Cause-specific mortality in 13,099 patients with metabolic dysfunction-associated steatotic liver disease in Sweden

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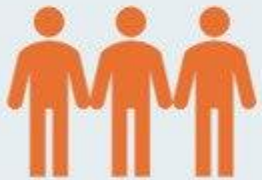
Cause-specific mortality in 13,099 patients with metabolic dysfunction-associated steatotic liver disease: A national population-based cohort study

Cause-specific mortality

Nationwide Swedish cohort study 2002-2020

Patients with MASLD (n=13,099)

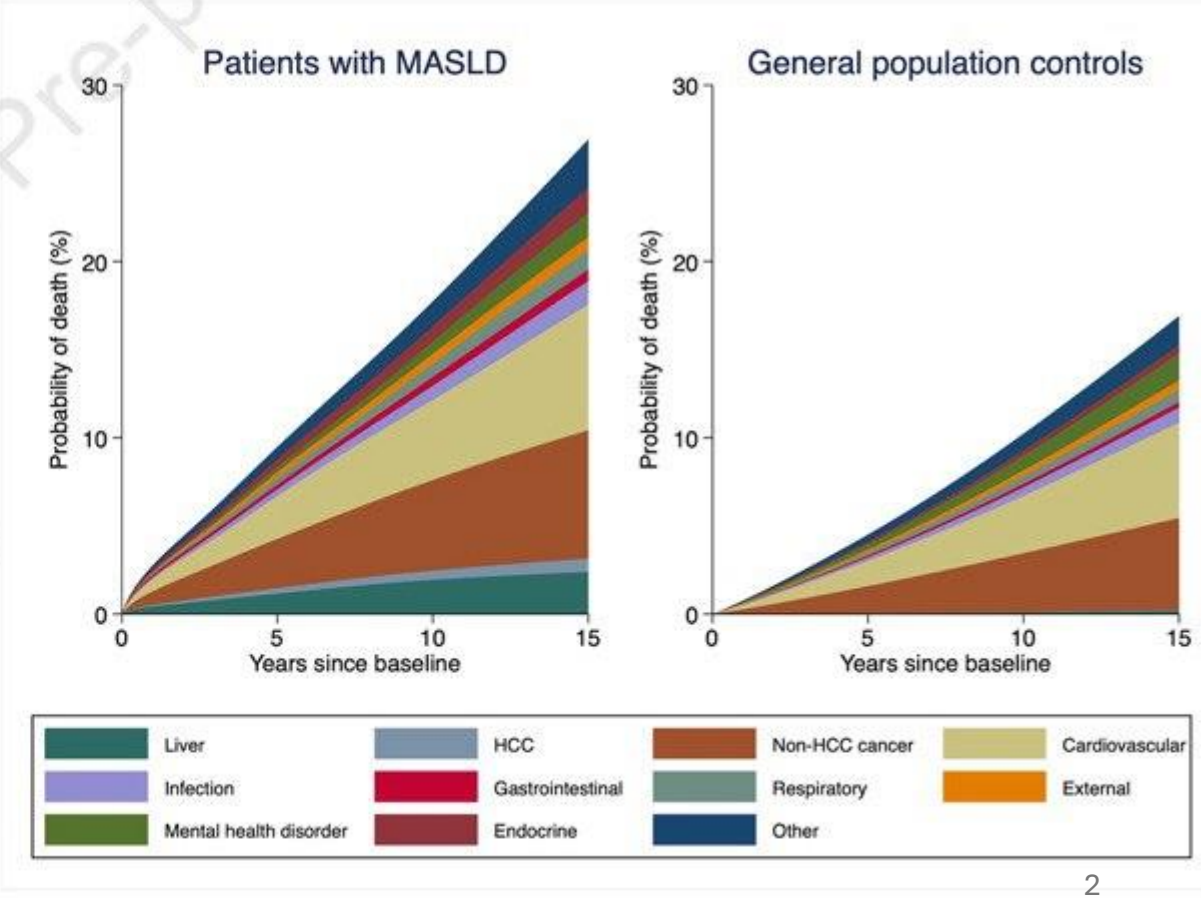
General population controls (n=118,884)



