.4–11.3)	1.98 (1.67–2.33)	1.55 (1.27–1.90)
≥10	3072 (57.4)	7572 (71.7)	716 (23.3)	1167 (15.4)	22.9 (21.2–24.6)	14.2 (13.3–15.0)	1.78 (1.58–2.01)	1.43 (1.23–1.66)
≥1	4870 (90.9)	10,423 (98.7)	1466 (30.1)	1989 (19.1)	22.0 (20.9–23.1)	12.1 (11.5–12.6)	1.99 (1.83–2.16)	1.49 (1.35–1.65)
Sex								
Women	2155 (40.2)	5299 (50.2)	761 (35.3)	972 (18.3)	30.1 (28.0–32.2)	10.9 (10.3–11.6)	2.20 (1.88–2.57)	1.32 (1.08–1.61)
Men	3200 (59.8)	5265 (49.8)	970 (30.3)	1114 (21.2)	20.9 (19.6–22.2)	12.9 (12.1–13.6)	2.09 (1.83–2.39)	1.48 (1.25–1.75)
Age, y								
18–<40	1503 (28.1)	2878 (27.2)	363 (24.2)	430 (14.9)	13.9 (12.4–15.3)	7.3 (6.6–8.0)	1.96 (1.63–2.35)	1.33 (1.05–1.68)
40–<60	2780 (51.9)	5673 (53.7)	972 (35.0)	1151 (20.3)	25.2 (23.6–26.8)	11.8 (11.1–12.5)	2.33 (2.08–2.61)	1.51 (1.31–1.75)
≥60	1072 (20.0)	2013 (19.1)	396 (36.9)	505 (25.1)	57.3 (51.6–62.9)	26.2 (24.0–28.5)	2.70 (2.21–3.31)	1.73 (1.34–2.24)
Year								
1966–1980	25 (0.5)	44 (0.4)	18 (72.0)	15 (34.1)	33.9 (18.2–49.5)	10.0 (5.0–15.1)	5.01 (1.76–14.28)	4.37 (1.28–14.99)
1981–1990	671 (12.5)	1467 (13.9)	290 (43.2)	419 (28.6)	19.4 (17.2–21.7)	10.6 (9.6–11.6)	2.15 (1.78–2.60)	1.61 (1.25–2.06)
1991–2000	2110 (39.4)	4213 (39.9)	715 (33.9)	992 (23.5)	20.2 (18.7–21.7)	11.8 (11.1–12.5)	1.88 (1.67–2.10)	1.40 (1.21–1.61)
2001–2010	1688 (31.5)	3295 (31.2)	513 (30.4)	517 (15.7)	30.3 (27.6–32.9)	12.4 (11.3–13.5)	2.71 (2.34–3.15)	1.71 (1.43–2.06)
2011–2017	861 (16.1)	1545 (14.6)	195 (22.6)	143 (9.3)	50.8 (43.6–57.9)	16.5 (13.8–19.2)	3.08 (2.38–3.98)	1.99 (1.42–2.78)
Year – infection during the first 5 y of follow-up								
1966–1980	25 (0.5)	44 (0.4)	2 (8.0)	1 (2.3)	17.0 (0.0–40.6)	4.5 (0.0–13.5)	1.98 (0.13–30.81)	–
1981–1990	671 (12.5)	1467 (13.9)	52 (7.7)	40 (2.7)	16.6 (12.1–21.1)	5.5 (3.8–7.3)	2.98 (1.87–4.73)	1.54 (0.79–3.00)
1991–2000	2110 (39.4)	4213 (39.9)	195 (9.2)	154 (3.7)	20.7 (17.8–23.6)	7.5 (6.3–8.7)	2.87 (2.28–3.62)	1.84 (1.37–2.47)
2001–2010	1688 (31.5)	3295 (31.2)	253 (15.0)	172 (5.2)	36.2 (31.7–40.6)	10.9 (9.2–12.5)	3.35 (2.69–4.17)	1.86 (1.41–2.47)
2011–2014	579 (10.8)	1045 (9.9)	117 (20.2)	76 (7.3)	52.2 (42.7–61.6)	15.3 (11.8–18.7)	3.49 (2.47–4.92)	1.98 (1.27–3.08)
Country of birth								
Nordic	5269 (98.4)	10,386 (98.3)	1710 (32.5)	2057 (19.8)	24.2 (23.1–25.4)	11.9 (11.4–12.4)	2.23 (2.07–2.41)	1.54 (1.40–1.70)
Other	86 (1.6)	178 (1.7)	21 (24.4)	29 (16.3)	18.7 (10.7–26.7)	11.4 (7.2–15.5)	2.92 (1.22–7.00)	2.72 (0.60–12.44)
Education, y								
≤9	1453 (27.1)	3085 (29.2)	600 (41.3)	785 (25.4)	32.0 (29.4–34.5)	15.0 (14.0–16.1)	2.27 (1.89–2.71)	1.37 (1.10–1.73)
10–12	2635 (49.2)	5193 (49.2)	809 (30.7)	961 (18.5)	22.5 (21.0–24.1)	11.1 (10.4–11.8)	2.13 (1.85–2.46)	1.58 (1.32–1.89)
>12	1263 (23.6)	2265 (21.4)	321 (25.4)	336 (14.8)	18.9 (16.9–21.0)	9.3 (8.3–10.3)	2.37 (1.80–3.11)	1.44 (1.01–2.05)
NAFLD subgroup								
Simple steatosis	3636 (67.9)	7236 (68.5)	1159 (31.9)	1482 (20.5)	21.7 (20.4–22.9)	11.6 (11.0–12.2)	2.03 (1.85–2.22)	1.42 (1.27–1.60)
NASH without fibrosis	610 (11.4)	1164 (11.0)	178 (29.2)	200 (17.2)	24.8 (21.1–28.4)	11.2 (9.6–12.7)	2.48 (1.94–3.16)	1.68 (1.21–2.33)
Noncirrhotic fibrosis	856 (16.0)	1634 (15.5)	274 (32.0)	312 (19.1)	30.5 (26.9–34.1)	14.4 (12.8–16.0)	2.37 (1.95–2.89)	1.69 (1.33–2.15)
Cirrhosis	253 (4.7)	530 (5.0)	120 (47.4)	92 (17.4)	60.0 (49.3–70.7)	11.6 (9.2–14.0)	7.56 (4.94–11.56)	4.06 (2.30–7.18)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-years.

