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ALT levels, alcohol use, and metabolic risk factors have prognostic relevance for liver-related outcomes in the general population

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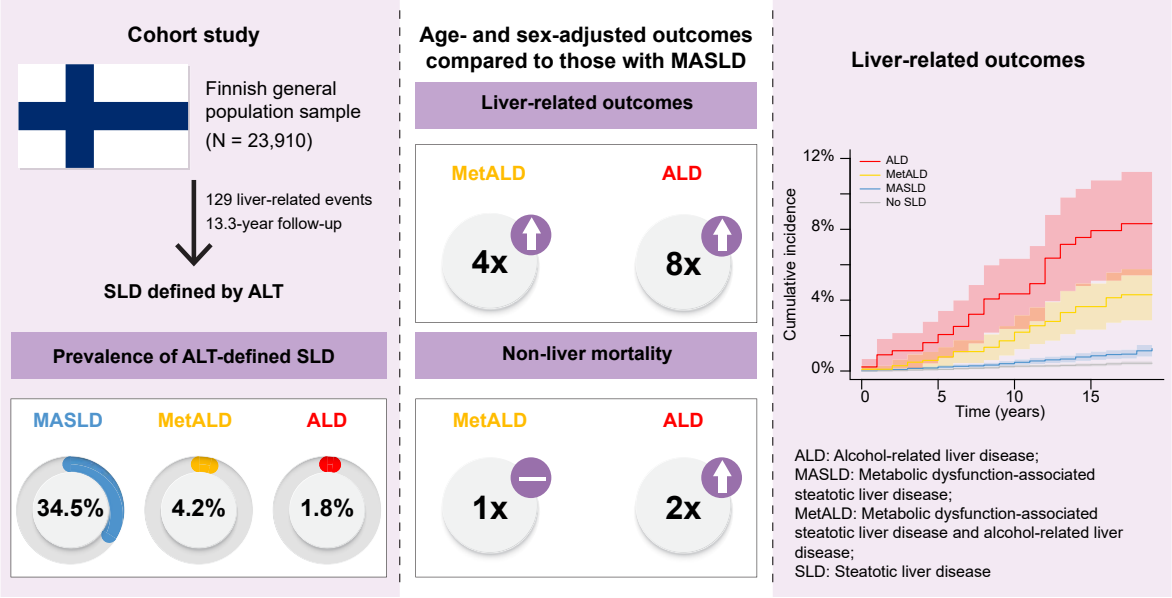
Graphical abstract



Highlights:

- Nearly all individuals with ALD exhibit metabolic risk factors.
- Among SLD subclasses, ALD presents the highest risk for both liver-related and non-liver-related outcomes.
- Alcohol use increases liver-related outcome risk in individuals with MASLD.

Impact and implications:

This study provides important information for physicians, researchers, and patients, demonstrating that the new classification of steatotic liver disease (SLD) has prognostic relevance at the population level. Evaluating the SLD subclass for a patient helps in understanding the magnitude of the risk for liver- and non-liver-related outcomes. In particular, the risks are highest in those with alcohol-related liver disease (ALD), but also increased in individuals with coexisting metabolic dysfunction-associated steatotic liver disease (MASLD) and ALD (MetALD) when compared with those with MASLD. However, alcohol use increased the risk of liver-related outcomes also in individuals with MASLD, highlighting the importance of evaluating alcohol use in every patient with SLD. Nearly all individuals with ALD have metabolic risk factors, and it is important to treat these factors to improve the survival of these patients.

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Research article

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ALT levels, alcohol use, and metabolic risk factors have prognostic relevance for liver-related outcomes in the general population

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Background & Aims: A new nomenclature and subclassification for steatotic liver disease (SLD) was recently introduced. We validated the prognostic value of SLD subclasses in a Finnish population-based cohort and explored the impact of metabolic risk factors and alcohol consumption on liver-related outcomes and death.

Methods: The study included 23,910 individuals (47% men, mean age 50.5 ± 14.0 years, BMI 27.0 ± 4.7 kg/m^2) from the FINRISK and Health 2000 health examination surveys with healthcare registry linkage for severe liver-related outcomes and deaths. SLD was identified by alanine aminotransferase (ALT) levels >20 U/L in women and >30 U/L in men (primary analysis) or fatty liver index (FLI) ≥60 (sensitivity analysis).

Results: The prevalence of ALT-defined SLD was 43% (n = 10,380), with subclass rates of 34.5% for metabolic dysfunction-associated steatotic liver disease (MASLD), 4.2% for coexistent MASLD and alcohol-related liver disease (ALD) (i.e., MetALD), and 1.8% for ALD. During a median 13.3-year follow-up, we observed 129 liver-related events. MetALD and ALD increased the age- and sex-adjusted liver-related outcome risk by fourfold (HR 3.83, 95% CI 2.51–5.84, p <0.001) and eightfold (HR 7.90, 95% CI 5.16–12.30, p <0.001), respectively, compared with patients with MASLD. ALD was also associated with the highest risk for non-liver mortality. Metabolic risk factors were present in 93% and 96% of individuals with ALT-defined SLD and ALD, respectively. Alcohol use amplified the risk of liver-related outcomes in individuals with MASLD. Sensitivity analyses by the FLI were similar.

Conclusion: SLD is a significant public health concern. Nearly all ALD cases exhibit metabolic risk factors. Among ALT-defined SLD subclasses, ALD presents the highest risk for both liver-related and non-liver-related outcomes. Alcohol use increases the risk of liver-related outcomes in individuals with MASLD.