Mortality rates

All-cause, HR=1.85
Liver, HR=26.9
HCC, HR=35.0
Non-HCC cancer, HR=1.47
CVD, HR=1.54
Infection, HR=1.79
Gastrointestinal, HR=2.73
Respiratory disease, HR=1.65
External causes, HR=1.88
Mental health, HR=1.03
Endocrine disorders, HR=3.86
Other, HR=1.71

Absolute risks of death



MASLD

MASLD:
Metabolic dysfunction-associated steatotic liver disease

Defined as hepatic steatosis—identified by imaging or biopsy—in the presence of ≥ 1 metabolic risk factor and in the absence of other causes of hepatic steatosis[1]

MASH:
Metabolic dysfunction-associated steatohepatitis

Characterized by hepatic steatosis with active hepatocyte ballooning and liver inflammation, with or without hepatic fibrosis[2,3]

Prevalence of MASLD is High and Continuing to Rise

An estimated 24% of US adults have MASLD; ~1.5%-6.5% of US adults have MASH

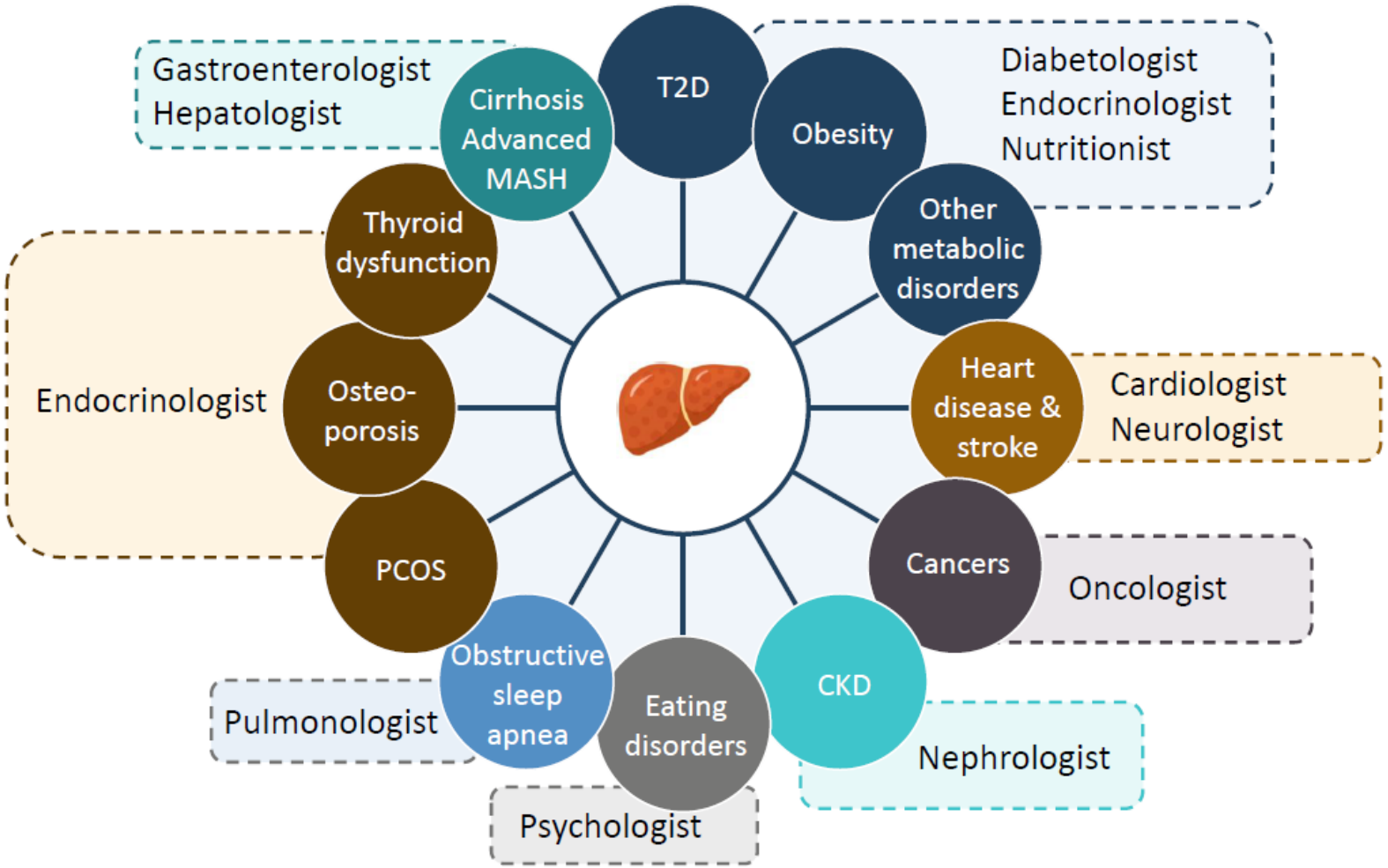
United States:

