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Metabolic Dysfunction-Associated Steatotic Liver Disease and Pancreatic Disease—A Population-Based Nationwide Cohort and Sibling-Controlled Study

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ABSTRACT

Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) has been linked to pancreatic diseases, but evidence from population-based studies with liver histology is lacking.

Aims and methods: In this population-based cohort including all Swedish adults (n = 8563) with biopsy-proven MASLD, we aimed to investigate incidences of pancreatic diseases compared with matched reference individuals from the general population (n = 38,858) and full siblings (n = 6696). Using Cox proportional hazard models, we calculated multivariable adjusted hazard ratios (aHRs) and confidence intervals (CIs).

Results: We documented 359 incidents of pancreatic diseases in MASLD patients and 880 events in matched reference individuals, resulting in an incidence rate difference of 1.54 (95% CI, 1.25–1.84). The relative risk of pancreatic disease was highest in the first two years after MASLD diagnosis (aHR, 2.19 [95% CI, 1.92–2.50), but remained statistically significant increased even up to ten years [aHR, 1.60 (95% CI, 1.38–1.85)]. The most common pancreatic disease in individuals with MASLD was acute non-biliary pancreatitis (1.44 vs. 0.44 events/1000 PY), followed by chronic pancreatitis (0.54 vs. 0.12/1000 PY) and pancreatic cancer (0.88 vs. 0.47/1000 PY). We documented 130 versus 344 pancreas-related deaths among individuals with MASLD and their matched comparators, yielding an absolute risk difference of 0.51/1000 PY and an aHR of 2.41 (95%CI = 1.95–2.97). The findings were consistent in sibling-controlled analyses with an aHR of 2.21 (95%CI = 1.69–2.90).

Conclusions: MASLD was associated with significantly higher rates of acute and chronic pancreatitis of predominantly non-biliary origin, as well as an increased risk of pancreatic cancer and pancreas-related mortality.

Abbreviations: ESPRESSO, epidemiology strengthened by histoPathology reports in Sweden; HR, hazard ratio; ICD, international classification of diseases; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PERT, pancreatic enzyme replacement therapy; SnoMed CT-System, Systematized Nomenclature of Medicine—Clinical Terms.

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Summary

- MASLD was associated with significantly higher rates of acute non-biliary pancreatitis, chronic pancreatitis, and pancreatic cancer compared with matched reference individuals.
- The risk of pancreas-related mortality was more than twofold higher in individuals with MASLD.
- Patients with MASLD were more than twice as likely to develop any pancreatic disease, with an absolute excess rate of 2.74 per 1000 person-years.
- The risk of pancreatic disease increased progressively with worsening histological severity of MASLD, with the highest risks observed in individuals with liver fibrosis or cirrhosis.
- A more than twofold increased risk of pancreatic disease was also observed in individuals with simple steatosis or non-fibrotic MASH.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD)—formerly known as nonalcoholic fatty liver disease (NAFLD)—is the most common chronic liver disease in Western countries, affecting approximately one-third of the adult general population [1]. In parallel with the global rise in obesity and metabolic syndrome, the incidence and prevalence of MASLD are expected to further increase [2–4]. MASLD is a multisystem disorder [5] associated with a variety of extrahepatic conditions and adverse outcomes including cardiovascular disease [6], chronic kidney disease [7], and increased risk of both infections [8] and overall mortality [9].

Recent studies suggest that MASLD might also increase the risk of pancreatic disorders, such as pancreatic cancer [10], as well as affecting the severity of acute pancreatitis (AP) [11]. Pathophysiologically, fatty pancreas is the most common pathology of the pancreas associated with metabolic syndrome, with an estimated prevalence of 16% among the general population. The fatty pancreas shares the same contributing factors as MASLD (i.e., central obesity, hypertriglyceridemia, and insulin resistance) [12].

In this nationwide longitudinal cohort study involving all adults in Sweden with biopsy-proven MASLD, we aimed to investigate the overall incidences of any acute or chronic pancreatic disease including acute pancreatitis (biliary and non-biliary origins), chronic pancreatitis, pancreatic cancer, and pancreas-related mortality compared to matched reference individuals from the general population, as well as to full siblings to account for intrafamilial confounding.

2 | Methods

This was a population-based cohort study using the Epidemiology Strengthened by histopathology Reports in Sweden (ESPRESSO) cohort [13], which included all individuals with liver histopathology in Sweden between 1965 and 2017. Using the unique Swedish personal identity number, several validated nationwide registers were linked to obtain data on demographics, inpatient and outpatient diagnoses, prescribed medications, incident cancers, and causes of death [14–17]. ESPRESSO was approved by the Stockholm Regional Ethics Committee, which waived individual informed consent. This study followed the Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) reporting guidelines [18] (Supplementary Appendix).

2.1 | Patient Population

We included all adult patients (≥ 30 years) in Sweden who underwent a liver biopsy between 1965 and 2017 consistent with MASLD, without the presence of any other competing liver disease. Using a validated algorithm, we excluded patients with a history of alcohol abuse/misuse, other etiologies of acute or chronic liver disease, previous liver transplantation, or emigration from Sweden before the date of liver biopsy (i.e., the index date) (Supporting Information S1: Table S1). This methodology has been shown to have a positive predictive value (PPV) for MASLD of 92% [9]. Each patient with MASLD was then matched to up to five reference individuals from the general population without a diagnosis of MASLD. Matching was performed according to sex, age at index date, calendar year, and county of residence, and identical exclusion criteria were applied to the reference individuals.