Introduction

Chronic liver disease represents a substantial global healthcare challenge, and liver diseases associated with obesity, metabolic disturbances (formerly non-alcoholic liver disease, NAFLD), and alcohol-related liver disease (ALD) are the most common liver diseases in most countries worldwide.[1] A global consensus paper has recently proposed a revised nomenclature for hepatic disorders precipitated by hepatic fat accumulation. Steatotic liver disease (SLD) was selected to describe the condition based on panel voting. The condition formerly called NAFLD is now referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), diagnosed when SLD and at least one metabolic risk factor is present and alcohol consumption is within defined limits (<140 g and <210 g for women and men, respectively). A new category combines MASLD and ALD, called coexistent MASLD and ALD (MetALD), which encompasses liver disease with both metabolic risk factors and more alcohol consumption than in MASLD. In MetALD, weekly alcohol use can be between 140 g and 350 g and between 210 g and 420 g for women and men, respectively. In ALD, weekly alcohol use exceeds the limits defining MetALD. Other possible causes for SLD are, for example, drug-induced liver injury, monogenic diseases, and hepatitis C.[2]

SLD can progress to liver cirrhosis. MASLD also increases the risk of cardiovascular disease and cancer.[3–5] Recently, a Danish-led research group demonstrated that liver-related outcome risk is highest among patients with ALD, followed by those with MetALD and MASLD. However, the study did not include a population-based cohort, and the MASLD group consisted only of individuals with a history of excessive alcohol use. Almost all (98%) patients with ALD had at least one metabolic risk factor,[6] highlighting the interaction between alcohol use and metabolic risk factors for severe liver disease development.[7–9]

Metabolic disturbances are major risk factors for disease progression in ALD.[10] In a Finnish population-based cohort

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with a 10-year follow-up, 22% of those who developed severe liver disease drank alcohol at least moderately but also had at least one metabolic risk factor reflecting population habits and characteristics and was in line with multifactorial aetiology of severe liver disease.[11]

Here, we validated the prognostic relevance of the new SLD nomenclature in a Finnish population-based sample by assessing differences in the incidence of liver-related outcomes and non-liver deaths among the SLD subclasses. Furthermore, we evaluated the relevance of the number of metabolic disturbances and alcohol consumption within these SLD subclasses.

Methods

Study population

In this study, 27,383 individuals with available registry linkages were included from the FINRISK 2002, 2007, and 2012, and Health 2000 cohorts. The FINRISK studies were systematic and standardised cross-sectional population-based health examination surveys conducted in Finland every 5 years from 1972 to 2012 by the Finnish Institute for Health and Welfare. The FINRISK studies aimed to assess the risk factors for chronic diseases in representative population samples of adults aged 25–74 years, retrieved from the Finnish Population Information System, stratified by sex, 10-year age group, and four to six geographic areas of Finland. The number of invitees varied over the years, from 7,927 to 13,498, with participation rates ranging from 65–76%.[12]

The Health 2000 Survey was conducted by the Finnish Institute for Health and Welfare and originally comprised 8,028 adults aged ≥30 years. The participation rate for the complete examination was 80%.[13] This cohort was considered representative of the entire Finnish population as the participants were selected through a regional two-stage stratified cluster sampling procedure. The methods, measurements, and protocols used in the FINRISK and Health 2000 surveys were consistent and similar.[12,14]

Data were collected from each participant at baseline via interviews, questionnaires, and health examinations by trained physicians and/or nurses, using standardised procedures using the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) and European Health Risk Monitoring Projects.[15] Blood samples were collected at baseline for a broad spectrum of laboratory measurements and handled using a standardised protocol. Detailed descriptions of the study protocols have been published previously.[12,14]

All participants provided signed informed consent, and the study was approved by the Coordinating Ethical Committee of Helsinki and Uusimaa Hospital District and was conducted according to the Declaration of Helsinki. Previous studies were approved by the Institutional Review Board of the National Public Health Institute in Helsinki, Finland. According to the Finnish Biobank Act, the FINRISK 2002–2012 Health 2000 sample collections were transferred to the THL Biobank in 2015.

Definition of study groups

SLD was defined as ALT >20 U/L in females and >30 U/L in males, in line with previously suggested cut-off values.[16–18] ALT has been shown to discriminate steatosis with an area under the receiver operating characteristic curve (AUC) of 0.93.[18] MASLD was defined as SLD with daily alcohol use <20 g in females and <30 g in males combined with the presence of at least one metabolic risk factor, such as BMI ≥25 kg/m^2; waist circumference >94 cm for males and >80 cm for female; fasting glucose ≥5.6 mmol/L or ≥7.8 mmol/L at 2 h in glucose tolerance test or diagnosed type 2 diabetes; blood pressure >130/85 mmHg or medication; triglycerides >1.7 mmol/L or medication; or HDL cholesterol ≤1.0 mmol/L (male) or ≤1.3 mmol/L (female) or medication.[2]

MetALD was defined as the presence of SLD with daily alcohol use between 20 and 50 g for females and between 30 and 60 g for males, combined with at least one of the metabolic disturbances described above. ALD was defined as SLD with daily alcohol use of >50 g for females and >60 g for males without the requirement of having any metabolic risk factors.[2]

Outcomes

Baseline data were linked to the National Hospital Discharge Register (HILMO) for hospitalisation data, the Finnish Cancer Registry for malignancies, and Statistics Finland for causes of death. The law mandates data collection in these registries; the coverage and general quality of the data is consistent and complete.[19] Linkage was performed using a unique personal identity code assigned to all Finnish residents. Follow-up for deaths and hospitalisation was conducted until December 2019, and for malignancies until December 2021.

