

Incidence of major cardiovascular events in patients with metabolic dysfunction-associated steatotic liver disease in the general population

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Received 17 February 2025; revised 15 August 2025; accepted 9 September 2025; online publish-ahead-of-print 26 September 2025

Aims

Major adverse cardiovascular events (MACE) related to cardiovascular disease are a major cause of death in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). We explored the impact of MASLD on incident MACE and overall mortality in the general population in Germany.

Methods and results

A total of 14 575 patients were included for the analysis. Elevated liver enzymes were present in 21.7% and MASLD, defined with a positive fatty liver index (FLI) in the absence of relevant alcohol use, was detected in 37% of participants. MACE were defined as a three-item composite endpoint of acute myocardial infarction (AMI), stroke and cardiovascular mortality (3-point MACE) and extended MACE (eMACE) including MACE criteria, incident atrial fibrillation and pulmonary embolism. In the group with a positive FLI (≥ 60) a higher rate of male sex and a higher age as well as a higher prevalence of metabolic and cardiovascular risk factors compared to the group with a negative FLI (< 30) were present. At 5 years of follow-up, 475 patients (3.7%) developed 3-point MACE and 577 (4.9%) developed eMACE. In the subgroup with MASLD, the incidence of eMACE was higher (7.1% vs. 3.7%; $p < 0.0001$). Using Cox regression analysis with a stepwise adjustment strategy, we were able to show an independent prediction of MACE and eMACE by hepatic steatosis under consideration of various confounders. The presence of MASLD was associated with an increased risk of developing MACE by 62.3% ($p < 0.0001$) and eMACE by 44.0% ($p < 0.0001$). Importantly, MASLD was associated with an increased risk for all-cause mortality (hazard ratio 1.55; $p < 0.0001$).

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Conclusions

Metabolic dysfunction-associated steatotic liver disease is an independent risk factor for MACE and is associated with a significantly increased risk of all-cause mortality. In the management of patients with cardiovascular risk, identification of MASLD can potentially refine their disease trajectory.

Keywords

Major cardiovascular events • Cardiovascular diseases • Population-based study • Fatty liver disease • Metabolic dysfunction-associated steatotic liver disease

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease today, with an estimated prevalence of 30% among the global adult population.^{1,2} In recent decades, the number of patients has steadily increased, accompanied by the growing epidemic of obesity and type 2 diabetes mellitus in the world.^{3,4} According to the Global Burden of Disease study, MASLD is one of the leading contributors to the worldwide burden of disease and disability caused by chronic liver disease.⁵ The related socio-economic costs in Western countries are immense^{6,7} – recent data from the United States' United Network of Organ Sharing (UNOS) suggest that MASLD will soon become the leading indication for liver transplantation in the United States.^{8–10} To emphasize the metabolic dysfunction underlying the pathogenesis of the disease, the former term of non-alcoholic fatty liver disease (NAFLD) has been replaced by a new fatty liver disease nomenclature proposed by an international Delphi consensus statement.¹¹ MASLD is now defined by the presence of hepatic steatosis in patients with at least one out of five cardiometabolic risk factors and no other likely cause of steatotic liver disease like excessive alcohol consumption or drug-induced liver injury.¹² The five risk factors include overweight or obesity, dysglycaemia or type 2 diabetes, hypertension, elevated plasma triglycerides, and reduced high-density lipoprotein (HDL) cholesterol.^{12,13} MASLD must be differentiated from alcohol-associated liver disease (ALD) and an overlap syndrome called MetALD, which represent new subcategories under the overarching term of steatotic liver disease (SLD).^{14,15} MASLD encompasses the entities of metabolic dysfunction-associated steatotic liver (MASL) and metabolic dysfunction-associated steatohepatitis (MASH), which replace the former terms of NAFL and NASH.^{14,16} Retrospective studies show high concordance rates of $\geq 99\%$ between the MASLD and NAFLD patient cohorts.¹⁷ MASL is characterized by macro vesicular steatosis in $\geq 5\%$ of hepatocytes, whereas MASH additionally shows aspects of lobular inflammation and cellular injury.¹⁸ MASH is often accompanied by hepatic fibrosis and can eventually progress into liver cirrhosis with its various complications like acute-on-chronic liver failure or hepatocellular carcinoma.¹⁹ The most common cause of death in MASLD patients is cardiovascular disease (CVD) followed by extrahepatic malignancy.^{20–22} CVD include a wide spectrum of pathological conditions affecting the heart and the blood circulatory system.²³ They can result in acute, potentially life-threatening events like acute myocardial infarction or ischaemic stroke, which are summarized by the umbrella term of major adverse cardiovascular events (MACE).²⁴ However, they

can also lead to chronic organ dysfunction like congestive heart failure or vascular dementia, which contribute to reduced quality of life, disability and premature death.²⁵ A central pathogenic mechanism is the atherosclerotic degeneration of small and large blood vessels (atherosclerotic CVD) and a lot of risk factors are well-known including dyslipidaemia, diabetes, hypertension and smoking.²⁶ In the past years, observational studies in different countries have been published, which showed a significant association between MASLD as pre-existing condition and the development of CVD.^{22,27–29} In 2021, a systematic meta-analysis of 36 studies involving more than 5.8 million patients has identified MASLD as an independent risk factor for fatal and non-fatal CVD. Also, the risk increased with the severity of MASLD and especially the degree of fibrosis.³⁰ The current analysis was performed in order to get further insight into epidemiological characteristics of MASLD in the German general population as well as to evaluate the impact of MASLD on incident MACE over 5-year follow-up.

Methods

Patients and study description

We analysed cross-sectional data of 15 010 participants enrolled in the Gutenberg Health Study (GHS) between April 2007 and April 2012 and whose data were available at the time of follow-up after 5 years. The GHS is a single-centre, population-based, prospective, and observational cohort study in the Rhine-Main Region in Western Germany. Its design has been described in detail.³¹ Individuals between the ages of 35 and 74 years were selected randomly from local governmental registries with a sampling procedure that was stratified for sex, residential area (urban vs. rural), and decades of age. All invited participants had the opportunity to decline participation and provide a reason for doing so. The GHS has obtained ethical approval from the local ethics committee and has been approved by both the local and federal data safety commissioners.

Baseline and 5-year follow-up examination

At the baseline examination and at the 5-year follow-up examination in the study centre, clinical variables and prevalent classical comorbidities were evaluated, along with a computer-assisted personal interview, laboratory examinations using venous blood samples, and blood pressure and anthropometric measurements. All examinations were conducted according to standard operating procedures by certified medical technical assistants.