We applied strict eligibility criteria to exclude any previous diagnoses or alternative causes of pancreatic disease, as well as established risk factors for acute and chronic pancreatitis. In brief, patients were excluded if they had any evidence of any previous pancreatic diseases (e.g., any pancreatitis or pancreatic cancer), surgery of the liver or biliary system, postprocedural or post-pancreatectomy-related diabetes mellitus, IgG4-related disease, inflammatory bowel disease, hyperparathyroidism, or previous medication with pancreatic enzyme replacement therapy (PERT) or class 1 medications for drug-induced acute pancreatitis [19] (see all definitions of exclusion criteria in Supporting Information S1: Table S2).

We used histology reports from clinical routine for the diagnosis and subclassification of MASLD. Information on the number of pathologists evaluating each histological slide was not available. To perform stratified analyses according to the different stages of MASLD disease severity, patients meeting the criteria were subsequently classified into three histological subgroups using SNOMED (Systematized Nomenclature of Medicine) definitions [20] for coherent nationwide histopathology reporting in Sweden: simple steatosis, metabolic dysfunction-associated steatohepatitis (MASH) without fibrosis, and MASLD with fibrosis or cirrhosis. The definitions of each category were in line with previous validation work and are summarized in Supporting Information S1: Table S3 [9]. We ascertained demographic data (e.g. age, sex, and emigration from Sweden) using the Total Population Register [14]. Data on education level served as a proxy for socioeconomic

status and were collected from the prospective LISA (longitudinal integrated database for health insurance and labor market studies) database [21].

2.2 | Primary and Secondary Outcomes

The primary endpoint of pancreatic disease was a composite of acute non-biliary pancreatitis, chronic pancreatitis, and pancreatic cancer. Secondary outcomes included each of the single outcomes as well as acute biliary pancreatitis and pancreas-related mortality. Detailed definitions of all outcomes are summarized in Supporting Information S1: Table S4.

Outcomes were obtained from the Swedish National Patient Register, which prospectively includes all data from hospitalizations since 1964 (nationwide since 1987) and specialized outpatient care visits from 2001 onwards [15]. Previous validation studies confirmed PPVs for clinical diagnoses of 85%–95% [15]. Pancreas-related death was identified through the Cause of Death Register, which has almost complete coverage of all deaths in Sweden [17].

2.3 | Statistical Analysis

Incidence rates for any pancreatic disease were calculated per 1000 person-years (PYs) of follow-up. Patients were followed from index date until the first incident of pancreatic disease, death, emigration from Sweden, or end of follow-up on December 31, 2021, whichever came first.

Using Cox proportional hazard models, we estimated multivariable adjusted hazard ratios (aHRs) for two models. The first model was conditioned on all matching factors (age, sex, county of residence, and calendar year of biopsy) without additional adjustment. In the fully multivariable adjusted model, we further adjusted for educational attainment, country of birth, and an a priori defined list of relevant baseline covariates: diabetes mellitus, obesity, dyslipidemia, hypertension, celiac disease, inflammatory bowel disease, and time-varying new-onset of alcohol-related disorders [22]. The associations between MASLD and pancreatic disease were investigated in stratified analyses according to sex, age categories (30 < 45, 45–59, and ≥ 60 years), duration of follow-up (< 2, 2–9, and ≥ 10 years), calendar period of the start of follow-up, country of birth (Nordic [Sweden, Denmark, Finland, Norway, and Iceland] and others), and diagnosis of metabolic comorbidities (i.e., obesity, diabetes mellitus, dyslipidemia, or hypertension). The proportional hazard assumption was tested. We constructed Kaplan-Meier failure curves to present cumulative risk.

We conducted several sensitivity analyses to test the robustness of our results. First, we repeated the primary and secondary analyses after comparing the MASLD patients with their full siblings without MASLD to account for potential confounding owing to shared genetic and early environmental factors. Second, we censored anyone diagnosed with any pancreatic disease within ≤ 90 days of follow-up or anyone within ≤ 2 years of follow-up to assess the potential influence of detection bias. Third, to minimize potential bias related to the primary indication for liver biopsy, we restricted our data to individuals who had all undergone liver biopsy (with histologically defined MASLD) and performed a sensitivity analysis with simple steatosis as the reference. This further allowed us to characterize the gradient of pancreas-related outcome risk associated with progressive MASLD histological severity. Statistical analyses were conducted using R software (V.3.6.1, R Foundation for Statistical Computing, Vienna, Austria). A two-sided $p < 0.05$ was considered statistically significant.

3 | Results

3.1 | Patient Characteristics

The baseline characteristics of all patients with MASLD and reference individuals are summarized in Table 1. In total, 8563 patients with biopsy-proven MASLD and 38,858 matched reference individuals were included (Supporting Information S1: Figure S1). Among MASLD patients, the average age at index biopsy was 54.5 years, and 56.9% were male. Most patients had simple steatosis (n = 5804; 67.8%), while 963 (11.2%) had non-fibrotic MASH, and 1796 (21.0%) were diagnosed with liver fibrosis or cirrhosis due to MASLD. With increasing MASLD histologic severity, the rates of diabetes mellitus, hypertension, and dyslipidemia increased in a dose-dependent manner (Table 1). Median follow-up was 15.1 years (interquartile range, IQR 6.85–23.27) among MASLD patients, and 19.4 years (IQR 11.66–25.73) among population comparators.