The primary outcome was incident advanced liver disease requiring hospital admission or causing liver cancer or liver-related death defined in line with a recent consensus paper[20] and by any of the following International Classification of Diseases (ICD) codes: K70.1, K70.3, K70.4, K72.1, K72.9, K74.6, K76.6, K76.7, C22.0, I85.0, I85.9, I98.2, I98.3, and Z94.4. We excluded those with hospitalisation due to liver disease at or before baseline (ICD8 or ICD9-codes 570-573, 155.0, ICD10-codes K70–K77, C22.0), those with chronic viral hepatitis, those with missing ALT values, and those with missing data on metabolic risk factors or alcohol use. Thus, the final study cohort comprised of 23,910 individuals.

Diagnosis of alcohol use disorder (AUD) was made based on ICD codes (ICD8 or ICD9-codes 291, alcoholic psychoses; 303, alcoholism; 980, alcohol intoxication, or ICD10-codes F10, alcohol use disorder; Z50.2, rehabilitation due to alcoholism; Z71.4, counselling for alcohol abuse).

Exploratory analyses

We studied the age- and sex-adjusted influences of alcohol use and the number of metabolic factors on liver-related outcomes within each SLD subclass.

Sensitivity analysis

We repeated the analyses using the Fatty Liver Index (FLI) instead of ALT level as a proxy for SLD. FLI ≥60 was used as the cut-off to define SLD.[21] We did not use the FLI in the primary analyses because it included measurements of metabolic disturbances and, therefore, inherently inflates the metabolic load in its definition of SLD, which would likely have influenced the results.[22]

Statistical analyses

To compare the groups, we used the chi-squared or Mann–Whitney tests, as appropriate. Cumulative incidences were estimated using the non-parametric cumulative incidence function (Aalen–Johansen method), considering death without liver disease as a competing risk event. The relative rates of liver-related outcomes and non-liver deaths were calculated using Cox regression analyses, with MASLD as the reference group. These analyses were performed both unadjusted and after adjusting for age and sex. Within the SLD subclasses, we tested the impact of alcohol use and the number of metabolic risk factors, both as continuous variables and as dichotomised variables (1–2 risk factors vs. 3–5 risk factors), on the outcomes using age- and sex-adjusted Cox regression. We used logistic regression to estimate the age-adjusted probability of advanced liver fibrosis in a subset of the Health 2000 cohort with available baseline data on the Enhanced Liver Fibrosis (ELF) test. Advanced liver fibrosis was defined as an ELF test score >9.8. Statistical significance was defined as a two-tailed *p*-value <0.05. Data were analysed using R software v.4.3.1.

Table 1. Baseline characteristics of the study population.