Anthropometric data

Weight, height, waist circumference (WC), and hip circumference were measured following a standardized manual. To measure WC, a tape measure was placed midway between the lowest rib and the pelvis during expiration. A WC of <94 cm in men and <80 cm in women was considered within the normal range as recommended by the International Diabetes Federation.³²

Presence of comorbidities

Body mass index (BMI) was calculated as weight (kg)/height (m)². Obesity was defined as BMI ≥30 kg/m², while overweight was defined as BMI >25–<30 kg/m². Type 2 diabetes was defined based on self-reported physician diagnosis, medication use, fasting plasma glucose ≥126 mg/dl after an overnight fasting of at least 8 h or rather a blood glucose level of ≥200 mg/dl after a fasting period <8 h. Glycated haemoglobin (HbA1c) values were categorized into three groups: low (HbA1c <5.7%), intermediate (HbA1c 5.7–6.5%), and high (HbA1c >6.5%). HbA1c values >6.5% were considered elevated. Hypertension was defined based on self-reported physician diagnosis, medication use, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg in the second and third standardized measurement after 8 and 11 min of rest. Dyslipidaemia was defined based on self-reported physician diagnosis, medication use, or a low-density lipoprotein (LDL)/HDL ratio of >3.5. The presence of the metabolic syndrome was defined according to the criteria established in the joint scientific statement for harmonizing the metabolic syndrome.³³ Pre-existing chronic liver disease was self-assessed by replying to the following question: 'Have you ever been medically diagnosed with liver disease?' The study did not specifically test for chronic viral hepatitis or autoimmune liver disease. As the reported prevalence of hepatitis C or B virus in Germany is 0.3% at the population level, this will not significantly alter the findings and conclusions. Smoking was categorized into non-smokers (no nicotine and ex-nicotine consumption) and smokers (including occasional consumption of less than one cigarette per day). Alcohol consumption was recorded using a questionnaire. This included quantitating regular alcohol use and the types of drinks in detail with breakdown on weekdays and weekend. The specified quantities were then converted to alcohol in g/week. Relevant alcohol consumption was defined as an average daily intake of ≥20 g of pure alcohol for women and ≥30 g for men.¹¹ High regular daily consumption was defined as an intake of ≥40 g for women and ≥60 g for men leading to exclusion from the study analysis, which was aligned with MASLD diagnostic criteria.³⁴

Reference values for elevated liver enzymes

Reference values were as follows: gamma-glutamyl transferase (gGT) >64 U/L in men and >36 U/L in women, alanine aminotransferase (ALT) >50 U/L in men and >35 U/L in women, aspartate aminotransferase (AST) >35 U/L in men and >31 U/L in women. One surrogate marker for hepatic steatosis (fatty liver index [FLI])³⁵ and one for fibrosis (fibrosis-4 [FIB-4] score; lower-cut off 1.3; upper-cut off 2.67) were evaluated, and advanced fibrosis was defined based on previously published cut-offs.^{36,37} FLI is calculated as: $FLI = (e^{0.953 \times \log_e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log_e(\text{ggt}) + 0.053 \times WC - 15.745}) / (1 + e^{0.953 \times \log_e(\text{triglycerides}) + 0.139 \times BMI + 0.718 \times \log_e(\text{ggt}) + 0.053 \times WC - 15.745}) \times 100$.³⁵ FLI was seen as positive with values ≥60. Changes in FIB-4 categories were examined between baseline and the 5-year follow-up. In epidemiological studies, FLI has been used repeatedly and is a validated approach.^{38,39} The presence of MASLD was defined as the presence

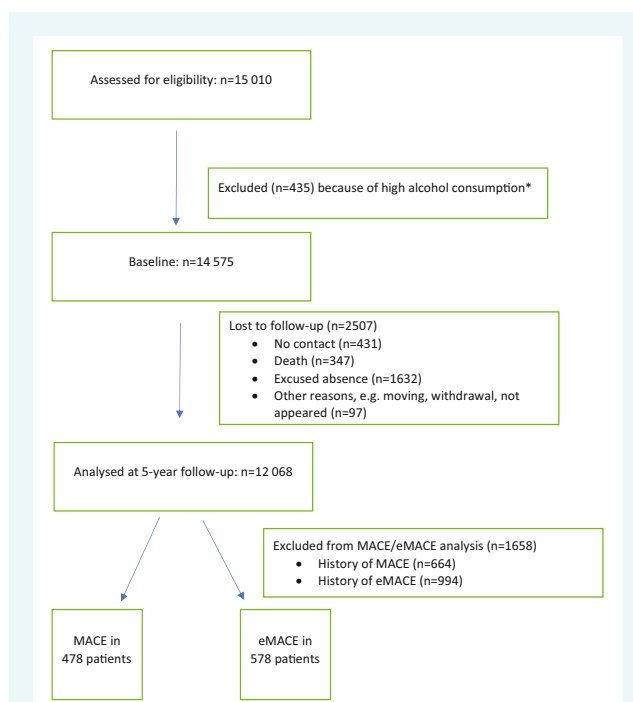


Figure 1 Participant flow chart. eMACE, extended major adverse cardiovascular events; MACE, major adverse cardiovascular events. *High alcohol consumption: defined as a daily intake of ≥40 g for women and ≥60 g for men.

of steatosis of the liver with a positive FLI and the exclusion of other chronic liver disease or high alcohol consumption.¹¹

Major adverse cardiovascular events

Major adverse cardiovascular events were defined as a three-item composite endpoint of acute myocardial infarction, stroke and cardiovascular mortality as originally proposed by the United States Food and Drug Administration (FDA).^{24,40} Extended MACE (eMACE) included primary MACE plus incident atrial fibrillation and pulmonary embolism.^{41,42} A preexisting MACE or eMACE at baseline was an exclusion criterion for corresponding statistical analyses.

Detailed study information

Of the 15 010 participants in the GHS baseline cohort, 435 patients had to be excluded from the analyses due to excessive alcohol consumption. Within 5 years of follow-up (median follow-up time: 5.03 years), 2507 participants were lost to follow-up, thus leaving 12 068 participants for analysis (Figure 1). The endpoints MACE and eMACE were analysed using a time-to-event approach. Medical records, as well as information from physicians and from the study participants themselves, were collected and submitted to a team of experts. Mortality data were obtained through quarterly queries to the official registry offices and the mortality registry of Rhineland-Palatine, Germany, that cover all deaths. Models for death and mortality were available for 15 years of observation.

The team of experts was composed of two physicians and an epidemiologist and evaluated the documents in regular meetings. The

Table 1 Baseline characterization of the study cohort and fatty liver index according to demographic characteristics and comorbidities

Parameter	All ^a (n = 14 575)	FLI <60 (n = 9160)	FLI ≥60 (n = 5373)	p-value (FLI <60 vs. FLI ≥60)
Age (years)	54.9 ± 11.1	53.5 ± 11.2	57.4 ± 10.6	< 0.0001
Female sex	7287 (50)	5421 (59.2)	1841 (34.3)	< 0.0001
BMI (kg/m ²)	26.6 (23.9–30.0)	24.7 (22.7–26.6)	31.1 (28.8–34.0)	< 0.0001
Waist circumference (cm)	94.4 ± 13.9	86.7 ± 9.1	107.6 ± 10.2	< 0.0001
Obesity	3670 (25.2)	325 (3.5)	3332 (62.0)	< 0.0001
Diabetes mellitus type 2	1348 (9.3)	379 (4.1)	963 (17.9)	< 0.0001
Hypertension	7183 (49.3)	3417 (37.3)	3741 (69.7)	< 0.0001
Dyslipidaemia	5030 (34.6)	2294 (25.1)	2725 (50.8)	< 0.0001
Hyperuricemia	1340 (9.5)	432 (4.1)	903 (17.5)	< 0.0001
Metabolic syndrome	3347 (23.0)	725 (7.9)	2619 (48.7)	< 0.0001
Chronic liver disease	1196 (8.3)	612 (6.7)	580 (10.9)	< 0.0001
Cancer	1311 (9.0)	801 (8.8)	510 (9.5)	0.13
Smoker	2786 (19.2)	1781 (19.5)	998 (18.6)	0.2
Triglycerides (mg/dl)	105 (78–147)	88 (68–114)	147 (112–196)	< 0.0001
Cholesterol (mmol/L)	221 ± 41	219 ± 40	223 ± 42	< 0.0001
HDL (mg/dl)	57 ± 16	62 ± 16	49 ± 12	< 0.0001
LDL (mg/dl)	139 ± 36	138 ± 35	141 ± 36	< 0.0001
ALT (U/L)	32 (26–42)	29 (25–36)	40 (31–51)	< 0.0001
AST (U/L)	25 (22–29)	24 (21–28)	27 (23–32)	< 0.0001
gGT (U/L)	24 (17–37)	19	36	< 0.0001