3.2 | Primary Endpoint

Overall, we documented 359 incidents of pancreatic disease in MASLD patients (2.74 per 1000 PYs) and 880 events in matched reference individuals (1.19 per 1000 PYs), resulting in an incidence rate difference of 1.54 (95% CI, 1.25–1.84) (Table 2, Figure 1A). After multivariable adjustment, the aHR for incident pancreatic disease was 2.19 (95% CI; 1.92–2.50) in the fully adjusted model. This corresponds to a 20-year absolute excess risk of 3.1%, or equivalent to one additional case of pancreatic disease per 32 individuals with MASLD over 20 years of follow-up.

The significant, positive association was independent of sex, age category, or the presence of metabolic syndrome features such as obesity, diabetes mellitus, or dyslipidemia ($P_{\text{for heterogeneity}} > 0.05$; Supporting Information S1: Table S5). The relative risk of pancreatic disease was highest in the first two years after histologic MASLD diagnosis (aHR, 2.19 [95% CI, 1.92–2.50]) but remained statistically significantly increased even up to ten years (aHR, 1.60 [95% CI, 1.38–1.85]). Compared to reference individuals, the incidence rate differences and corresponding aHRs increased with worsening histologic MASLD severity, with 2.46 per 1000 PYs (aHR, 2.07 [95% CI, 1.77–2.43]) in simple steatosis, 3.39 per 1000 PYs (aHR, 2.69 [95% CI, 1.83–3.96]) in non-fibrotic MASH, and 3.56 per 1000 PYs (aHR, 2.53 [95% CI, 1.87–3.43]) in patients with MASLD-associated fibrosis or cirrhosis (Table 3, Figure 1B).

TABLE 1 | Baseline characteristics of individuals with biopsy-Proven MASLD and matched reference individuals.

		MASLD			
	Reference individuals (n = 38858)	**Total (n = 8563)**	**Simple steatosis (n = 5804)**	**Non-fibrotic MASH (n = 963)**	**Fibrosis or cirrhosis (n = 1796)**
Sex					
Male	22153 [57.01]	4873 [56.91]	3324 [57.27]	519 [53.89]	1030 [57.35]
Female	16705 [42.99]	3690 [43.09]	2480 [42.73]	444 [46.11]	766 [42.65]
Age at start follow-up (yrs)					
Mean [SD]	54.08 [12.79]	54.47 [12.88]	53.60 [13.05]	54.86 [12.90]	57.05 [11.96]
Range, min–max	30–92	30–91	30–88	30–88	30–91
30–< 45	10050 [25.86]	2145 [25.05]	1601 [27.58]	225 [23.36]	319 [17.76]
45 < 60	15069 [38.78]	3280 [38.30]	2237 [38.54]	377 [39.15]	666 [37.08]
≥ 60	13739 [35.36]	3138 [36.65]	1966 [33.87]	361 [37.49]	811 [45.16]
Country of birth					
Nordic	35593 [91.60]	7697 [89.89]	5266 [90.73]	849 [88.16]	1582 [88.08]
Other	3265 [8.40]	866 [10.11]	538 [9.27]	114 [11.84]	214 [11.92]
Education					
Compulsory school (≤ 9 years)	1796 [22.00]	420 [22.22]	183 [19.78]	58 [21.48]	179 [25.76]
Upper secondary school (10–12 years)	3583 [43.90]	864 [45.71]	423 [45.73]	136 [50.37]	305 [43.88]
College or university (≥ 13 years)	2619 [32.09]	477 [25.24]	250 [27.03]	55 [20.37]	172 [24.75]
Missing	164 [2.01]	129 [6.83]	69 [7.46]	21 [7.78]	39 [5.61]
Start of follow-up					
1965–1989	8414 [21.65]	1793 [20.94]	1407 [24.24]	149 [15.47]	237 [13.20]
1990–2005	23161 [59.60]	5077 [59.29]	3579 [61.66]	568 [58.98]	930 [51.78]
2006–2017	7283 [18.74]	1693 [19.77]	818 [14.09]	246 [25.55]	629 [35.02]
Comorbidities					
Diabetes mellitus	1055 [2.72]	936 [10.93]	482 [8.30]	111 [11.53]	343 [19.10]
Dyslipidemia	1342 [3.45]	615 [7.18]	290 [5.00]	89 [9.24]	236 [13.14]
Obesity	111 [0.29]	300 [3.50]	177 [3.05]	34 [3.53]	89 [4.96]
Hypertension	2602 [6.70]	1481 [17.30]	787 [13.56]	196 [20.35]	498 [27.73]
Inflammatory bowel disease	6 [0.02]	110 [1.28]	70 [1.21]	15 [1.56]	25 [1.39]
Celiac disease	9 [0.02]	61 [0.71]	36 [0.62]	8 [0.83]	17 [0.95]

Abbreviations: MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; SD, standard deviation.