	No SLD	SLD	*p* values	MASLD	MetALD	ALD	*p* values
n	13,530	10,380		8,239	1,003	437	
Age (years)	50.7 ± 14.8	50.2 ± 12.9	0.003	51.37 ± 12.82	48.70 ± 11.11	49.00 ± 11.26	<0.001
Women, n (%)	7,279 (53.8)	5,465 (52.6)	0.080	4,558 (55.3)	320 (31.9)	88 (20.1)	<0.001
Education, n (%)			0.486				<0.001
Low	4,554 (34.1)	3,544 (34.5)		2,915 (35.8)	295 (29.6)	160 (37.1)	
Average	4,415 (33.0)	3,421 (33.3)		2,715 (33.3)	323 (32.4)	154 (35.7)	
High	4,398 (32.9)	3,303 (32.2)		2,514 (30.9)	378 (38.0)	117 (27.1)	
Employment, n (%)			<0.001				<0.001
Part-or full time employed	7,866 (58.7)	6,515 (63.4)		4,974 (61.1)	734 (73.5)	280 (65.0)	
Other	1,536 (11.5)	1,231 (12.0)		936 (11.5)	99 (9.9)	61 (14.2)	
Retired	3,995 (29.8)	2,522 (24.6)		2,231 (27.4)	166 (16.6)	90 (20.9)	
Marital status, n (%)			0.372				<0.001
Married/partnership	9,783 (72.5)	7,587 (73.2)		6,085 (74.0)	718 (71.8)	280 (64.2)	
Single	1,743 (12.9)	1,284 (12.4)		932 (11.3)	143 (14.3)	74 (17.0)	
Widow, separated, divorced	1,975 (14.6)	1,489 (14.4)		1,206 (14.7)	139 (13.9)	82 (18.8)	
BMI (kg/m^2)	25.91 ± 4.23	28.35 ± 5.00	<0.001	28.80 ± 4.89	28.83 ± 4.78	28.68 ± 4.58	0.871
Waist circumference (cm)	88.53 ± 12.68	95.43 ± 14.10	<0.001	96.27 ± 13.36	99.72 ± 13.56	100.82 ± 12.92	<0.001
Type 2 diabetes, n (%)	931 (6.9)	1,117 (10.8)	<0.001	958 (11.6)	109 (10.9)	50 (11.4)	0.775
Systolic blood pressure (mmHg)	132.58 ± 19.89	135.82 ± 19.39	<0.001	136.77 ± 19.13	139.72 ± 18.83	141.21 ± 19.14	<0.001
Diastolic blood pressure (mmHg)	78.43 ± 11.00	81.85 ± 11.20	<0.001	82.13 ± 10.80	85.62 ± 11.13	86.36 ± 11.49	<0.001
Alcohol use (g/week)	69.21 ± 123.23	92.03 ± 155.15	<0.001	43.11 ± 50.58	267.38 ± 71.73	664.83 ± 240.81	<0.001
Alcohol use status, n (%)			<0.001				<0.001
Life-time abstainer	1,366 (10.2)	897 (8.7)		851 (10.5)	0 (0.0)	0 (0.0)	
Current abstainer	708 (5.3)	449 (4.4)		427 (5.2)	0 (0.0)	0 (0.0)	
Alcohol user	11,285 (84.5)	8,930 (86.9)		6,865 (84.3)	1,001 (100.0)	434 (100.0)	
Smoking status, n (%)			<0.001				<0.001
Current	3,192 (23.7)	2,347 (22.7)		1,613 (19.7)	371 (37.1)	212 (48.7)	
Former	3,019 (22.4)	2,576 (24.9)		2,030 (24.8)	304 (30.4)	123 (28.3)	
Never	7,260 (53.9)	5,407 (52.3)		4,555 (55.6)	324 (32.4)	100 (23.0)	
Frequency of exercise for 20-30 mins, n (%)			<0.001				<0.001
At least 2 times a week	6,774 (62.0)	4,674 (58.0)		3,784 (59.3)	411 (49.9)	152 (43.6)	
2-4 times a month	2,625 (24.0)	2,046 (25.4)		1,595 (25.0)	230 (27.9)	100 (28.7)	
Less often	1,528 (14.0)	1,340 (16.6)		998 (15.6)	182 (22.1)	97 (27.8)	
Overweight, n (%)	8,371 (61.9)	8,424 (81.2)	<0.001	7,156 (86.9)	896 (89.3)	372 (85.1)	0.042
Elevated triglycerides, n (%)	2,671 (19.7)	3,648 (35.1)	<0.001	3,006 (36.5)	441 (44.0)	201 (46.0)	<0.001
Low HDL cholesterol, n (%)	2,487 (18.4)	2,684 (25.9)	<0.001	2,453 (29.8)	175 (17.4)	56 (12.8)	<0.001
Elevated blood pressure, n (%)	8,705 (64.4)	7,737 (74.6)	<0.001	6,529 (79.3)	837 (83.5)	371 (84.9)	<0.001
Elevated glucose, n (%)	2,842 (47.6)	2,575 (59.9)	<0.001	2,158 (60.6)	295 (67.2)	122 (66.7)	0.009
Number of metabolic risk factors, n (%)			<0.001				<0.001
0	2,101 (15.5)	720 (6.9)		0 (0.0)	0 (0.0)	19 (4.3)	
1	3,455 (25.5)	1,663 (16.0)		1,467 (17.8)	149 (14.9)	47 (10.8)	
2	4,054 (30.0)	3,156 (30.4)		2,703 (32.8)	315 (31.4)	138 (31.6)	
3	2,499 (18.5)	2,804 (27.0)		2,316 (28.1)	339 (33.8)	149 (34.1)	
4	1,089 (8.0)	1,504 (14.5)		1,284 (15.6)	152 (15.2)	68 (15.6)	
5	332 (2.5)	533 (5.1)		469 (5.7)	48 (4.8)	16 (3.7)	
ALT (U/L)	17.31 ± 5.46	38.56 ± 22.91	<0.001	37.63 ± 22.09	45.83 ± 27.21	50.09 ± 29.07	<0.001
AST (U/L)	24.08 ± 5.70	33.62 ± 25.71	<0.001	32.59 ± 25.44	38.49 ± 24.60	44.14 ± 27.83	<0.001
GGT (U/L)	26.82 ± 28.47	44.32 ± 65.95	<0.001	40.97 ± 46.08	64.86 ± 125.35	87.92 ± 150.82	<0.001

Components of metabolic syndrome: waist circumference >94 cm for men, >80 cm for women; triglycerides >1.7 mmol/L; HDL cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women; blood pressure ≥130/85 mmHg; and fasting glucose ≥5.6 mmol/L. The difference between study groups was tested with Mann-Whitney test and Pearson Chi-Square test (categorial variables). A *p* value <0.05 was considered statistically significant. Mean ± SD or number and percentage shown.

ALD, alcohol-related liver disease; ALT used as a proxy of liver steatosis. ALT, alanine aminotransferase; AST, aspartate aminotransferase, BMI, body mass index; GGT, g-glutamyltransferase; HDL, high-density lipoprotein; MASLD, metabolic dysfunction associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease; SLD, steatotic liver disease.

Results

After applying the exclusion criteria, the study cohort included 23,910 individuals (47% men, mean age 50.5 ± 14.0 years, BMI 27.0 ± 4.7 kg/m^2, Table S1). In the study cohort, 10,380 (43.4%) individuals exhibited ALT-defined SLD. The sex distributions of patients with and without steatosis were similar; however, almost all other characteristics and measurements differed between the groups. For example, individuals with ALT-defined SLD were significantly more often (centrally) obese, had more metabolic risk factors, and consumed more alcohol. However, they exercised and smoked less often (Table 1).

Among individuals with ALT-defined SLD, 8,239 (79.4%) were classified as MASLD, 1003 (9.7%) as having MetALD, 437 (4.2%) as having ALD, and 701 (6.8%) as having other types of SLD. Thus, the overall prevalence of the ALT-defined SLD subclasses was 34.5%, 4.2%, and 1.8% for MASLD, MetALD, and ALD, respectively (Fig. 1) BMI, prevalence of diabetes, or LDL cholesterol levels were not significantly different between the groups. Although several other characteristics differed between the groups, no clear trend showing worse metabolic health in the MASLD group than in the other ALT-defined SLD subclasses was observed. However, ALT, aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and FLI levels were lowest in individuals with MASLD and highest in those with ALD (Table 2). The proportion of individuals who exhibited at least one metabolic risk factor was 93% (9,660/10,380) among individuals with ALT-defined SLD and 96% (418/437) among those with ALD.