[a]Conditioned on family and further adjusted for age and sex;

[b]Conditioned on family and further adjusted for age, sex, education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

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Supplementary Table 10. Risk of Specific Infections in Patients With NAFLD and Their Siblings

	N events		Incidence rate (95% CI) per 1000 PY			
Infection	NAFLD	Siblings	NAFLD	Siblings	HR[a] (95% CI)	HR[b] (95% CI)
Any infection	1731 (32.3)	2086 (19.7)	24.2 (23.0–25.3)	11.9 (11.4–12.4)	2.23 (2.07–2.41)	1.54 (1.40–1.70)
Sepsis	404 (7.5)	366 (3.5)	4.9 (4.5–5.4)	1.9 (1.7–2.1)	2.88 (2.43–3.42)	1.85 (1.50–2.29)
Respiratory tract	784 (14.6)	980 (9.3)	10.0 (9.3–10.7)	5.3 (5.0–5.7)	2.09 (1.87–2.33)	1.51 (1.31–1.73)
Gastrointestinal	298 (5.6)	268 (2.5)	3.7 (3.2–4.1)	1.4 (1.3–1.6)	2.68 (2.22–3.24)	1.54 (1.20–1.98)
SBP	112 (2.1)	44 (0.4)	1.3 (1.1–1.6)	0.2 (0.2–0.3)	7.01 (4.51–10.89)	5.43 (3.15–9.38)
Urogenital	584 (10.9)	733 (6.9)	7.3 (6.7–7.9)	3.9 (3.7–4.2)	2.00 (1.76–2.28)	1.34 (1.14–1.58)
Musculoskeletal, skin, and soft tissue	402 (7.5)	375 (3.5)	5.0 (4.5–5.4)	2.0 (1.8–2.2)	2.64 (2.24–3.11)	1.66 (1.35–2.04)
Other	671 (12.5)	753 (7.1)	8.4 (7.7–9.0)	4.0 (3.7–4.3)	2.39 (2.11–2.70)	1.59 (1.36–1.86)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PY, person-years.
SBP, spontaneous bacterial peritonitis.
[a]Conditioned on family and further adjusted for age and sex.
[b]Conditioned on family and further adjusted for age, sex, education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