3.3 | Acute Pancreatitis

Compared to reference individuals, the most common pancreatic disease in individuals with biopsy-proven MASLD was acute non-biliary pancreatitis, with 1.44 versus 0.44 events per 1000 PYs, resulting in an aHR of 2.24 (95% CI, 1.83–2.75; Table 2, Figure 2A). Among histologic subgroups, the risk was highest in those with MASLD-associated fibrosis or cirrhosis (1.56 per 1000 PYs; aHR 3.09 [95% CI, 1.90–5.02]) when compared with those with simple steatosis (1.13 per 1000 PYs; aHR 2.19 [95% CI, 1.72–2.79]; Table 3). By comparison, incidence rates of acute biliary pancreatitis were much lower but were also more frequent compared to the general population (0.42 vs. 0.25 per 1000 PYs; aHR 1.73 [95% CI, 1.26–2.38]). When stratified into histological subgroups, the risk of acute biliary pancreatitis did not increase with the histologic severity of MASLD ($P_{\text{for trend}} > 0.05$).

3.4 | Chronic Pancreatitis

Consistent with the results on acute pancreatitis, individuals with MASLD had significantly higher rates of developing chronic pancreatitis (0.54 vs. 0.12 per 1000 PY; aHR 3.78, 95% CI 2.70–5.29) (Table 2, Figure 2B). Among individuals with biopsy-proven MASLD, the highest risk of chronic pancreatitis was seen in those with a diagnosis of MASLD-associated fibrosis or cirrhosis (aHR 7.57 [95% CI, 3.60–15.94]; Table 3).

TABLE 2 | Incident pancreatic events in patients with biopsy-Proven MASLD and matched reference individuals.

Outcomes	No. of events (Incidence rate, per 1000 PY)		Incidence rate difference (95% CI), per 1000 PY	HR (95% CI)	
	Reference individuals (n = 38858)	MASLD (n = 8563)		Model 1[a]	Model 2[b]
Primary outcome					
Pancreatic disease[c]	880 (1.19)	359 (2.74)	1.54 [1.25–1.84]	2.45 [2.16–2.77]	2.19 [1.92–2.50]
Secondary outcomes					
Acute non-biliary pancreatitis	326 (0.44)	157 (1.44)	0.75 [0.55–0.94]	2.77 [2.29–3.36]	2.24 [1.83–2.75]
Acute biliary pancreatitis	182 (0.25)	56 (0.42)	0.17 [0.06–0.29]	1.84 [1.36–2.48]	1.73 [1.26–2.38]
Chronic pancreatitis	88 (0.12)	72 (0.54)	0.42 [0.29–0.55]	4.68 [3.42–6.39]	3.78 [2.70–5.29]
Pancreatic cancer	352 (0.47)	118 (0.88)	0.41 [0.24–0.58]	2.09 [1.69–2.57]	2.07 [1.66–2.58]
Pancreas-related mortality	344 (0.46)	130 (0.97)	0.51 [0.33–0.68]	2.41 [1.96–2.95]	2.41 [1.95–2.97]

Abbreviations: CI, confidence interval; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; PY, person-year.
[a]Conditioned on the matching variables (birth year, sex, county of residence, and calendar year).
[b]Further adjusted for educational attainment, country of birth, diabetes mellitus, obesity, hypertension, dyslipidemia, celiac disease, and inflammatory bowel disease.
[c]Composite of acute non-biliary pancreatitis, chronic pancreatitis, and pancreatic cancer.

3.5 | Pancreatic Cancer

Compared to matched reference individuals, MASLD patients had significantly higher rates of incident pancreatic cancer (0.88 vs. 0.47 per 1000 PY), resulting in an absolute rate difference of 0.41 per 1000 PY, which corresponds to one excess cancer in 122 persons in a 20-year period. After multivariable adjustment, patients with biopsy-proven MASLD had a twofold increased relative risk of developing pancreatic cancer compared with matched individuals from the general population (95% CI, 1.66 to 2.58; Table 2; Figure 2C). The increased risk was already evident in individuals with simple steatosis (0.77 per 1000 PY; aHR 1.99 [95% CI, 1.52–2.61]), and was highest among individuals with non-fibrotic MASH (1.75 per 1000 PY; aHR 4.70 [95% CI, 2.64–8.39]). Compared with matched reference individuals, the rate of incident pancreatic cancer was higher in MASLD patients with histological evidence of liver fibrosis or cirrhosis (0.86 vs. 0.47 per 1000 PY), but the multivariable-adjusted HR did not reach statistical significance (aHR 1.41 [95% CI, 0.81–2.47]).

3.6 | Pancreas-Related Mortality

We documented 130 versus 344 pancreas-related deaths among individuals with MASLD and their matched comparators (0.97 vs. 0.46 per 1000 PY), yielding an absolute risk difference of 0.51 per 1000 PY and an aHR of 2.41 (95% CI 1.95−2.97; Table 2; Figure 2D). After 20 years, this corresponded to an absolute excess risk of liver-related mortality of 1.02% or one additional pancreas-related death in 98 individuals with MASLD. Individuals with simple steatosis already had a twofold increased risk of pancreas-related mortality (0.92 vs. 0.46 deaths per 1000 PY; aHR 2.41 [95% CI, 1.88–3.11]), which was further increased in those with MASH (1.68 per 1000 PY; aHR 4.72 [95% CI, 2.65–8.41]). By contrast, individuals with histological evidence of fibrosis or cirrhosis did not have a higher relative risk of death from pancreatic causes (aHR 1.47 [95% CI, 0.82–2.64]).