ALD is associated with eight-to nine-fold increased risk for liver outcomes compared with MASLD

During the median follow-up of 13.3 ± 4.7 years, 177 liver-related events were observed, of which 65 deaths were in the MASLD group, 34 in the MetALD group, 30 in the ALD group, and 48 in no SLD group. The incidence of liver-related outcomes for these three groups per 100,000 person-years was 59.5, 248.7, 541.6, and 26.2, respectively (Table 2). The incidence of non-liver death was considerably higher in each group: 818.7, 738.8, 1,372.1, and 1,065.1 per 100,000 person-years in those with MASLD, MetALD, ALD, and no SLD, respectively (Table 2). The cumulative incidences of liver events and non-liver-related deaths were the highest in patients with ALD, followed by those with MetALD and MASLD (Table 2, Fig. 2, and Fig. S1). At 10 years, the cumulative incidences of liver-related outcomes were 0.5% for MASLD, 2.2% for MetALD, and 4.4% for ALD, and the cumulative incidences of non-live-related deaths were 6.3%, 6.3%, and 9.5%, respectively. In addition, by age and sex-adjusted Cox regression analysis, those with MetALD had fourfold (HR 3.83, 95% CI 2.51–5.84, p <0.001) and those with ALD eightfold (HR 7.90, 95% CI 5.16–12.30, p <0.001) increase in liver-related outcomes compared with those with MASLD (Table 2). However, the non-liver-related mortality risk did not significantly differ between those with MASLD and MetALD (HR 1.23, 95% CI 1.00–1.43, p = 0.051), whereas those with ALD had a twofold higher risk of non-liver-related death than those with MASLD (HR 2.23, 95% CI 1.76–2.83, p <0.001). When we analysed the primary causes

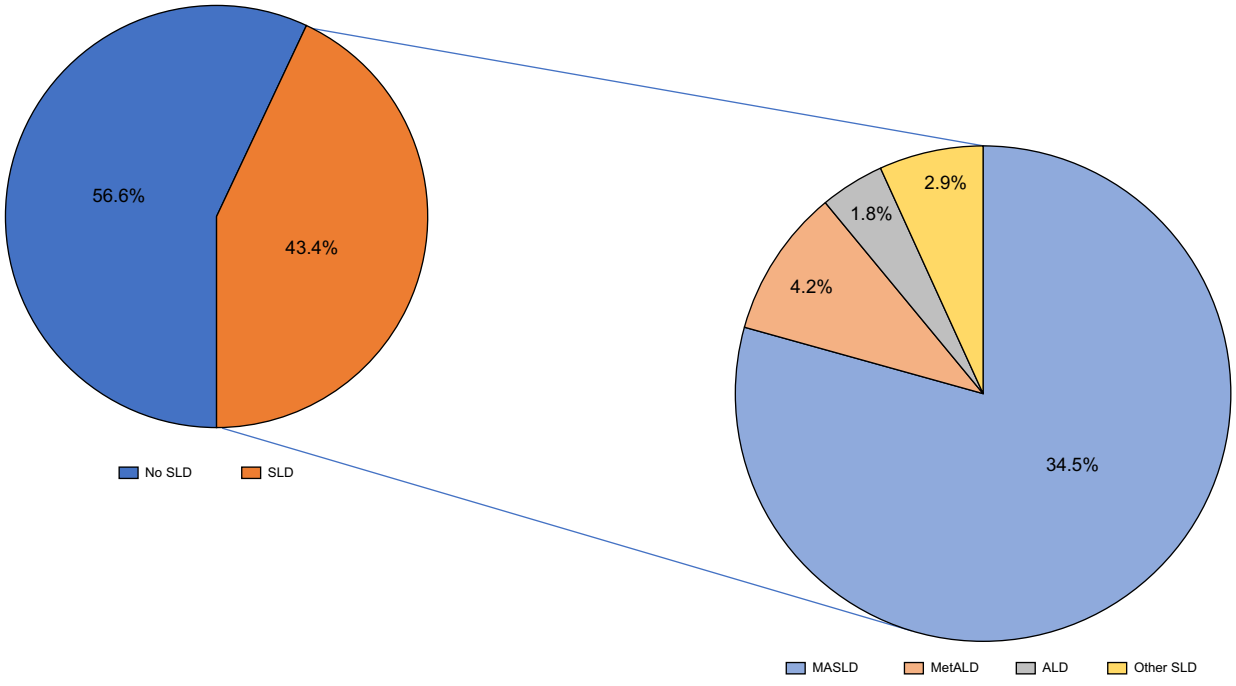

Fig. 1. The overall prevalence of ALT-defined steatotic liver disease (SLD) and its subclasses. Metabolic dysfunction associated steatotic liver disease (MASLD), co-existent MASLD and alcohol-related liver disease (ALD) (MetALD).

Table 2. Incidence of liver-related outcomes and non-liver death in steatotic liver disease subclasses.