- Prevalence of MASH estimated to increase from 17.23 million to 27 million by 2030 (a 56% relative increase)
- 2nd most common reason for liver transplantation (after ALD)
- The Hispanic population has a higher prevalence both in the US and worldwide

Worldwide:

- ~32% prevalence
- South America: highest MASLD prevalence (44%)
- Western Europe: lowest MASLD prevalence (25%)

MASLD & Comorbidities



Adams LA, et al. *Gut*. 2017;66(6):1138-1153; Jiang F, et al. *Med*. 2024;5(11):1413-1423.e3; Righetti R, et al. *Expert Rev Gastroenterol Hepatol*. 2024;18(7):303-313; Rinella M, et al. *Hepatology*. 2023;77(5):1797-1835; Zoncapè M, et al. *Hepatobiliary Surg Nutr*. 2022;11(4):586-591.

Introduction

Previous studies on cause-specific mortality in MASLD were:

- Small (often <650 patients)
- Restricted to liver-related mortality only
- Based on **biopsy-proven** cohorts, introducing **selection bias** (Simon and colleagues)
- Drawn mainly from **old cohort**
- Did **not quantify the *absolute risks* of death**, essential for clinicians and policymakers to:
  - Inform patients about prognosis
  - Implement clinical and public health strategies to reduce premature mortality

Aim

- **To determine the rate and risk of death from different causes** in patients with MASLD compared to the general population, using a **nationwide population-based cohort** of all patients with a formal MASLD diagnosis in Sweden.

Identification of Study Population

- **DELIVER cohort (De**coding the epidemiology of **LIVER** disease**)**
  - → includes all patient with ICD coding for any chronic liver disease patients and matched population controls (1964-2020)
- **all individuals with first diagnosis of MASLD** (ICD-10: K76.0, K75.8)
  - → Between **Jan 1, 2002 – Dec 31, 2020**
- their **matched population controls** (from DELIVER)
  - for age, sex, municipality and calendar year
- **Look-back period (1997–2001):**
  - used to exclude pre-existing MASLD → ensures **newly diagnosed cases**
- **Follow up**
  - From MASLD diagnosis until death, emigration, other liver disease, or Dec 31, 2020

Data Sources

1. **Swedish National Patient Register (NPR)**
   - Inpatient care since 1964 & specialized outpatient care since 2001
2. **Total Population Register**
   - Country & date of birth, death and migration
3. **National Causes of Death Register**
   - Data on both primary and contributing causes of death
4. **Longitudinal integrated database for health insurance and labor market register**
   - Data on education

Limitation?

Study population & follow up

Data sources:

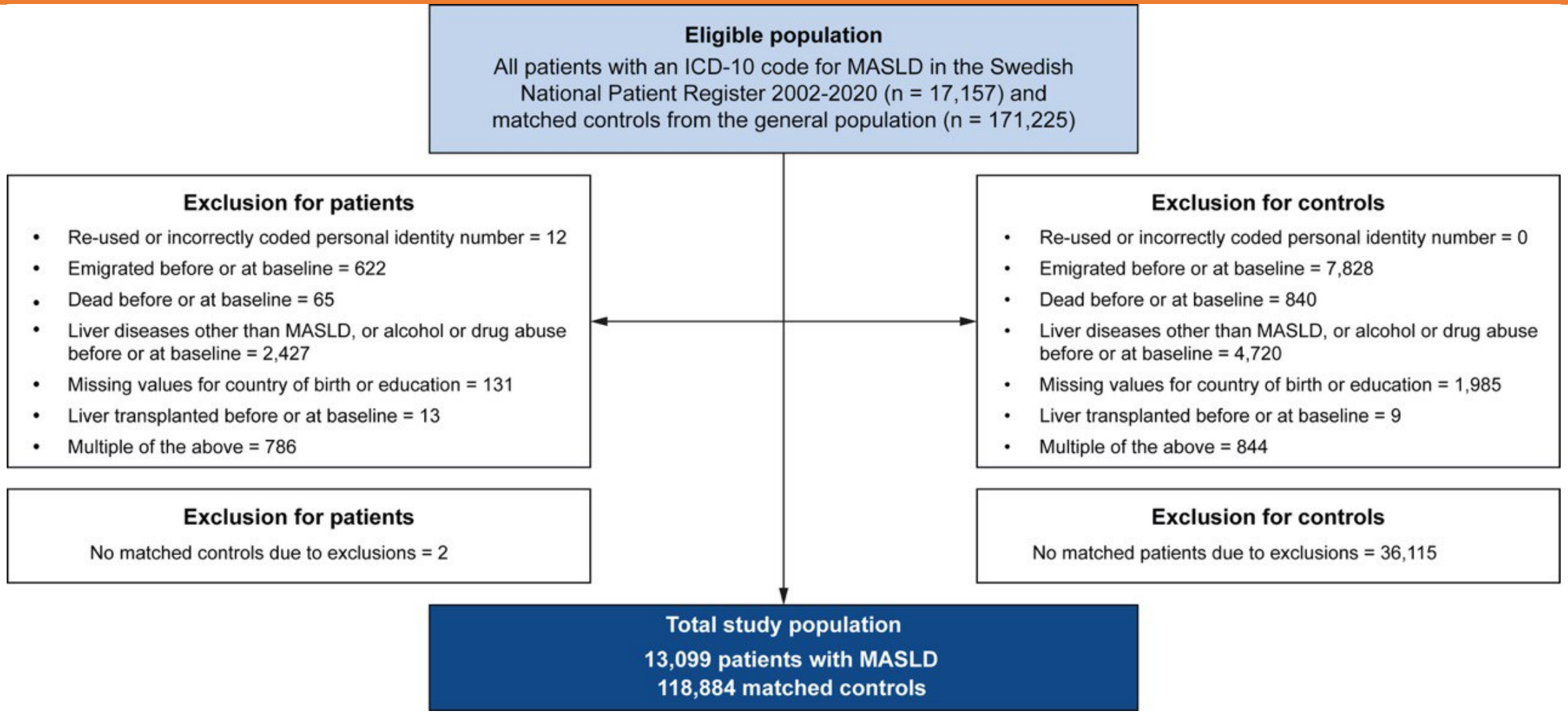
- National Patient Register
- Total Population Register
- National Cause of Death Register

DELIVER cohort

- DEcoding the epidemiology of LIVER disease

This study

Exclusion Criteria



Methods

Primary outcomes

- **11 predefined causes of mortality categories:**
  - Non-HCC liver disease
  - Hepatocellular carcinoma (HCC)
  - Non-HCC cancer
  - Cardiovascular disease
  - Infections
  - Gastrointestinal disease
  - Respiratory disease
  - External causes (e.g., injury, trauma)
  - Endocrine disorders
  - Mental health disorders (including dementia)
  - Other causes