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Supplementary Table 11. Cumulative Incidence and Absolute Risk Difference in Patients With NAFLD and their Siblings

	1-year follow-up			10-year follow-up			20-year follow-up		
Infection	NAFLD	Siblings	Risk difference (95% CI)	NAFLD	Siblings	Risk difference (95% CI)	NAFLD	Siblings	Risk difference (95% CI)
Any infection	5.1 (4.5–5.7)	0.9 (0.8–1.1)	4.1 (3.8–4.4)	21.3 (20.1–22.5)	9.4 (8.9–10.0)	11.8 (11.2–12.5)	35.9 (34.4–37.5)	20.2 (19.3–21.1)	15.7 (14.9–16.4)
Sepsis	0.9 (0.7–1.2)	0.2 (0.1–0.2)	0.7 (0.6–0.9)	4.6 (4.0–5.2)	1.4 (1.2–1.7)	3.2 (2.9–3.5)	8.7 (7.8–9.7)	3.7 (3.3–4.1)	5.0 (4.6–5.5)
Respiratory tract	1.7 (1.4–2.1)	0.4 (0.3–0.5)	1.4 (1.2–1.5)	9.3 (8.5–10.2)	3.9 (3.6–4.4)	5.3 (4.9–5.8)	16.8 (15.6–18.1)	9.4 (8.8–10.1)	7.4 (6.8–7.9)
Gastrointestinal	0.8 (0.6–1.0)	0.1 (0.1–0.2)	0.7 (0.5–0.8)	3.5 (3.0–4.1)	1.3 (1.0–1.5)	2.2 (2.0–2.5)	6.7 (6.0–7.6)	2.8 (2.4–3.2)	4.0 (3.6–4.4)
SBP	0.4 (0.3–0.7)	0.0 (0.0–0.1)	0.4 (0.3–0.5)	1.4 (1.1–1.8)	0.2 (0.1–0.3)	1.2 (1.1–1.4)	2.5 (2.0–3.0)	0.4 (0.3–0.6)	2.1 (1.8–2.3)
Urogenital	0.9 (0.7–1.2)	0.2 (0.1–0.2)	0.7 (0.6–0.9)	6.2 (5.6–7.0)	2.9 (2.6–3.2)	3.4 (3.0–3.7)	12.5 (11.4–13.6)	7.1 (6.5–7.7)	5.3 (4.8–5.9)
Musculoskeletal, skin, and soft tissue	0.6 (0.4–0.8)	0.2 (0.1–0.3)	0.4 (0.3–0.5)	4.7 (4.1–5.3)	1.6 (1.4–1.9)	3.1 (2.8–3.4)	9.1 (8.2–10.1)	3.5 (3.1–4.0)	5.5 (5.1–6.0)
Other	1.4 (1.1–1.8)	0.2 (0.1–0.3)	1.2 (1.1–1.4)	7.3 (6.6–8.1)	2.5 (2.2–2.9)	4.8 (4.4–5.2)	14.1 (13.0–15.4)	7.2 (6.6–7.8)	6.9 (6.4–7.5)

CI, Confidence interval; NAFLD, nonalcoholic fatty liver disease; SBP, spontaneous bacterial peritonitis.