Liver-related outcomes	No SLD (n = 13,530)	MASLD (n = 8,239)	MetALD (n = 1,003)	ALD (n = 437)
Events, n	48	65	34	30
Incidence per 100,000 (95% CI)	26.2 (18.8–33.7)	59.5 (45.1–74.0)	248.7 (165.1–332.3)	541.6 (347.8–735.4)
10-year cumulative incidence (95% CI)	0.3% (0.2–0.4%)	0.5% (0.3–0.7%)	2.2% (1.2–3.1%)	4.4% (2.4–6.4%)
Hazard ratio (95% CI), unadjusted	0.44 (0.30–0.64, p <0.001)	Reference	4.15 (2.74-6.29, p <0.001)	9.16 (5.94–14.11, p <0.001)
Hazard ratio (95% CI), age- and sex-adjusted	0.42 (0.29–0.60, p <0.001)	Reference	3.83 (2.51–5.84, p <0.001)	7.90 (5.07–12.30, p <0.001)
Non-liver death				
Events, n	1,949	894	101	76
Incidence per 100,000 (95% CI)	1,065.1 (1,017.8–1,112.4)	818.7 (765.0-872.4)	738.8 (594.7–882.9)	1,372.1 (1,063.6–1,680.6)
10-year cumulative incidence (95% CI)	8.7% (8.2-9–2%)	6.3% (5.7-6.8%)	6.3% (4.8–7.9%)	9.5% (6.7–12.4%)
Hazard ratio (95% CI), unadjusted	0.89 (0.72-1.09, p <0.001)	Reference	0.89 (0.72–1.09, p = 0.268)	1.69 (1.33–2.13, p <0.001)
Hazard ratio (95% CI), age- and sex-adjusted	1.09 (1.00-1.18, p <0.042)	Reference	1.23 (1.00–1.51, p = 0.051)	2.23 (1.76–2.83, p <0.001)

Hazards ratios were calculated using Cox regression. A p value <0.05 was considered statistically significant.
ALD, alcohol-related liver disease; MASLD, metabolic dysfunction associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease; SLD, steatotic liver disease.

of death by ALT-defined SLD subclasses, we noticed a higher proportion of deaths from external causes in ALD (21%) compared with MetALD (14%) or MASLD (8%). External causes were most commonly accidental deaths and intoxications (Fig. S2).

Individuals with no ALT-defined SLD had lower risk for liver-related outcomes than those with ALT-defined SLD. However, the risk for non-liver-related death was slightly higher in individuals with no SLD compared with those with MASLD (HR 1.09, 95% CI 1.00–1.81, p = 0.042, Table 2).

Alcohol use amplified the risk of liver-related outcomes in individuals with MASLD

In an exploratory analysis, weekly alcohol consumption within the MASLD criteria was significantly associated with an increased risk of liver-related outcomes. However, these associations were not significant in the MetALD and ALD subclasses. The number of metabolic risk factors was significantly associated with liver-related outcomes in MASLD subclasses, observed when assessing the number of metabolic risk factors as a continuous variable (1–5 factors) and as a dichotomised variable (1–2 risk factors vs. 3–5 risk factors). Within the MetALD and ALD subclasses, the number of metabolic risk factors was not associated with liver-related outcomes (Table 3).

Liver fibrosis in ALT-defined SLD subclasses

We estimated the prevalence of liver fibrosis using the ELF test. In a subset of 2,030 individuals with ALT-defined SLD from the Health 2000 study, the age-adjusted prevalences of ELF ≥9.8 were 7.7% (95% CI 6.3–9.4%) in MASLD, 11.7% in MetALD (95% CI 7.5–17.6%), and 20.4% (95% CI 12.2–32.2%) in ALD. This increasing trend between groups was statistically significant (p for a linear trend across groups = 0.0004).

History of alcohol use disorder amplified the risks for adverse outcomes

Considering a record of AUD at or before baseline as a marker of previous heavy alcohol use, we found that a history of AUD increased the risk of liver-related outcomes across all ALT-defined SLD subclasses compared with those with no history of AUD. More specifically, compared with those with MASLD without previous AUD, the risk for liver-related outcomes was eightfold, sevenfold, and 29-fold higher in those with a history of AUD and MASLD, MetALD and ALD, respectively. Similarly, the risk of non-liver-related death was twofold, sevenfold, and sevenfold higher in these groups, respectively (Table S2).

Sensitivity analysis defining SLD by the FLI

The prevalence of SLD was 32.3% when we used FLI as a proxy for SLD. Among individuals with SLD, 6,498 (84.1%), 840 (10.9%), 369 (4.8%), and 16 (0.2%) had MASLD, MetALD, ALD, and other SLD, respectively. Thus, the overall prevalence of FLI-defined SLD subclasses was 27.5% for MASLD, 3.6% for MetALD, and 1.6% for ALD. In each group, ≥99.7% of individuals had at least one metabolic risk factor. Consistent with our primary findings, the ALD group exhibited the highest risk of liver-related outcomes, followed by the MetALD and MASLD groups. The 10-year cumulative incidences according to the FLI-defined SLD subclass were 0.5%, 1.7%, and 4.0% for MASLD, MetALD, and ALD, respectively. Moreover, additional results were aligned with those obtained when defining SLD based on the ALT criteria (Tables S3–S5).

Discussion

In this study, using a representative Finnish population-based sample, we demonstrated for the first time that liver-related outcomes and non-liver deaths are more common in individuals with ALD than in those with MetALD or MASLD at the population level. Furthermore, we found a discernible decreasing risk gradient with the same group order. The risk of liver-related outcomes was approximately eightfold higher in individuals with ALD than in those with MASLD. Our study suggests similar survival trends as in a recent clinical study.[6] In addition, a recent registry study in Sweden showed that patients with MASLD with a previous diagnosis of alcohol-related liver disease or alcohol use disorder had a higher risk of liver cirrhosis and overall death during follow-up than those with MASLD alone.[23]

An important strength of our study is its large sample size, which is representative of the Finnish general population. Furthermore, since our data derived from health examination studies, they were not subject to selection bias as is the case for studies based on clinical patient samples. We also had extensive data on metabolic factors and alcohol use assessed using standardised approaches, and we were able to perform