Secondary outcome

- All-cause mortality

Methods

Covariates

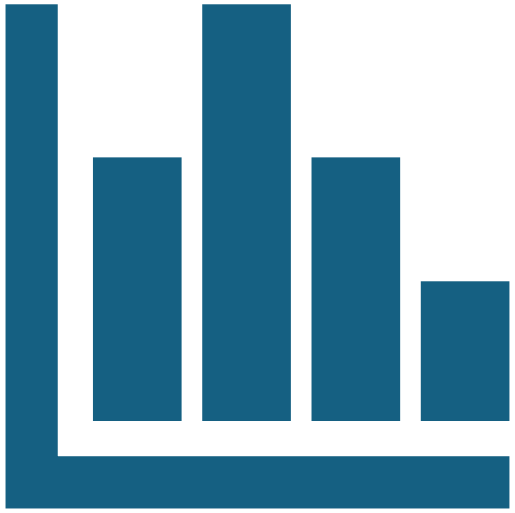
- **Country of birth:** Nordic vs non-Nordic
- **Education:** <10, 10–12, >12 years
- **Comorbidities:** Charlson Comorbidity Index (Swedish version; *liver disease excluded*)

Subgroups

- Age (<55 vs ≥55 years)
- Sex
- Type 2 diabetes (yes/no)
- Cirrhosis status (no, compensated, decompensated)
- Setting of diagnosis (inpatient vs specialized outpatient)

Statistical Methods

- Cox regression to estimate **hazard ratios** and 95% CIs for 11 different primary causes of death
- Aalen-Johansen estimator to calculate the **cumulative incidences** of the different causes of death at 1, 5, 10 and 15 years of follow-up



Results

Baseline characteristics

Table 1. Baseline characteristics of study participants.

	Patients with MASLD	Control population
Included persons, n	13,099	118,884
Follow-up		
Median (IQR) in years	4.7 (2.0-9.2)	5.8 (2.7-10.5)
Person-years	79,668	824,622
Sex, n (%)		
Men	6,594 (50.3)	59,050 (49.7)
Women	6,505 (49.7)	59,834 (50.3)
Age at baseline in years, median (IQR)	56 (43-66)	56 (43-66)
Period of inclusion n (%)		
2002-2005	1,600 (12.2)	14,973 (12.6)
2006-2010	2,425 (18.5)	22,415 (18.9)
2011-2015	3,688 (28.2)	33,561 (28.2)
2016-2020	5,386 (41.1)	47,935 (40.3)
Country of birth, n (%)		
Nordic	10,637 (81.2)	102,145 (85.9)
Other	2,462 (18.8)	16,739 (14.1)
Education in years, n (%)		
<10	3,061 (23.4)	23,929 (20.1)
10-12	6,340 (48.4)	52,803 (44.4)
>12	3,698 (28.2)	42,152 (35.5)
Cirrhosis status, n (%)		
No cirrhosis	12,483 (95.3)	118,880 (100)
Compensated cirrhosis	435 (3.3)	4 (0.0)
Decompensated cirrhosis	181 (1.4)	0 (0.0)
Type 2 diabetes, n (%)	2,422 (18.5)	4,688 (3.9)
Charlson comorbidity index, n (%)		
0	8,699 (66.4)	95,609 (80.4)
1	2,007 (15.3)	10,733 (9.0)
2	1,331 (10.2)	7,760 (6.5)
≥3	1,062 (8.1)	4,782 (4.0)

Rate of death

- 1,628 (12.4%) deaths in MASLD and 9,119 (7.7%) in controls
- MASLD was associated with higher **all-cause mortality** (HR 1.85, 95% CI 1.74-1.96) and higher rates of **all specific causes of death** except mental health disorder
- The **strongest associations:**
  - Non-HCC liver-related mortality (**HR 26.9**, 95% CI 19.4-37.3)
  - HCC related mortality (**HR 35.0**, 95% CI 17.0-72.1)
- The weakest association --> CVD & non-HCC cancer

Table 2. Rates of death in patients with MASLD compared to matched controls from the general population.