3.7 | Sensitivity Analyses

The findings were robust across all sensitivity analyses. First, to account for intrafamilial susceptibilities, we restricted the cohort to patients with MASLD who had ≥ 1 full sibling without recorded MASLD and then compared each MASLD patient with 6696 full sibling(s). Sibling analyses confirmed an increased risk of pancreatic disease in patients with MASLD (2.59 vs. 1.18 per 1000 PY; aHR, 2.21; 95% CI, 1.69–2.90; Supporting Information S1: Table S6). Second, we repeated the primary analysis and observed similar associations after excluding the first 90 days of follow-up (difference 1.19 per 1000 PY; aHR 1.88 [95%CI, 1.63–2.16]; Supporting Information S1: Table S7) and the first two years of follow-up (difference 0.87 per 1000 PY; aHR 1.68 [95% CI, 1.44–1.95]; Supporting Information S1: Table S8). After restricting the population to patients with biopsy-confirmed MASLD, the absolute rates of incident pancreatic disease increased with worsening

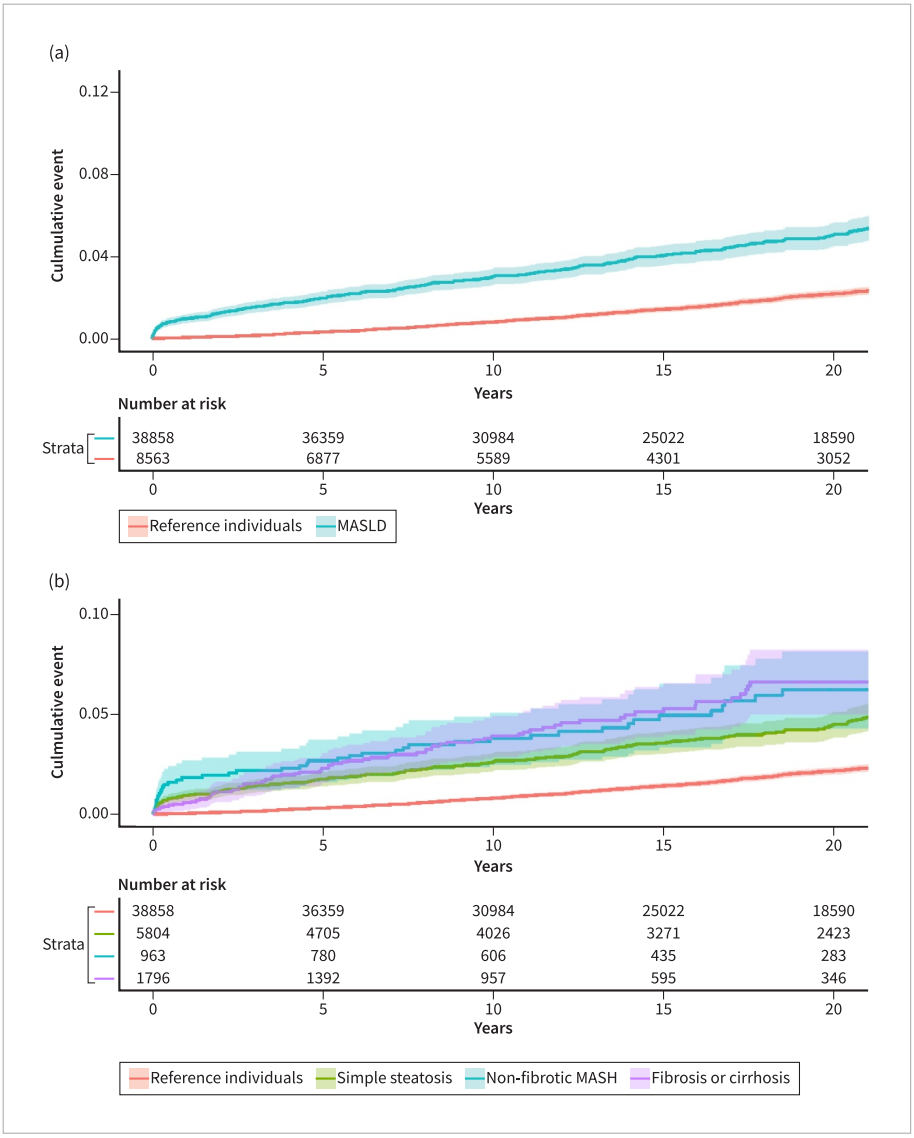

FIGURE 1 | Cumulative incidence curves of time to any pancreatic disease (A) in all patients with biopsy-proven MASLD and (B) among histological subgroups* of MASLD severity compared to matched reference individuals. *Histological severity of MASLD was defined in three categories: simple steatosis, non-fibrotic MASH, and fibrosis or cirrhosis.

MASLD histological severity, with the highest rates observed with MASLD-associated fibrosis or cirrhosis (Supporting Information S1: Table S9). Specifically, compared to simple steatosis, the absolute excess rates of pancreatic disease with non-fibrotic MASH and fibrosis/cirrhosis were 0.94 and 1.10 per 1000 PY, respectively. After multivariable adjustment, this translated to a 22% higher relative risk of incident pancreatic disease in patients with fibrosis or cirrhosis, compared to those with simple steatosis (aHR 1.22, 95% CI 0.93–1.61).