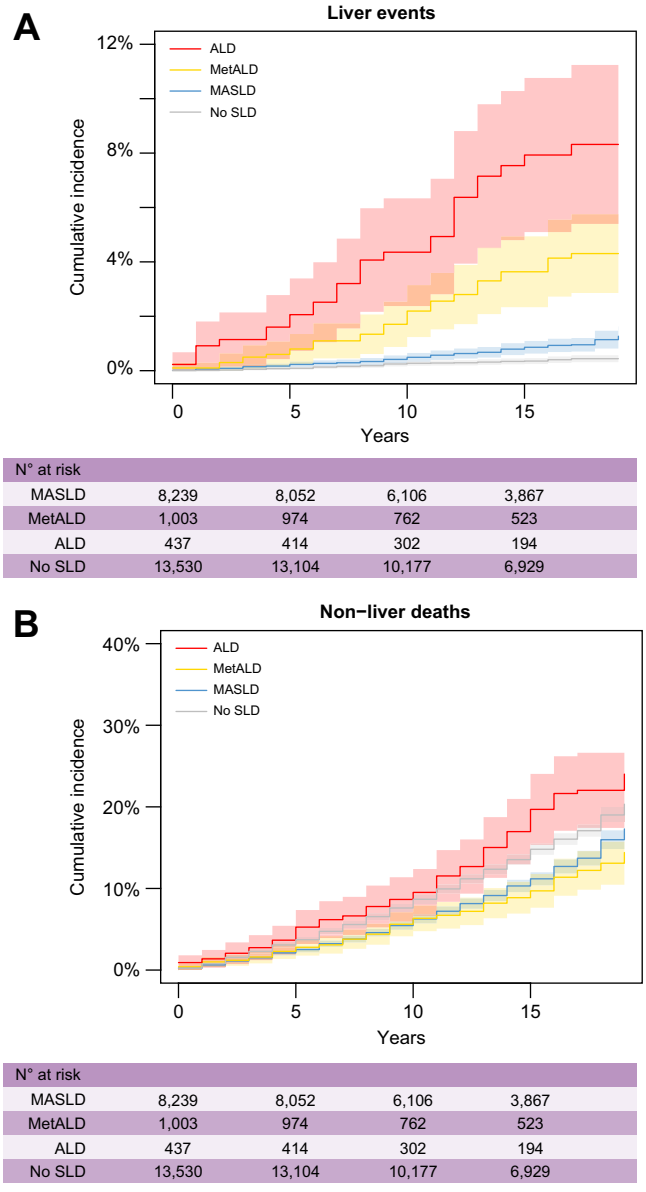

Fig. 2. The cumulative incidence of liver events and non-liver deaths in patients with steatotic liver disease and no steatotic liver disease. (A) Liver events and (B) non-liver death in individuals with metabolic dysfunction associated steatotic liver disease (MASLD), co-existent MASLD and alcohol-related liver disease (MetALD), alcohol-related liver disease (ALD), and no steatotic liver disease (no SLD). Cumulative incidence was determined using the Aalen-Johansen method.

Table 3. Impact of the number of metabolic risk factors and alcohol use for liver-related outcomes in those with steatotic liver disease by Cox regression adjusted for age and sex.

MASLD	Hazard ratio (95% CI)	*p* values
Number of metabolic factors (1-5)	1.46 (1.17–1.82)	<0.001
1-2 risk factors	Reference	
3-5 risk factors	1.96 (1.12–3.45)	0.019
Alcohol use (g/week)	1.01 (1.00–1.01)	<0.001
MetALD		
Number of metabolic factors (1-5)	1.13 (0.81–1.58)	0.468
1-2 risk factors	Reference	
3-5 risk factors	1.86 (0.82–4.20)	0.135
Alcohol use (g/week)	1.00 (1.00–1.01)	0.508
ALD		
Number of metabolic factors (0-5)	1.20 (0.84–1.71)	0.326
1-2 risk factors	Reference	
3-5 risk factors	0.93 (0.44–1.94)	0.838
Alcohol use (g/week)	1.00 (1.00–1.00)	0.050

A *p* value <0.05 was considered statistically significant.
ALD, alcohol-related liver disease; MASLD, metabolic dysfunction associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease.

registry linkages for liver-related outcomes during long-term follow-up. The general quality of registries in Finland is good, consistent, and complete.[19] Previous publications focusing on the new SLD nomenclature did not report on liver-related outcomes estimated in the population,[24] or the cohort was not necessarily representative of the general population.[6]

In the present study, we investigated the population-wide prevalence of SLD and its subclasses in Finland. We found that 43.4% of Finnish adults had SLD when ALT was used as a SLD proxy and that 34.5%, 4.2%, and 1.8% of patients had MASLD, MetALD, and ALD, respectively. The ALT-defined SLD estimate was high. However, the global prevalence of NAFLD alone in studies published after 2016 was estimated to be 38%.[25] Furthermore, a recent biopsy study from Finland demonstrated that the prevalence of SLD in organ donors was 40%.[26] In our sensitivity analysis using the FLI to define SLD, the prevalence of SLD was 32.3%, 27.5% for MASLD, 3.6% for MetALD, and 1.6% for ALD. The prevalence of FLI-defined SLD was similar (38.1%) in a recent publication from the NHANES sample.[24] The study used the controlled attenuation parameter from vibration-controlled transient elastography for SLD diagnosis in a sample of 4,263 individuals and found that 22.5% had MASLD, 11.0% had MetALD, and 3.0% had ALD. Compared with these proportions, we had explicitly higher frequencies of MASLD and lower frequencies of MetALD and ALD.

Why do individuals with ALD have the highest risk for liver-related outcomes and non-liver deaths?