Continuous variables are shown as mean ± standard deviation and tested with t-test, or as median (interquartile range) and tested with U test. Binary variables are described through relative and absolute frequencies and tested with chi-squared test.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FLI, fatty liver index; gGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aThe FLI data available for 14 533 patients.

team reviewed the information to identify diseases relevant to the study.³¹

Baseline characterization of the study cohort was also standardized according to European Standard Population 1976.⁴³

Statistical analysis

Statistical analysis was conducted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>). Continuous variables are reported as mean values (standard deviation) or as median (interquartile range) for skewed distributions. Categorical variables were described as absolute and relative frequencies. Adjusted proportional hazards models with consideration of competing events were used to analyse the relationship between the presence of hepatic steatosis and time-to-event outcome. All p-values correspond to two-tailed tests and the threshold of significance was set to 0.05. No adjustments were made for multiple comparisons, as this was an exploratory study. Consequently, p-values should be interpreted with caution and in conjunction with effect size estimates.

Results

Patient characteristics

A total of 15 010 participants were enrolled in the GHS and after exclusion of patients with preexisting MACE or harmful alcohol consumption, 14 575 patients were final analysed. The mean

age in this cohort was 54.9 ± 11.1 years with equal gender distribution. Baseline characteristic including demographic data, laboratory values and prevalence of comorbidities are presented in Table 1. Metabolic and cardiovascular risk factors were significantly more frequent in men, with arterial hypertension in 54.0% of men and 44.6% of women ($p < 0.0001$). Likewise, diabetes (11.3% vs. 7.3%; $p < 0.0001$), obesity (26.2% vs. 24.2%; $p < 0.01$), dyslipidaemia (43.2% vs. 26.0%; $p < 0.0001$), hyperuricemia (12.9% vs. 6.1%; $p < 0.0001$), and metabolic syndrome (29.0% vs. 17.0%; $p < 0.0001$) were more prevalent in men. A history of liver disease was more prevalent in women (9.0% vs. 7.6%; $p < 0.01$) as well as cancer (10.1% vs. 8.0%; $p < 0.0001$). Baseline characterization of the study cohort was also standardized according to European Standard Population 1976 (online supplementary Table S1), where comparable results were shown with increased metabolic and cardiovascular risk factors in men.

Prevalence of elevated liver enzymes and surrogate scores of hepatic steatosis

Elevated liver enzymes at baseline were detected in one out of five participants with increased ALT levels in 21.7%, increased AST levels in 12.4% and elevated gGT levels in 13.4%. Considering sex specific cut-offs, ALT > upper limit of normal (ULN) was seen in 20.9% of men and 22.4% of women ($p < 0.05$).

Table 2 Cox regressions stepwise analysing risk factors for major adverse cardiovascular events (MACE) and extended MACE

	HR (95% CI), <i>p</i> -value	
	MACE	eMACE
Hepatic steatosis (FLI $\geq$ 60)		
Basic model: adjusted for sex and age	1.62 (1.31–2.01), <i>p</i> < 0.0001	1.44 (1.21–1.72), <i>p</i> < 0.0001
Additionally adjusted for waist-to-height ratio	1.33 (1.01–1.76), <i>p</i> = 0.046	1.098 (0.87–1.39); <i>p</i> = 0.44
Additionally adjusted for arterial hypertension	1.46 (1.18–1.81), <i>p</i> < 0.001	1.31 (1.10–1.57), <i>p</i> < 0.01
Additionally adjusted for dyslipidaemia	1.52 (1.23–1.88), <i>p</i> < 0.0001	1.38 (1.16–1.65); <i>p</i> < 0.001
Additionally adjusted for diabetes mellitus	1.53 (1.23–1.89), <i>p</i> < 0.001	1.41 (1.18–1.69); <i>p</i> < 0.001
Adjusted for all relevant variables for MACE and eMACE		
Hepatic steatosis (FLI $\geq$ 60)	1.16 (0.87–1.54), <i>p</i> = 0.32	0.97 (0.76–1.23), <i>p</i> = 0.78
Sex	0.50 (0.40–0.63), <i>p</i> < 0.0001	0.56 (0.47–0.67), <i>p</i> < 0.0001
Age	1.07 (1.06–1.08), <i>p</i> < 0.0001	1.07 (1.06–1.08), <i>p</i> < 0.0001
BMI	1.04 (0.99–1.10), <i>p</i> = 0.09	1.07 (1.03–1.11), <i>p</i> < 0.01
Waist-to-height ratio	0.26 (0.01–7.47), <i>p</i> = 0.43	0.20 (0.01–3.36), <i>p</i> = 0.26
Arterial hypertension	1.57 (1.22–2.03), <i>p</i> < 0.001	1.44 (1.17–1.76), <i>p</i> < 0.001
Dyslipidaemia	1.45 (1.18–1.79), <i>p</i> < 0.001	1.29 (1.09–1.54), <i>p</i> < 0.01
Diabetes mellitus	1.38 (1.05–1.80), <i>p</i> = 0.019	1.03 (0.80–1.33), <i>p</i> = 0.82

BMI, body mass index; CI, confidence interval; FLI, fatty liver index; HR, hazard ratio.

AST was elevated > ULN in 13.8% of men and 11.0% of women (*p* < 0.0001) and gGT > ULN in 12.3% of men and 14.4% of women (*p* < 0.001).

The FLI as surrogate score of hepatic steatosis was positive (FLI $\geq$ 60) in 37% (*n* = 5373) of the participants at baseline. In the subgroup with a positive FLI, men were overrepresented compared to women (65.7% vs. 34.3%; *p* < 0.0001). Regarding age, FLI was more frequently positive in elderly persons ($\geq$ 55 vs. < 55 years: 43.8% vs. 29.6%; *p* < 0.0001) at baseline. Also, participants with positive FLI showed significantly more metabolic and cardiovascular risk factors than participants with negative FLI (Table 1). In the standardized study cohort, there was a prevalence of hepatic steatosis (FLI $\geq$ 60) of 34.6% (*n* = 5045).

Fibrosis-4 was used as non-invasive surrogate score for hepatic fibrosis. At baseline 0.8% (*n* = 116) of patients exhibited a FIB-4 above the upper cut-off of 2.67, and increasing FIB-4 was significantly more frequent in men (*p* < 0.001).