4 | Discussion

In this population-based cohort composed of all Swedish adults with biopsy-confirmed MASLD of all histological stages and matched reference individuals from the general population, MASLD was associated with significantly higher rates of acute non-biliary pancreatitis, chronic pancreatitis, and pancreatic cancer, all of which led to a higher risk of pancreas-related mortality. By contrast, the risk of acute biliary pancreatitis was only slightly increased. Compared to reference individuals, patients with MASLD were more than twice as likely to develop any pancreatic disease with an absolute excess rate of 2.74 per 1000 PY, which corresponds to one additional incident pancreatic disease per 32 patients with MASLD over 20 years of follow-up. While rates of both fatal and non-fatal pancreatic diseases increased with worsening histologic severity of MASLD, with the highest risks among those with histological evidence of liver fibrosis or cirrhosis, we observed a more than twofold increased risk of pancreatic disease in individuals with simple steatosis or non-fibrotic MASH. The findings were robust to several sensitivity analyses, including comparisons of MASLD patients with their full siblings. This latter analysis addresses genetic and intrafamilial susceptibility to pancreatitis or pancreatic cancer.

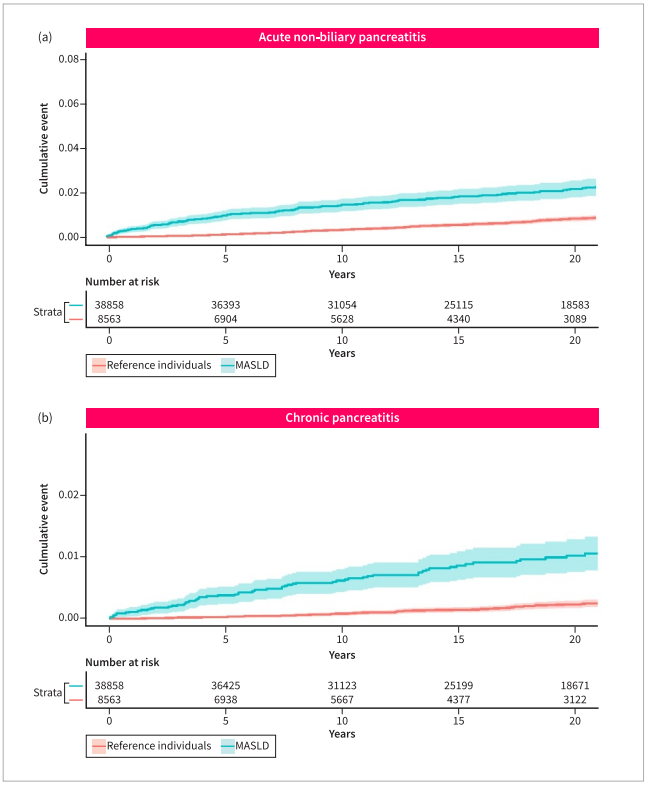

FIGURE 2 | Cumulative incidence curves of time to acute non-biliary pancreatitis (A), chronic pancreatitis (B), pancreatic cancer (C), and pancreas-related mortality (D) in patients with biopsy-proven MASLD and compared to matched reference individuals.

All incident pancreatic diseases observed during the study period represented the first clinical manifestation of pancreatic disease in the cohort, as we rigorously excluded anyone with a history of pancreatic disease. While the most common causes of acute and chronic pancreatitis are usually related to either excessive alcohol consumption or biliary etiology (e.g., cholelithiasis), we carefully excluded anyone with alcohol use disorder or known alcohol-related liver disease. Furthermore, in our fully adjusted model, we additionally accounted for any new-onset alcohol-related disorders. We also applied extensive exclusion criteria related to biliary disease, autoimmune pancreatitis type 1 (i.e., patients with a diagnosis of IgG4-related disease), autoimmune pancreatitis type 2 (i.e., patients with inflammatory bowel disease, which is often associated with autoimmune pancreatitis type 2), and hereditary pancreatitis (i.e., patients younger than 30 years). Patients were also excluded if they had a history of liver or biliary surgery, postoperative or post-pancreatectomy diabetes mellitus, hyperparathyroidism, or any medication with PERT or class one drugs that have been shown to cause drug-induced acute pancreatitis. By using these strict exclusion criteria, we were able to narrow down the possible etiology of pancreatic disease in these patients to metabolic dysfunction-associated causes. In addition, we adjusted our analyses for cardiometabolic risk factors for pancreatic disease including obesity and diabetes mellitus —both components of metabolic syndrome—which have been shown to have a major impact on the progression of pancreatic disease and are established risk factors for pancreatic cancer [23].

Despite the high global prevalence of MASLD, only a subset of affected individuals will develop pancreatic disease. We can only speculate on the underlying mechanisms and risk factors and hypothesize that pancreatic disease follows a sequence starting with an initial episode of an acute pancreatitis—and depending on the duration and severity of the metabolic syndrome—some individuals will either develop further symptomatic or even asymptomatic acute episodes or progress directly to chronic pancreatitis, putting individuals at risk for pancreatic cancer.