	N events (%), patients with MASLD	N events (%), controls	Incidence rate/1,000 PY (95% CI), patients with MASLD	Incidence rate/1,000 PY (95% CI), controls	HR (95% CI)
All-cause	1,628 (12.4)	9,119 (7.7)	20.4 (19.5-21.5)	11.1 (10.8-11.3)	1.85 (1.74-1.96)
Non-HCC liver disease	175 (1.3)	76 (0.1)	2.2 (1.9-2.5)	0.1 (0.1-0.1)	26.90 (19.41-37.29)
HCC	49 (0.4)	18 (0.02)	0.6 (0.5-0.8)	0.02 (0.01-0.03)	35.01 (17.00-72.13)
Non-HCC cancer	454 (3.5)	2,919 (2.5)	5.7 (5.2-6.2)	3.5 (3.4-3.7)	1.47 (1.32-1.63)
Cardiovascular disease	421 (3.2)	2,903 (2.4)	5.3 (4.8-5.8)	3.5 (3.4-3.7)	1.54 (1.38-1.72)
Infection	73 (0.6)	435 (0.4)	0.9 (0.7-1.2)	0.5 (0.5-0.6)	1.79 (1.36-2.35)
Gastrointestinal disease: with exclusion of liver disease	44 (0.3)	173 (0.2)	0.6 (0.4-0.7)	0.2 (0.2-0.2)	2.73 (1.88-3.96)
Respiratory disease with exclusion of infectious etiology	67 (0.5)	389 (0.3)	0.8 (0.7-1.1)	0.5 (0.4-0.5)	1.65 (1.24-2.20)
External cause	48 (0.4)	286 (0.2)	0.6 (0.5-0.8)	0.3 (0.3-0.4)	1.88 (1.36-2.62)
Mental health disorder including dementia	70 (0.5)	779 (0.7)	0.9 (0.7-1.1)	0.9 (0.9-1.0)	1.03 (0.80-1.33)
Endocrine disorders including diabetes	85 (0.7)	251 (0.2)	1.1 (0.9-1.3)	0.3 (0.3-0.3)	3.86 (2.83-5.25)
Other or unknown cause of death	142 (1.1)	890 (0.8)	1.8 (1.5-2.1)	1.1 (1.0-1.2)	1.71 (1.41-2.06)

Cumulative incidence of death

- At 15 years, 26.9% of patients with MASLD had died from any cause compared to 16.9% of the controls.
- Highest15-year **cumulative incidences** of death in patients with MASLD:
  - non-HCC cancer (7.3%)
  - cardiovascular disease (7.2%).

Table 3. Cumulative incidence of death in patients with MASLD and matched controls from the general population.

	Patients with MASLD				Controls			
	1-year (%), 95% CI	5-year (%), 95% CI	10-year (%), 95% CI	15-year (%), 95% CI	1-year (%), 95% CI	5-year (%), 95% CI	10-year (%), 95% CI	15-year (%), 95% CI
All-cause	2.7 (2.4-3.0)	9.4 (8.9-10.0)	17.7 (16.8-18.7)	26.9 (25.5-28.4)	0.8 (0.7-0.8)	4.5 (4.4-4.6)	10.3 (10.0-10.5)	16.9 (16.5-17.3)
Non-HCC liver disease	0.4 (0.3-0.5)	1.2 (1.0-1.4)	1.9 (1.6-2.2)	2.4 (2.0-2.8)	0.0 (0.0-0.0)	0.0 (0.0 - 0.0)	0.1 (0.1-0.1)	0.2 (0.1-0.2)
HCC	0.1 (0.1-0.2)	0.3 (0.2-0.4)	0.5 (0.4-0.7)	0.8 (0.5-1.1)	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.1)
Non-HCC cancer	0.8 (0.6-0.9)	2.8 (2.5-3.1)	5.1 (4.6-5.6)	7.3 (6.5-8.1)	0.3 (0.2-0.3)	1.6 (1.5-1.6)	3.4 (3.2-3.5)	5.2 (5.0-5.4)
Cardiovascular disease	0.7 (0.5-0.8)	2.4 (2.1-2.7)	4.5 (4.1-5.1)	7.2 (6.4-8.0)	0.3 (0.2-0.3)	1.4 (1.3-1.5)	3.3 (3.1-3.4)	5.4 (5.2-5.7)
Infection	0.1 (0.1-0.2)	0.4 (0.3-0.5)	0.8 (0.6-1.0)	1.3 (1.0-1.7)	0.0 (0.0-0.0)	0.2 (0.2-0.2)	0.5 (0.4-0.5)	0.9 (0.8-1.0)
Gastrointestinal disease: with exclusion of liver disease	0.1 (0.1-0.2)	0.2 (0.2-0.3)	0.5 (0.4-0.7)	0.6 (0.4-0.9)	0.0 (0.0-0.0)	0.1 (0.1-0.1)	0.2 (0.2-0.2)	0.3 (0.3-0.4)
Respiratory disease with exclusion of infectious etiology	0.1 (0.0-0.1)	0.4 (0.3-0.6)	0.8 (0.6-1.0)	1.1 (0.8-1.5)	0.0 (0.0-0.0)	0.2 (0.2-0.2)	0.5 (0.4-0.5)	0.7 (0.6-0.8)
External cause	0.1 (0.0-0.1)	0.3 (0.2-0.4)	0.6 (0.4-0.8)	0.7 (0.5-1.0)	0.0 (0.0-0.0)	0.1 (0.1-0.2)	0.3 (0.3-0.4)	0.5 (0.4-0.6)
Mental health disorder including dementia	0.0 (0.0-0.1)	0.3 (0.2-0.4)	0.8 (0.6-1.0)	1.4 (1.0-1.8)	0.1 (0.1-0.1)	0.3 (0.3-0.4)	0.8 (0.8-0.9)	1.6 (1.4-1.7)
Endocrine disorders including diabetes	0.2 (0.1-0.3)	0.4 (0.3-0.6)	0.9 (0.7-1.1)	1.4 (1.1-1.9)	0.0 (0.0-0.0)	0.1 (0.1-0.2)	0.3 (0.2-0.3)	0.4 (0.4-0.5)
Other or unknown cause of death	0.2 (0.1-0.3)	0.7 (0.5-0.9)	1.4 (1.2-1.7)	2.7 (2.2-3.4)	0.1 (0.0–0.1)	0.4 (0.4-0.5)	0.9 (0.9-1.0)	1.7 (1.6-1.8)