Major adverse cardiovascular events

At 5-year follow-up, 478 patients (3.7%) developed a MACE. Patients with a positive FLI at baseline showed significantly more MACE than those with a negative FLI (5.7% vs. 2.6%; *p* < 0.0001). An eMACE was even more frequent in both groups: in total 578 patients (4.9%) developed eMACE with more eMACE in the group with a positive FLI at baseline (7.1% vs. 3.7%; *p* < 0.0001). We applied a proportional hazards model accounting for mortality as a competing event, hence being able to further specify whether people who have been censored during the time to event are further at risk or not, which enhances statistical interpretability. With regard to eMACE there was only one event and for MACE there were 164 competing events. Adjusting for age and sex, the

presence of hepatic steatosis was associated with an increased risk of developing MACE by 62.3% (hazard ratio [HR] 1.623, 95% confidence interval [CI] 1.31–2.01; *p* < 0.0001) and eMACE by 44.0% (HR 1.440, 95% CI 1.21–1.72; *p* < 0.0001). Furthermore, hepatic steatosis was also associated with an increased risk for all-cause mortality (HR 1.55, 95% CI 1.41–1.71; *p* < 0.0001) in the follow-up time of 15 years.

A Cox regression model with a stepwise adjustment strategy was developed to identify the risk factors mediating MACE and eMACE. First, we conducted a basic model with adjustments for sex and age. In a next step, we additionally adjusted for further risk factors like waist-to-height ratio, arterial hypertension and other risk factors (Table 2). In the analysis, a significant association of hepatic steatosis with MACE and eMACE was found, even after adjusting for single, known risk factors. The increase in HR, when adjusting for factors like arterial hypertension, dyslipidaemia and diabetes mellitus in Table 2 implies that hepatic steatosis, if present without these factors, represents a higher risk factor for MACE. In a Cox regression model adjusted simultaneously for all relevant variables for MACE and eMACE, we see that FLI is no longer significantly associated with MACE and eMACE (Table 2). This indicates that the factors remaining relevant in the model explain the association between hepatic steatosis and MACE. Interestingly, in this model, the risk factors BMI for MACE and 'diabetes mellitus for eMACE also lose their significance in predicting the outcome.

The presence of hepatic steatosis showed an increased cumulative incidence of developing MACE (Figure 2A) and eMACE (Figure 2B), even after considering waist-to-height ratio, arterial hypertension, dyslipidaemia and type 2 diabetes mellitus as confounders (Figure 2C,D) and an increased cumulative incidence of all-cause mortality for 15 years of observation (Figure 3A).

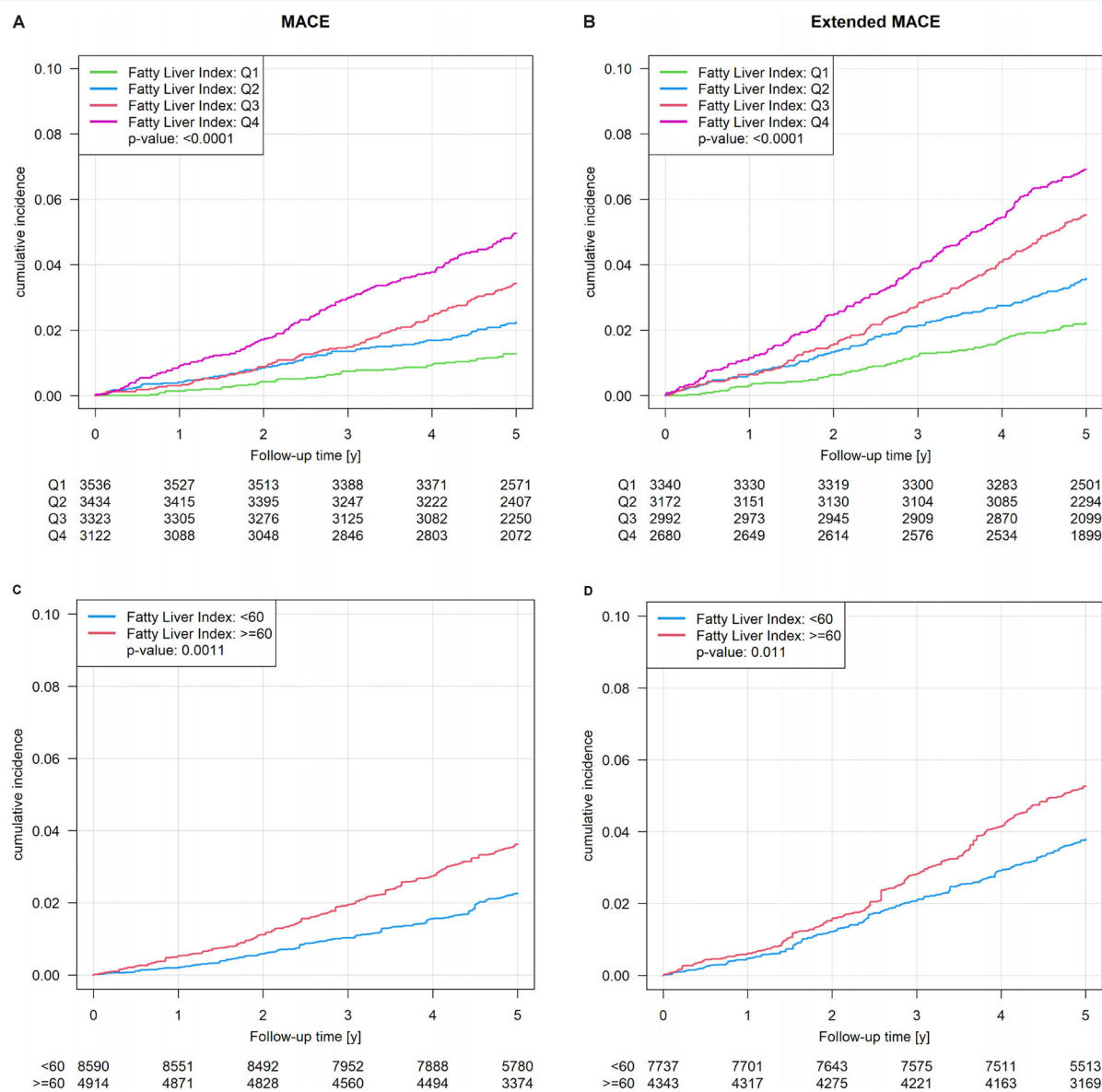


Figure 2 (A, B) Cumulative incidence of developing major adverse cardiovascular events (MACE) and extended MACE associated with the presence of hepatic steatosis. (C, D) Cumulative incidence of developing MACE and extended MACE associated with the presence of hepatic steatosis adjusted for waist-to-height ratio, arterial hypertension, dyslipidaemia and type 2 diabetes mellitus. Quartiles: Q1 = <18.23; Q2 = 18.23–<44.11; Q3 = 44.11–<74.72; Q4 = ≥74.72. P-value: log-rank test.