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Supplementary Table 12. Risk of Any and Specific Infections in Patients With NAFLD and Matched General Population Comparators Using Both Inpatient and Outpatient Care

	N events		Incidence rate (95% CI) per 1000 PY			
Infection	NAFLD	Comparators	NAFLD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Any infection	5904 (48.7%)	21,049 (36.6%)	46.7 (45.5–47.8)	25.3 (24.9–25.6)	2.24 (2.17–2.32)	1.65 (1.59–1.72)
Sepsis	1045 (8.6%)	2595 (4.5%)	6.4 (6.0–6.8)	2.7 (2.6–2.8)	3.07 (2.82–3.33)	2.09 (1.89–2.31)
Respiratory tract	2874 (23.7%)	10,320 (17.9%)	19.2 (18.5–19.9)	11.3 (11.1–11.5)	2.02 (1.93–2.11)	1.51 (1.43–1.60)
Gastrointestinal	903 (7.4%)	2226 (3.9%)	5.6 (5.2–6.0)	2.3 (2.2–2.4)	2.80 (2.57–3.05)	1.95 (1.76–2.16)
SBP	226 (1.9%)	298 (0.5%)	1.4 (1.2–1.5)	0.3 (0.3–0.3)	5.37 (4.40–6.54)	3.63 (2.84–4.63)
Urogenital	2299 (18.9%)	8237 (14.3%)	14.9 (14.3–15.5)	8.8 (8.7–9.0)	2.24 (2.12–2.36)	1.58 (1.48–1.68)
Musculoskeletal, skin, and soft tissue	1448 (11.9%)	4080 (7.1%)	9.1 (8.7–9.6)	4.3 (4.2–4.4)	2.41 (2.26–2.58)	1.78 (1.64–1.93)
Other	2226 (18.3%)	6709 (11.7%)	14.3 (13.7–14.9)	7.1 (7.0–7.3)	2.42 (2.29–2.56)	1.79 (1.68–1.91)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, spontaneous bacterial peritonitis.
[a]Conditioned on matching set (age, sex, county, and calendar period).
[b]Conditioned on matching set and further adjusted for education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

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Supplementary Table 13. Risk of Any and Specific Infections in Patients with NAFLD vs Matched General Population Comparators Using Main Diagnosis

	N events		Incidence rate (95% CI) per 1000 PY			
Infection	NAFLD	Comparators	NAFLD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Any infection	3302 (27.2%)	10,693 (18.6%)	22.5 (21.8–23.3)	11.7 (11.5–12.0)	2.41 (2.31–2.52)	1.67 (1.58–1.77)
Sepsis	603 (5.0%)	1478 (2.6%)	3.7 (3.4–3.9)	1.5 (1.4–1.6)	3.15 (2.82–3.51)	2.08 (1.82–2.38)
Respiratory tract	1527 (12.6%)	5523 (9.6%)	9.6 (9.1–10.1)	5.8 (5.7–6.0)	2.06 (1.93–2.20)	1.47 (1.36–1.59)
Gastrointestinal	491 (4.0%)	1112 (1.9%)	3.0 (2.7–3.3)	1.2 (1.1–1.2)	3.07 (2.72–3.45)	1.97 (1.70–2.29)
SBP	88 (0.7%)	117 (0.2%)	0.5 (0.4–0.6)	0.1 (0.1–0.1)	5.48 (3.99–7.51)	3.54 (2.36–5.32)
Urogenital	906 (7.5%)	3005 (5.2%)	5.6 (5.2–5.9)	3.1 (3.0–3.2)	2.40 (2.20–2.61)	1.69 (1.52–1.87)
Musculoskeletal, skin and soft tissue	591 (4.9%)	1546 (2.7%)	3.6 (3.3–3.9)	1.6 (1.5–1.7)	2.67 (2.41–2.97)	1.76 (1.54–2.00)
Other	464 (3.8%)	1211 (2.1%)	2.8 (2.6–3.1)	1.3 (1.2–1.3)	2.79 (2.47–3.15)	1.91 (1.65–2.21)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, spontaneous bacterial peritonitis.
[a]Conditioned on matching set (age, sex, county, and calendar period);
[b]Conditioned on matching set and further adjusted for education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

Supplementary Table 14. Risk of Any and Specific Infections in Patients With NAFLD and Matched General Population Comparators From 2005 (n NAFLD = 3308; n comparators = 15,114)