Our results lead to a discussion of the underlying causes and mechanisms and to hypothesis-generating considerations. Considering the broad exclusion criteria and meticulous adjustments of our analyses, it can be hypothesized that in line with liver steatosis, pancreatic fat accumulation and subsequent tissue inflammation may be one possible pathophysiological explanation. Different wordings have been used to describe fatty pancreas, such as pancreatic lipomatosis, pancreatic steatosis, fatty replacement, fatty infiltration, fatty pancreas, lipomatous pseudohypertrophy, and nonalcoholic fatty pancreas disease [24]. Smits and van Geenen proposed a distinction between the process of fatty replacement of the pancreas, which is defined by the death of acinar cells with subsequent replacement with adipocytes, and fatty infiltration, which describes an infiltration of adipocytes owing to obesity or metabolic syndrome. The authors proposed the term “nonalcoholic fatty pancreas disease” which, in line with MASLD, may also lead to nonalcoholic fatty steatopancreatitis, defined as pancreatitis due to an increased pancreatic fat accumulation [24]. The similarity of these proposed pancreatological terms to the classification and nomenclature of steatotic liver disease is obvious. A recent systematic review identified 17 studies with 2956 patients and concluded that a fatty pancreas is six times more common among

TABLE 3 | Pancreatic diseases according to MASLD histology.

Outcomes	Reference individuals (n = 38858)	MASLD		
		Simple steatosis (n = 5804)	Non-fibrotic MASH (n = 963)	Fibrosis or cirrhosis (n = 1796)
Pancreatic disease[c]	880	236	46	77
Incidence rate[a], per 1000 PY (95% CI)	1.19 [1.12–1.27]	2.46 [2.16–2.78]	3.39 [2.55–4.44]	3.56 [2.85–4.40]
Incidence rate difference[a] (95% CI)	0 (ref.)	1.26 [0.94–1.59]	2.20 [1.22–3.18]	2.37 [1.57–3.17]
Multivariable-adjusted HR[b] (95% CI)	1 (ref.)	2.07 [1.77–2.43]	2.69 [1.83–3.96]	2.53 [1.87–3.43]
Acute non-biliary pancreatitis	326	109	14	34
Incidence rate[a], per 1000 PY (95% CI)	0.44 [0.40–0.49]	1.13 [0.93–1.35]	1.03 [0.62–1.63]	1.56 [1.12–2.12]
Incidence rate difference[a] (95% CI)	0 (ref.)	0.69 [0.47–0.90]	0.59 [0.05–1.13]	1.11 [0.59–1.64]
Multivariable-adjusted HR[b] (95% CI)	1 (ref.)	2.19 [1.72–2.79]	1.62 [0.83–3.16]	3.09 [1.90–5.02]
Acute biliary pancreatitis	182	35	10	11
Incidence rate[a], per 1000 PY (95% CI)	0.25 [0.21–0.28]	0.36 [0.26–0.49]	0.73 [0.40–1.25]	0.50 [0.28–0.84]
Incidence rate difference[a] (95% CI)	0 (ref.)	0.11 [−0.01–0.24]	0.49 [0.03–0.94]	0.25 [−0.04–0.55]
Multivariable-adjusted HR[b] (95% CI)	1 (ref.)	1.43 [0.97–2.11]	2.94 [1.27–6.84]	2.88 [1.36–6.07]
Chronic pancreatitis	88	45	3	24
Incidence rate[a], per 1000 PY (95% CI)	0.12 [0.10–0.14]	0.46 [0.35–0.61]	0.22 [0.08–0.53]	1.10 [0.74–1.58]
Incidence rate difference[a] (95% CI)	0 (ref.)	0.34 [0.21–0.48]	0.10 [−0.15–0.35]	0.98 [0.54–1.42]
Multivariable-adjusted HR[b] (95% CI)	1 (ref.)	3.79 [2.54–5.67]	0.57 [0.12–2.67]	7.57 [3.60–15.94]
Pancreatic cancer	352	75	24	19
Incidence rate[a], per 1000 PY (95% CI)	0.47 [0.43–0.53]	0.77 [0.61–0.95]	1.75 [1.18–2.52]	0.86 [0.55–1.29]
Incidence rate difference[a] (95% CI)	0 (ref.)	0.29 [0.11–0.47]	1.28 [0.57–1.98]	0.39 [0.00–0.78]
Multivariable-adjusted HR[b] (95% CI)	1 (ref.)	1.99 [1.52–2.61]	4.70 [2.64–8.39]	1.41 [0.81–2.47]
Pancreas-related mortality	344	90	23	17
Incidence rate[a], per 1000 PY (95% CI)	0.46 [0.42–0.51]	0.92 [0.75–1.12]	1.68 [1.12–2.43]	0.77 [0.48–1.18]
Incidence rate difference[a] (95% CI)	0 (ref.)	0.46 [0.26–0.65]	1.21 [0.53–1.90]	0.31 [−0.06–0.68]
Multivariable-adjusted HR[b] (95% CI)	1 (ref.)	2.41 [1.88–3.11]	4.72 [2.65–8.41]	1.47 [0.82–2.64]

Abbreviations: CI, confidence interval; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis, PY, person-year.

[a]Incidence rate differences per 1000 PY. CIs for incidence rates and absolute rate differences were approximated by the normal distribution.