To examine whether the association between MASLD and MACE differs between obese and non-obese individuals, we performed a stratified analysis using a basic model with sex and age and an interaction term for the effect of FLI on outcome in obese (BMI ≥30 kg/m²) versus non-obese (BMI <30 kg/m²) individuals. The analysis revealed a significant interaction for both outcomes, MACE and eMACE. The effect of FLI on outcome was similar in both models with an approximately 1.02 times larger effect in obese than in non-obese individuals (Table 3). With regard to hepatic fibrosis, there was an increased risk of developing eMACE in patients with high FIB-4 score compared to those with low FIB-4

score (HR 2.15, 95% CI 1.11–4.18; $p = 0.02$), but no increased risk of developing MACE (HR 1.87, 95% CI 0.94–3.73; $p = 0.07$). An increased risk of all-cause mortality in patients with a high FIB-4 score (HR 2.53, 95% CI 1.94–3.31; $p < 0.0001$) and an indeterminate FIB-4 (HR 1.25, 95% CI 1.12–1.39; $p < 0.0001$) compared the low FIB-4 category was observed. An increased cumulative incidence of all-cause mortality in the presence of hepatic fibrosis was observed (Figure 3B).

To assess the clinical utility of MASLD in cardiovascular risk stratification, we evaluated whether adding MASLD to established risk prediction models improves predictive performance. Therefore,

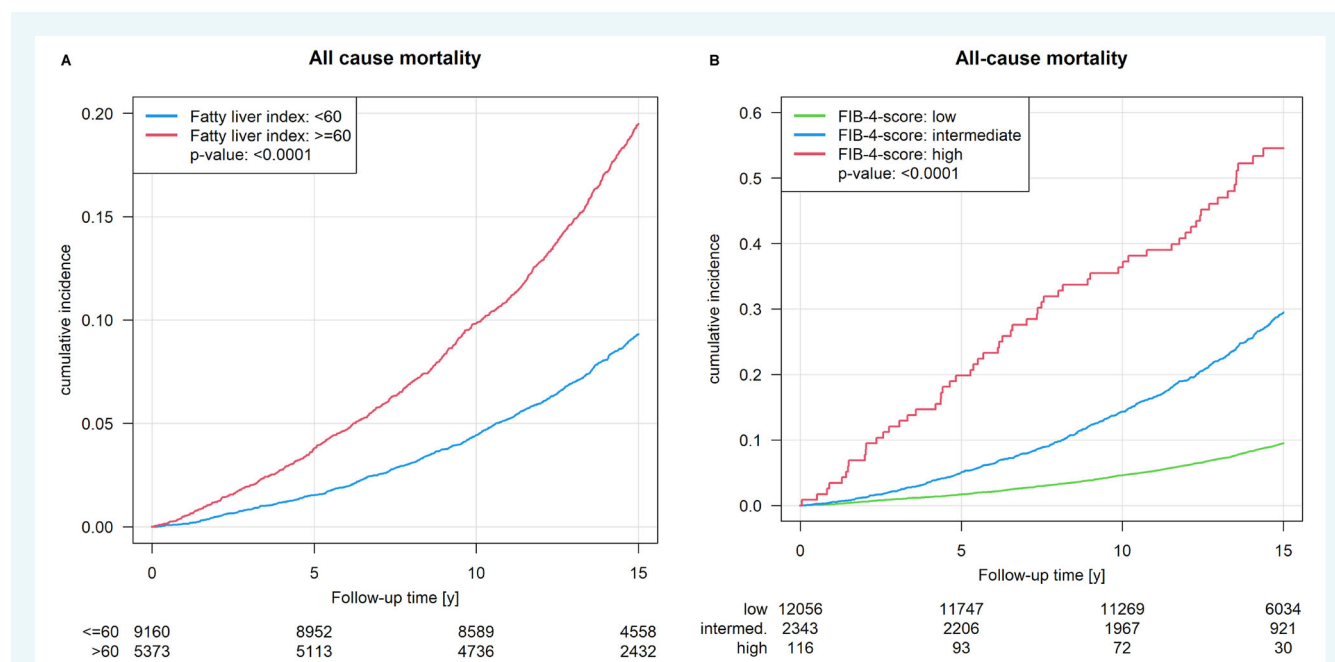


Figure 3 Cumulative incidence of all-cause mortality associated with the presence of hepatic steatosis (A) and hepatic fibrosis (B). P-value: log-rank test.

Table 3 Impact of fatty liver index on major adverse cardiovascular events (MACE) and extended eMACE in regard to body mass index

	BMI <30 kg/m ²	BMI ≥30 kg/m ²
MACE		
Sex (women)	0.51 (0.38–0.68), p < 0.0001	0.58 (0.40–0.84), p < 0.01
Age	2.22 (1.94–2.55), p < 0.0001	1.98 (1.63–2.40), p < 0.0001
FLI	1.01 (1.00–1.01), p = 0.02	1.03 (1.02–1.05), p < 0.001
Interaction term of FLI in obese vs. non-obese	1.023 (1.01–1.04), p = 0.008	
eMACE		
Sex (women)	0.59 (0.46–0.75), p < 0.0001	0.65 (0.47–0.88), p < 0.01
Age	2.15 (1.93–2.41), p < 0.0001	1.76 (1.51–2.06), p < 0.0001
FLI	1.00 (0.99–1.01), p = 0.08	1.03 (1.01–1.04), p < 0.001
Interaction term of FLI in obese vs. non-obese	1.02 (1.01–1.03), p = 0.004	

Data presented as hazard ratio (95% confidence interval).
BMI, body mass index; FLI, fatty liver index.

a comparison between a baseline model with Systematic COronary Risk Evaluation 2 (SCORE2) as a risk model that estimates the 10-year risk of CVD in adults without previous CVD or diabetes⁴⁴ and a model incorporating MASLD was conducted. For quantifying the improvement in predictive accuracy, the change in Harrell's C-index and the net reclassification index (NRI) were calculated to assess the extent to which MASLD enhances patient risk

classification (Table 4). FLI has independent predictive value after adjusting for SCORE2 and relevantly improves the C-index. The NRI indicated a correct reclassification by including FLI by approximately 20% for both MACE and eMACE.

Discussion

In this cohort study of 15 010 participants in the GHS, hepatic steatosis was highly prevalent and the FLI was positive in 37%. The FLI is a validated and well-established non-invasive test with an accuracy of 0.84.^{35,45,46} The estimated prevalence of 37% is in line with previously published data on the prevalence of MASLD in Europe and Germany.^{45,47} Accordingly, data from the past decades have also shown a marked increase in the prevalence of NAFLD from 15% in 2005 to 25% in 2010.⁴⁸ In a population-based study in young adults in the UK, the prevalence of steatosis was 20.7%, measured by transient elastography.⁴⁹ Data from the National Health and Nutrition Examination Survey (NHANES) database in the United States found a prevalence of 40.4% of hepatic steatosis in young adults utilizing transient elastography.⁵⁰ In the MASLD subgroup, men and elderly people were overrepresented and comorbidities including arterial hypertension and diabetes were found more frequently. These characteristics represent well-known risk factors for the development of MASLD, and the current findings underline the strong association of MASLD and metabolic comorbidities.^{1,2,11} Comparable epidemiologic data on liver fibrosis are scarce, but the prevalence of MASH in Western Europe is estimated to be about 4%.¹