Our findings highlight the importance of alcohol consumption as a determinant of outcomes in patients with SLD. The risk of both liver-related outcomes and non-liver death was highest in those with ALD, followed by patients with MetALD and MASLD. The risk of liver-related outcomes was eightfold higher in ALD than in MASLD. Interestingly, patients with MetALD also had a higher risk (eightfold higher) of liver events than those with MASLD. The MetALD group differed from the MASLD group only by higher alcohol consumption, thus demonstrating the importance of alcohol use in outcomes. Furthermore, almost all individuals with ALD presented at least one metabolic risk factor, implying an important role for metabolic dysfunction in ALD. Our analysis of the subset of the Health 2000 study suggested that more individuals with advanced fibrosis were present in those with ALD (20%) than in those with MASLD or MetALD at baseline. This could contribute to explaining the higher risk of liver-related outcomes in ALD than in the other SLD subclasses.

MASLD increases the risk of cardiovascular outcomes and cancer; consequently, death occurs before developing end-stage liver disease in many patients.[3,5] However, the risk of non-liver death was also the highest in those with ALD. Alcohol

use is a major risk factor for liver disease progression,[11] and those with ALD also have an increased risk of cancer[27] and cardiovascular diseases (at least those with a history of high alcohol use).[28] A recent meta-analysis (37 studies including 50,302 individuals and 155,820 patient-years of follow-up) reported that individuals with ALD had a 2.4-fold increased risk of death from cardiovascular causes, a 2.2-fold higher risk of death from non-hepatic cancers, and an 8.2-fold greater risk of death from infections than the general population.[29] When we analysed the primary causes of death according to ALT-defined SLD subclasses, we noticed that individuals with ALD experienced external causes of death more often than those with MASLD and MetALD (Fig. S2). A previous study from Denmark has shown that the leading non-liver causes of death were cardiovascular diseases, infections, and gastrointestinal bleeding, but also the risk of death from accidents, violence, and suicide was higher among ALD patients.[30]

Alcohol increased the risk of liver-related outcomes in those with MASLD

Our findings indicated that even mild alcohol consumption below the MASLD criteria is associated with an increased risk of liver-related outcomes. This is in agreement with a previous study, wherein individuals with SLD and metabolic risk factors, the amount of alcohol consumed was the major cause of liver-related deaths.[31] These findings underscore the interaction between alcohol intake and metabolic risk factors for the development of severe liver disease.[7–9]

History of alcohol use disorders significantly influenced clinical outcomes

The impact of lifetime alcohol use on the risk of liver-related and non-liver outcomes remains unclear.[6,32] We found that a history of a previous AUD, reflecting previous heavy alcohol use, was associated with an increased risk of liver-related outcomes across all SLD subgroups. The risk was highest in those with AUD and ALD. These findings might point to more advanced liver disease at baseline due to previous heavy alcohol use, despite having reduced their alcohol use during the previous year before study baseline. It is also known that although half of the individuals might be hazardous drinkers at some point, only a small percentage will maintain this behaviour throughout their lifetime,[33] and that among heavy drinkers, the course of alcohol consumption fluctuates.[34] Unfortunately, we did not have data on possible changes in alcohol consumption patterns during the follow-up of this study.

Metabolic load and the risk of liver-related outcomes

Although the metabolic load, defined as the number of metabolic risk factors, was significantly associated with liver-related outcomes in individuals with MASLD, there was no association among patients with MetALD or ALD, possibly suggesting that the amount of alcohol consumed is a stronger driver of disease progression in these subclasses. However, metabolic disturbances have been suggested to be important risk factors for aggressive ALD,[7,8,10] and in the present study, almost all patients with ALD had at least one metabolic risk factor.

Limitations

This study had some limitations. ALT (and FLI) levels were used as proxies for SLD, although these markers discriminate remarkably well in detection steatosis.[17,18,35] Furthermore, liver biopsies are not possible in population-based studies; ultrasound examinations have limitations in detecting mild steatosis, and ultrasound measurements were unavailable. We used a highly-sensitive cutoff for ALT levels, which allowed us to identify most individuals with steatosis. However, this may come at the expense of false positives. In addition, we performed analyses with the FLI, a widely used index for NAFLD in population studies, and it detected hepatic steatosis markedly well (positive predictive value up to 99%).[35] Analyses using FLI showed similar trends to those observed using ALT. Furthermore, liver-related outcomes were relatively rare in the general population, restricting the statistical power of some subgroup analyses.

Conclusions

This study found that the prevalence of SLD is notably high in the population, and SLD subclasses have prognostic relevance for liver-related outcomes in the general population. The prevalence of metabolic disturbances is also high in individuals with ALD. Alcohol use increases the risk of liver-related outcomes in those with MASLD.

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Abbreviations

ALD, alcohol-related liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; ELF, Enhanced Liver Fibrosis; FLI, fatty liver index; GGT, gamma-glutamyltransferase; HILMO, the National Hospital Discharge Register; ICD, International Classification of Diseases; MASLD, metabolic dysfunction associated steatotic liver disease; MetALD, metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease; SLD, steatotic liver disease.

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Conflicts of interest

The authors have no conflicts to report.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualisation: VM, FÅ. Resources: VS, AJ, AL, SM, MP. Data curation and formal analysis: FÅ. Methodology: VM, FÅ. Project administration: VS, AJ, AL, SM, MP. Software: FÅ. Supervision: FÅ. Visualisation: V.M, FÅ. Writing – original draft: VM. Writing –review & editing: VM, VS, AJ, AL, SM, MP, FÅ.

Data availability statement

FINRISK and Health 2000 Survey data are available from the THL Biobank based on a research application, as explained on the website of the THL Biobank (https://thl.fi/en/web/thl-biobank/for-researchers).

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101172.

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