	N events		Incidence rate (95% CI) per 1000 PY			
Infection	NAFLD	Comparators	NAFLD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Any infection	915 (27.7%)	1873 (12.4%)	45.7 (42.8–48.7)	15.4 (14.7–16.1)	3.48 (3.18–3.80)	2.19 (1.96–2.44)
Sepsis	219 (6.6%)	283 (1.9%)	9.8 (8.5–11.1)	2.2 (2.0–2.5)	5.53 (4.51–6.78)	3.07 (2.39–3.95)
Respiratory tract	333 (10.1%)	844 (5.6%)	15.2 (13.6–16.9)	6.7 (6.3–7.2)	2.66 (2.32–3.06)	1.77 (1.49–2.10)
Gastrointestinal	136 (4.1%)	201 (1.3%)	6.0 (5.0–7.1)	1.6 (1.4–1.8)	4.69 (3.67–5.99)	2.53 (1.86–3.43)
SBP	78 (2.4%)	37 (0.2%)	3.4 (2.7–4.2)	0.3 (0.2–0.4)	15.92 (9.82–25.82)	13.31 (6.44–27.52)
Urogenital	325 (9.8%)	704 (4.7%)	14.8 (13.2–16.4)	5.6 (5.2–6.0)	3.47 (2.99–4.03)	2.14 (1.79–2.56)
Musculoskeletal, skin, and soft tissue	166 (5.0%)	292 (1.9%)	7.4 (6.3–8.6)	2.3 (2.0–2.6)	3.63 (2.95–4.47)	2.51 (1.96–3.22)
Other	390 (11.8%)	650 (4.3%)	17.8 (16.0–19.6)	5.1 (4.7–5.5)	4.26 (3.69–4.91)	2.62 (2.20–3.11)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, spontaneous bacterial peritonitis.
[a]Conditioned on matching set (age, sex, county, and calendar period).
[b]Conditioned on matching set and further adjusted for education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.

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Supplementary Table 15. Risk of Any and Specific Infections in Patients With NAFLD and Matched General Population Comparators (n NAFLD = 11,000; n comparators = 50,977)

	N events		Incidence rate (95% CI) per 1000 PY			
Infection	NAFLD	Comparators	NAFLD	Comparators	HR[a] (95% CI)	HR[b] (95% CI)
Any infection	3931 (35.7%)	12,967 (25.4%)	29.6 (28.7–30.6)	16.1 (15.8–16.3)	2.35 (2.25–2.45)	1.75 (1.66–1.84)
Sepsis	876 (8.0%)	2098 (4.1%)	5.7 (5.3–6.1)	2.4 (2.3–2.5)	2.98 (2.73–3.27)	2.16 (1.94–2.42)
Respiratory tract	1857 (16.9%)	6543 (12.8%)	12.7 (12.1–13.2)	7.7 (7.5–7.9)	2.05 (1.93–2.17)	1.56 (1.45–1.67)
Gastrointestinal	564 (5.1%)	1358 (2.7%)	3.7 (3.4–4.0)	1.6 (1.5–1.6)	2.88 (2.58–3.21)	2.00 (1.74–2.30)
SBP	183 (1.7%)	252 (0.5%)	1.2 (1.0–1.3)	0.3 (0.3–0.3)	4.99 (4.01–6.19)	3.42 (2.60–4.50)
Urogenital	1556 (14.1%)	5363 (10.5%)	10.5 (9.9–11.0)	6.3 (6.1–6.4)	2.31 (2.17–2.47)	1.72 (1.58–1.86)
Musculoskeletal, skin, and soft tissue	717 (6.5%)	1878 (3.7%)	4.7 (4.4–5.0)	2.2 (2.1–2.3)	2.60 (2.37–2.87)	1.90 (1.69–2.14)
Other	1318 (12.0%)	3841 (7.5%)	8.7 (8.2–9.2)	4.4 (4.3–4.6)	2.54 (2.36–2.73)	1.94 (1.78–2.12)

CI, Confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, spontaneous bacterial peritonitis.
[a]Conditioned on matching set (age, sex, county, and calendar period).
[b]Conditioned on matching set and further adjusted for education, country of birth, baseline clinical comorbidities (diabetes, obesity, dyslipidemia, and hypertension), chronic obstructive pulmonary disease, and number of hospitalizations in the year preceding the index date.