In this cohort study the presence of advanced fibrosis as determined by the FIB-4 score with a cut-off >2.67 was 0.8%. This test

Table 4 Metabolic dysfunction-associated steatotic liver disease in cardiovascular risk stratification

	FLI	SCORE2 algorithm	SCORE2 algorithm + fatty liver index	Δ C-index p-value ^a
MACE				
HR (95% CI)	1.017 (1.013–1.020), $p < 0.0001$	1.006 (1.004–1.008), $p < 0.0001$	1.016 (1.012–1.019), $p < 0.0001$	
C-index	0.644	0.607	0.646	0.0016
NRI (95% CI)			0.22 (0.17–0.27), $p < 0.0001$	
eMACE				
HR (95% CI)	1.015 (1.012–1.018), $p < 0.0001$	1.004 (1.002–1.006), $p < 0.0001$	1.014 (1.011–1.017), $p < 0.0001$	
C-index	0.63	0.58	0.627	<0.0001
NRI (95% CI)		–	0.19 (0.138–0.23), $p < 0.0001$	

CI, confidence interval; eMACE, extended major adverse cardiovascular events; HR, hazard ratio; MACE, major adverse cardiovascular events; NRI, net reclassification index; SCORE2, Systematic COronary Risk Evaluation 2.

^a Δ C-index p-value between SCORE2 algorithm and SCORE2 algorithm + fatty liver index.

has been suggested as enrichment tool for referral pathways⁵¹ but will miss patients with early stages of hepatic fibrosis (F1–F2).⁵²

In the current analysis, MASLD patients were significantly more often affected by MACE and exhibited a more than two times higher all-cause mortality rate. After adjustment for age and gender, MASLD remained an independent risk factor for incident cardiovascular events on regression analysis. With the analysis, we were able to show that there is a connection between hepatic steatosis and MACE and eMACE, with various factors influencing this, such as hypertension, dyslipidaemia and diabetes mellitus. Hepatic steatosis, if present without these factors, represents a higher risk factor for MACE, which suggests that there might be different aetiologies included in the sample leading to the changes in the liver that are associated with different risks for MACE. The FLI score, and thus the MASLD diagnosis, therefore appears to group together different subgroups of diseases.

In the current analysis, MASLD confers a risk for developing MACE and eMACE with an approximately 1.02 times larger effect in obese (BMI ≥ 30 kg/m²) than in non-obese individuals. This is a central observation and could be related to a number of factors. The concept of metabolic inflammation⁵³ has been identified as a driver of the disease and outcomes and its impact is likely stronger in obese versus non-obese participants. Additionally, the non-obese group does include patients with a BMI defining normal weight (≤ 25 kg/m²). Within this group, that was formerly known as lean NASH, the degree of heterogeneity is larger. Still, based on its simplicity and availability, FLI can serve as a risk stratification tool in the general population to be used in clinical practice.

Our findings on the negative effect of hepatic steatosis on CVD complement a series of studies in several countries with comparable results.^{30,54} In the United States, Meyersohn *et al.*⁵⁵ showed in a smaller cohort study of 3756 participants, that hepatic steatosis detected by computed tomography imaging was associated with MACE independently of other cardiovascular risk factors. In South Korea, Moon *et al.*⁴⁶ analysed data of 351 068

citizens from a nationwide health screening database and found that individuals with MASLD (FLI > 60) were at an increased risk of developing CVD. In Sweden, Simon *et al.*⁵⁶ recorded MACEs in a population-based cohort of 10 422 adults with histologically confirmed MASLD and observed that the rate of incident MACE increases with MASLD disease stage. Data from Germany are scarce. In a smaller cohort of 1096 adults from the Study of Health in Pomerania in Northeastern Germany, data analysis showed an association between MASLD and cardiac remodelling detected by magnetic resonance imaging.⁴⁷

To assess the clinical utility of MASLD in cardiovascular risk stratification, we evaluated whether adding MASLD to established risk prediction models improves predictive performance. The models show an improved risk classification when adding FLI to the SCORE2. FLI has independent predictive value after adjusting for SCORE2 and relevantly improves the C-index. The NRI indicated a correct reclassification by including FLI by approximately 20% for both MACE and eMACE. The models show that FLI retains its predictive power despite the SCORE2 score. Therefore, FLI offers additional prognostic value beyond traditional risk factors and justify its inclusion in cardiovascular risk assessment.

In contrast, the preexistence of liver fibrosis did not confer an increased risk of MACE, but contributed to an increased risk of all-cause mortality. This might be due to the fact that the presence of fibrosis indicates more advanced disease stages, in which morbidity and mortality are mainly caused by the liver disease itself and its various complications including portal hypertension, decompensated cirrhosis and hepatocellular carcinoma.^{5,27,57–60} In fact, advanced liver fibrosis is known to be a strong predictor of mortality in patients with MASLD.^{61,62}

This study has limitations as it was based on a regional sample from the Mainz-Bingen area in Rhineland-Palatinate, Germany and may not be directly representative for other countries or other regions in Germany. When assessing the external validity or generalizability of the study, it must also be considered that persons with

severe health restrictions and persons without sufficient knowledge of German were fundamentally excluded from participation in the study. Furthermore, a history of liver disease was self-reported at baseline and in the current study, the reported prevalence of 8% of underlying liver disease is likely an overestimation. The presence of MASLD was defined as the presence of steatosis of the liver with a positive FLI and the exclusion of other chronic liver disease or high alcohol consumption. We did not utilize imaging techniques like sonography, transient elastography or magnetic resonance imaging as reference standard to identify steatosis. Also, alcohol consumption was self-reported and thus underreporting could have occurred. We choose waist-to-height ratio rather than BMI to overcome limitations in the categorization of obesity and body fat distribution.

Our findings support the concept that MASLD is a multisystem disease with a complex pathophysiology affecting not only the liver but also the cardiovascular system.⁶³ The effect of MASLD on incident CVD could in part be mediated through atherogenic dyslipidaemia as well as a systemic low-grade inflammation, which is seen in most MASLD patients.^{64,65} This contributes to chronic vascular inflammation, endothelial dysfunction and the remodelling of blood vessels with formation of atherosclerotic plaques.⁶⁶

The results of this large, prospective, population-based study underline the high burden of disease related to MASLD in the German general population and highlight the need for targeted therapies as well as efficient primary and secondary prevention strategies. International expert groups of cardiologists and hepatologists ask for more awareness among physicians and a standardized evaluation of cardiovascular risk in MASLD patients.^{67–69} The growing understanding of MASLD pathophysiology has led to new therapeutic approaches, which are aimed at ameliorating the metabolic function and suppress chronic inflammation. Existing drugs, which might have a beneficial effect on both MASLD and CVD, include for example incretins or the thyroid hormone receptor beta-agonist resmetirom.^{70,71}

With the emergence of these therapies, screening tools to identify individuals with advanced hepatic fibrosis related to MASLD are implemented. As these patients are increasingly identified, our data support the concept of screening for CVD to prevent incident MACE. In this context, the FLI that was used in this cohort study represents an easy, inexpensive, broadly available and non-invasive diagnostic tool, which is based on laboratory measurements (triglycerides, gGT) and basic physical examination (BMI, WC). Interestingly, Zou et al.⁴⁵ showed in a UK Biobank analysis that the FLI not only predicts MASLD but is also an independent risk factor for CVD. To replace FLI and FIB-4 liver elastography is available today to diagnose MASLD with high accuracy.³⁷ Nonetheless, the FLI has been included in regional guidelines and is a helpful diagnostic tool at a low resource level to identify patients with MASLD.