[b]The multivariable model was conditioned on the matching variables (birth year, sex, county of residence, and calendar year) and further adjusted for educational attainment, country of birth, diabetes mellitus, obesity, hypertension, dyslipidemia, celiac disease, and inflammatory bowel disease.

[c]Composite of acute non-biliary pancreatitis, chronic pancreatitis, and pancreatic cancer.

individuals diagnosed with pancreatic cancer. However, strong conclusions should be avoided due to considerable statistical and clinical heterogeneity among the studies [25]. It should also be considered that results from studies investigating risk factors for pancreatic cancer are often biased by confounding factors such as diabetes, alcohol consumption, and smoking [26].

Fatty pancreas does not have an International Classification of Diseases (ICD) code and therefore cannot be tracked through traditional healthcare registers. Fatty pancreas is not typically coded or reported in histology reports (and besides, most patients with fatty pancreas do not undergo biopsy). Instead, fatty pancreas tends to be detected through imaging.

A recently published systematic review and meta-analysis summarized the evidence on the association between MASLD and fatty pancreas, identifying 26 studies with 67,803 participants [27]. The authors observed a significant association between MASLD and fatty pancreas both before and after diagnosis of MASLD (odds ratios OR 6.18 and 9.56, respectively) [27]. However, conclusions on bidirectional associations between MASLD and fatty pancreas should be interpreted cautiously due to the substantial heterogeneity between the studies, especially in terms of patient selection and imaging methods used.

4.1 | Strengths and Limitations

This nationwide histology cohort of well-characterized individuals with biopsy-proven MASLD has a virtually complete follow-up for up to 54 years, which enabled us to assess incident pancreatic disease across the full histological spectrum of MASLD. We rigorously ruled out any known risk factors for pancreatic diseases such as alcohol use disorder, biliary diseases, or autoimmune diseases, so that the findings can be related to MASLD-associated metabolic dysfunction. In addition, we performed a series of sensitivity analyses confirming the robustness of our results, including a sibling-controlled analysis, which alleviated unmeasured confounding from shared familiar risk factors toward pancreatitis or pancreatic cancer.

However, we acknowledge several limitations. First, due to the register-based design of the study, we lacked detailed information on lifestyle factors, such as smoking and, most importantly, the amount of alcohol consumed. Although we excluded anyone with a known alcohol-related disorder, we cannot completely rule out unrecognized harmful alcohol consumption as a residual confounder that may indeed explain some cases of acute pancreatitis. Such behaviors, however, tend to cluster within families, and our main findings also persisted in sibling-controlled analysis. Second, we can only speculate about the underlying causes of the association between MASLD and adverse pancreatic outcomes since we lacked information on imaging (to investigate fatty pancreas) or laboratory parameters (to evaluate exocrine or endocrine pancreatic deficiency). Third, due to the design of the study, we were unable to examine the potential role of MASLD on the clinical course of pancreatic disease. We were not able to distinguish between mild and severe acute pancreatitis, but it can be assumed that most patients have moderate or severe pancreatitis since such disease is more likely to be registered in hospital. Finally, the study was conducted in Sweden; hence, the findings may not necessarily be generalized to other regions and ethnic groups.

5 | Conclusions

Within a large population-based cohort of more than 8500 adults with biopsy-proven MASLD and matched reference individuals, MASLD was associated with significantly higher rates of acute pancreatitis, chronic pancreatitis, and pancreatic cancer, all of which led to a more than twofold increased risk of pancreas-related mortality. The higher risk of adverse pancreatic outcomes was evident across the full spectrum of MASLD histology, but the magnitude of the risk increased progressively with worsening MASLD severity. Acute pancreatitis was predominantly of non-biliary etiology, which raises the hypothesis of whether pancreatic fat accumulation in the context of metabolic syndrome may contribute to these associations at least to some extent. Future mechanistic studies are warranted to investigate the underlying pathophysiological mechanisms that led to these observations. Finally, our study provides support for heightened awareness of pancreatic diseases among clinicians caring for individuals with MASLD, especially in adults with liver fibrosis or cirrhosis.

Author Contributions

All authors conceived and designed the study. MV, FE, and JFL wrote the first draft of the paper. JFL supervised the project. MV and JFL funded the study. BR carried out the statistics. All authors interpreted the data and contributed to the writing of this paper. All authors revised and approved the final version. BR takes responsibility for the accuracy of the data analyses. JFL takes responsibility for the integrity of the data and is the guarantor of the data.

Disclosure

Dr Ludvigsson has received funding for an unrelated study on IBD from Janssen. Dr Ludvigsson has also received financial support from MSD to develop a paper reviewing national healthcare registers in China, and financial support from Takeda for a project on celiac disease. Dr Vujasinovic and Dr Löhr have received lecture fees from Abbott and Viatris. Dr Vujasinovic and Dr Löhr have also received financial support to write a scientific book from Viatris. Dr Ebrahimi has served on an advisory board for Boehringer Ingelheim.

Ethics Statement

This study was approved by the Ethics Review Board in Stockholm, Sweden (2014/1287-31/4, 2018/972-32 and 2022-05774-02).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Other researchers can apply for our data through the various Swedish pathology departments, and through the Swedish National Board of Health and Welfare.

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Supporting Information

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