Discussion

Main findings:

1. All-cause mortality **≈2× higher** in MASLD vs. matched controls
2. MASLD was Associated with -> Higher mortality from **almost all causes** ***but not mental health disorders***
3. **Strongest relative association between MASLD & mortality of** (similar to Simon et al.'s)
    - **Non-HCC liver disease (HR ~27)**
    - **HCC (HR ~35)**
4. **Highest absolute risks of death (most deaths are attributable to):**
    - **Non-HCC cancer and**
    - **cardiovascular disease**

Clinical Implications of MASLD-Related Mortality

Main contributors to excess mortality:

Cardiovascular disease

Non-HCC cancer

Non-HCC liver disease

Implication: Preventive strategies should prioritize these conditions

Additional finding: Excess mortality also from other causes

Clinical takeaway: Early multidisciplinary care needed to reduce premature mortality

Strengths:

- Nationwide, population-based design (13,000 MASLD patients)
- Use of validated Swedish registers
- Matched general population controls
- Long follow-up (up to 18 years)
- Contemporary, real-world data (2002–2020)
- not limited to biopsy-confirmed cases

Limitations:

1. No data on liver disease **severity** or fibrosis stage
2. No **primary care** data → potential selection bias (hospital-based cases & specialized outpatient care) → Overestimation of mortality rates
3. Underdiagnosis possible → some **controls** may have **unrecorded** MASLD → Underestimation of mortality rates
4. No data on **alcohol consumption** other than AUD & Alcohol Related Liver Disease → possible misclassification bias
5. Some deaths are **misclassified**

Why These Findings Matter in Practice?

- **MASLD is not benign** — Think of MASLD as a **systemic metabolic condition**, not only a liver disease.
- **CVD and cancer drive most deaths**, not just liver failure → need for **broad risk management**.
- **Early identification** in primary care and **multidisciplinary management** (hepatology, cardiology, oncology, obesity, diabetes) can reduce mortality.
- **Primary care is central** in efficient MASLD management: early detection, risk stratification, risk factor modification, and early disease management
- Clinicians can use **absolute risk estimates** to discuss prognosis realistically with patients: "About 7% of people with MASLD die from heart disease within 15 years"

Thank you!