In conclusion, MASLD was shown to be an independent risk factor for MACE and MASLD patients displayed a significantly increased risk of all-cause mortality in the general population in Germany. Further investigations and longitudinal data over a more extended period are needed to clarify the role of MASLD on cardiovascular health.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

We would like to thank the participants of the Gutenberg Health Study. Open Access funding enabled and organized by Projekt DEAL.

Funding

The Gutenberg Health Study is funded through the government of Rhineland-Palatinate ('Stiftung Rheinland-Pfalz für Innovation', contract AZ 961-386261/733), the research programmes 'Wissen schafft Zukunft' and Center for Translational Vascular Biology (CTVB) of the Johannes Gutenberg-University of Mainz, and its contract with Boehringer Ingelheim and Philips Medical Systems, including an unrestricted grant for the Gutenberg Health Study. P.W. is funded by the Federal Ministry of Education and Research (BMBF 01EO1503); he is PI of the German Center for Vascular Research (DZHK) and PI of the DIASyM research core (BMBF 161L0217A).

Conflict of interest: J.H.P. is an employee of Boehringer Ingelheim International GmbH. M.M.W. has received honoraria as a speaker or board member from Boehringer Ingelheim, Ipsen, Lilly, MSD, Novartis, and Novo Nordisk. P.W. reports the submitted work grants from TRON gGmbH and Bayer AG, non-financial grants from Philips Medical Systems, grants and consulting fees from Boehringer Ingelheim, Novartis Pharma, Sanofi-Aventis, Daiichi Sankyo Europe, grants, consulting and lecturing fees from Bayer Health Care, lecturing fees from Pfizer Pharma, Bristol Myers Squibb, consulting fees from AstraZeneca, consulting fees and non-financial support from Diasorin and non-financial support from I.E.M., outside of the submitted work. J.M.S. declares consultant honorary from Akero, Alentis, Alexion, Altimune, AstraZeneca, 89Bio, Bionorica, Boehringer Ingelheim, Boston Pharmaceuticals, Gilead Sciences, GSK, HistoIndex, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals, PRO.MED.CS Praha a.s., Kriya Therapeutics, Eli Lilly, MSD Sharp & Dohme GmbH, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers; speaker honoraria from AbbVie, Boehringer Ingelheim, Gilead Sciences, Ipsen, Lilly, Novo Nordisk, Madrigal Pharmaceuticals, Stockholder options: Hepta Bio. All other authors have nothing to disclose.

References

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): A systematic review. *Hepatology* 2023;**77**:1335–1347. <https://doi.org/10.1097/HEP.0000000000000004>
2. Wong VW, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J Hepatol* 2023;**79**:842–852. <https://doi.org/10.1016/j.jhep.2023.04.036>
3. Tinajero MG, Malik VS. An update on the epidemiology of type 2 diabetes: A global perspective. *Endocrinol Metab Clin North Am* 2021;**50**:337–355. <https://doi.org/10.1016/j.ecl.2021.05.013>
4. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018;**67**:123–133. <https://doi.org/10.1002/hep.29466>
5. Paik JM, Golabi P, Younossi Y, Srishord M, Mishra A, Younossi ZM. The growing burden of disability related to nonalcoholic fatty liver disease: Data from the Global Burden of Disease 2007–2017. *Hepatol Commun* 2020;**4**:1769–1780. <https://doi.org/10.1002/hep4.1599>
6. Schattenberg JM, Lazarus JV, Newsome PN, Serfaty L, Aghemo A, Augustin S, et al. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: A cost-of-illness analysis. *Liver Int* 2021;**41**:1227–1242. <https://doi.org/10.1111/liv.14825>

7. Younossi ZM, Blissett D, Blissett R, Henry L, Stepanova M, Younossi Y, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology* 2016;**64**:1577–1586. <https://doi.org/10.1002/hep.28785>
8. Pais R, Barritt AS, Calmus Y, Scatton O, Runge T, Lebray P, et al. NAFLD and liver transplantation: Current burden and expected challenges. *J Hepatol* 2016;**65**:1245–1257. <https://doi.org/10.1016/j.jhep.2016.07.033>
9. Noureddin M, Vipani A, Bresee C, Todo T, Kim IK, Alkhouiri N, et al. NASH leading cause of liver transplant in women: Updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol* 2018;**113**:1649–1659. <https://doi.org/10.1038/s41395-018-0088-6>
10. Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al. Non-alcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol* 2021;**19**:580–589.e5. <https://doi.org/10.1016/j.cgh.2020.05.064>
11. Rinella ME, Lazarus JV, Ratzliff V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 2023;**79**:1542–1556. <https://doi.org/10.1016/j.jhep.2023.06.003>
12. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024;**81**:492–542. <https://doi.org/10.1016/j.jhep.2024.04.031>
13. Rinella ME. Examining the nomenclature change from NAFLD and NASH to MASLD and MASH. *Gastroenterol Hepatol (NY)* 2023;**19**:697–699.
14. Kanwal F, Neuschwander-Tetri BA, Loomba R, Rinella ME. Metabolic dysfunction-associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease. *Hepatology* 2024;**79**:1212–1219. <https://doi.org/10.1097/HEP.0000000000000670>
15. Kalligeros M, Vassilopoulos A, Vassilopoulos S, Victor DW, Mylonakis E, Noureddin M. Prevalence of steatotic liver disease (MASLD, MetALD, and ALD) in the United States: NHANES 2017–2020. *Clin Gastroenterol Hepatol* 2024;**22**:1330–1332.e4. <https://doi.org/10.1016/j.cgh.2023.11.003>
16. Targher G, Byrne CD, Tilg H. MASLD: A systemic metabolic disorder with cardiovascular and malignant complications. *Gut* 2024;**73**:691–702. <https://doi.org/10.1136/gutjnl-2023-330595>
17. Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. *J Hepatol* 2024;**80**:e76–e77. <https://doi.org/10.1016/j.jhep.2023.08.026>
18. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;**77**:1797–1835. <https://doi.org/10.1097/HEP.0000000000000323>
19. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;**64**:1388–1402. <https://doi.org/10.1016/j.jhep.2015.11.004>
20. Allen AM, Hicks SB, Mara KC, Larson JJ, Thorneau TM. The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity – a longitudinal cohort study. *J Hepatol* 2019;**71**:1229–1236. <https://doi.org/10.1016/j.jhep.2019.08.018>
21. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;**67**:328–357. <https://doi.org/10.1002/hep.29367>
22. Labenz C, Huber Y, Michel M, Nagel M, Galle PR, Kostev K, et al. Impact of NAFLD on the incidence of cardiovascular diseases in a primary care population in Germany. *Dig Dis Sci* 2019;**65**:2112–2119. <https://doi.org/10.1007/s10620-019-05986-9>
23. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;**74**:e177–e232. <https://doi.org/10.1016/j.jacc.2019.03.010>
24. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: A systematic review. *BMC Med Res Methodol* 2021;**21**:241. <https://doi.org/10.1186/s12874-021-01440-5>
25. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, et al. Reducing the global burden of cardiovascular disease, part 1: The epidemiology and risk factors. *Circ Res* 2017;**121**:677–694. <https://doi.org/10.1161/CIRCRESAHA.117.308903>
26. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. *Nat Rev Dis Primers* 2019;**5**:56. <https://doi.org/10.1038/s41572-019-0106-z>
27. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: Results from a nationwide cohort. *Gut* 2021;**70**:1375–1382. <https://doi.org/10.1136/gutjnl-2020-322786>
28. Sinn DH, Kang D, Chang Y, Ryu S, Cho SJ, Paik SW, et al. Non-alcoholic fatty liver disease and the incidence of myocardial infarction: A cohort study. *J Gastroenterol Hepatol* 2020;**35**:833–839. <https://doi.org/10.1111/jgh.14856>
29. Allen AM, Thorneau TM, Mara KC, Larson JJ, Watt KD, Hayes SN, et al. Women with nonalcoholic fatty liver disease lose protection against cardiovascular disease: A longitudinal cohort study. *Am J Gastroenterol* 2019;**114**:1764–1771. <https://doi.org/10.14309/ajg.0000000000000401>
30. Mantovani A, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: An updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021;**6**:903–913. [https://doi.org/10.1016/S2468-1253\(21\)00308-3](https://doi.org/10.1016/S2468-1253(21)00308-3)
31. Wild P, Zeller T, Beutel M, Blettner M, Dugi K, Lackner K, et al. The Gutenberg Health Study. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2012;**55**:824–829. <https://doi.org/10.1007/s00103-012-1502-7>
32. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. *Lancet* 2005;**366**:1059–1062. [https://doi.org/10.1016/S0140-6736\(05\)67402-8](https://doi.org/10.1016/S0140-6736(05)67402-8)
33. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of obesity. *Circulation* 2009;**120**:1640–1645. <https://doi.org/10.1161/CIRCULATIONAHA.109.192644>
34. Roeb E, Canbay A, Bantel H, Bojunga J, de Laffolie J, Demir M, et al. Amendment “Neue Nomenklatur zur MASLD (Metabolic Dysfunction Associated Steatotic Liver Disease; metabolische Dysfunktion assoziierte steatotische Lebererkrankung)” zur S2k-Leitlinie “Nicht-alkoholische Fettlebererkrankung” (v. 2.0/April 2022) der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). *Z Gastroenterol* 2024;**62**:1077–1087. <https://doi.org/10.1055/a-2309-6052>
35. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The fatty liver index: A simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol* 2006;**6**:33. <https://doi.org/10.1186/1471-230X-6-33>
36. Labenz C, Huber Y, Kalliga E, Nagel M, Ruckes C, Straub BK, et al. Predictors of advanced fibrosis in non-cirrhotic non-alcoholic fatty liver disease in Germany. *Aliment Pharmacol Ther* 2018;**48**:1109–1116. <https://doi.org/10.1111/apt.14976>
37. Michel M, Schattenberg JM. Liver-specific diagnostic for non-alcoholic fatty liver disease (NAFLD) – time to replace liver biopsy? *Z Gastroenterol* 2020;**58**:1233–1240. <https://doi.org/10.1055/a-1291-8483>
38. Cuthbertson DJ, Weickert MO, Lythgoe D, Sprung VS, Dobson R, Shoaib-Moradie F, et al. External validation of the fatty liver index and lipid accumulation product indices, using 1H-magnetic resonance spectroscopy, to identify hepatic steatosis in healthy controls and obese, insulin-resistant individuals. *Eur J Endocrinol* 2014;**171**:561–569. <https://doi.org/10.1530/EJE-14-0112>
39. Garteiser P, Castera L, Coupaye M, Doblas S, Calabrese D, Dioguardi Burgo M, et al. Prospective comparison of transient elastography, MRI and serum scores for grading steatosis and detecting non-alcoholic steatohepatitis in bariatric surgery candidates. *JHEP Rep* 2021;**3**:100381. <https://doi.org/10.1016/j.jhepr.2021.100381>
40. Sharma A, Pagidipati NJ, Califf RM, McGuire DK, Green JB, Demets D, et al. Impact of regulatory guidance on evaluating cardiovascular risk of new glucose-lowering therapies to treat type 2 diabetes mellitus: Lessons learned and future directions. *Circulation* 2020;**141**:843–862. <https://doi.org/10.1161/CIRCULATIONAHA.119.041022>
41. Mortensen EM, Halm EA, Pugh MJ, Copeland LA, Metersky M, Fine MJ, et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. *JAMA* 2014;**311**:2199–2208. <https://doi.org/10.1001/jama.2014.4304>
42. Karthikesalingam A, Bahia SS, Patterson BO, Peach G, Vidal-Diez A, Ray KK, et al. The shortfall in long-term survival of patients with repaired thoracic or abdominal aortic aneurysms: Retrospective case-control analysis of hospital

- episode statistics. *Eur J Vasc Endovasc Surg* 2013;**46**:533–541. <https://doi.org/10.1016/j.ejvs.2013.09.008>
43. Waterhouse J, Muir C, Correa P, Powell J. *Cancer incidence in five continents*. Lyon: International Agency for Research on Cancer; 1976. <https://pmc.ncbi.nlm.nih.gov/articles/PMC553232/>
 44. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: New models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J* 2021;**42**:2439–2454. <https://doi.org/10.1093/eurheartj/ehab309>
 45. Zou B, Yeo YH, Cheung R, Ingelsson E, Nguyen MH. Fatty liver index and development of cardiovascular disease: Findings from the UK Biobank. *Dig Dis Sci* 2021;**66**:2092–2100. <https://doi.org/10.1007/s10620-021-06954-y>
 46. Moon JH, Jeong S, Jang H, Koo BK, Kim W. Metabolic dysfunction-associated steatotic liver disease increases the risk of incident cardiovascular disease: A nationwide cohort study. *EClinicalMedicine* 2023;**65**:102292. <https://doi.org/10.1016/j.eclinm.2023.102292>
 47. Kostka F, Ittermann T, Groß S, Laqua FC, Bülow R, Völzke H, et al. Cardiac remodelling in non-alcoholic fatty liver disease in the general population. *Liver Int* 2024;**44**:1032–1041. <https://doi.org/10.1111/liv.15844>
 48. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;**64**:73–84. <https://doi.org/10.1002/hep.28431>
 49. Abeysekera KWM, Fernandes GS, Hammerton G, Portal AJ, Gordon FH, Heron J, et al. Prevalence of steatosis and fibrosis in young adults in the UK: A population-based study. *Lancet Gastroenterol Hepatol* 2020;**5**:295–305. [https://doi.org/10.1016/S2468-1253\(19\)30419-4](https://doi.org/10.1016/S2468-1253(19)30419-4)
 50. Alkhouli N, Almomani A, Le P, Payne JY, Asaad I, Sakkal C, et al. The prevalence of alcoholic and nonalcoholic fatty liver disease in adolescents and young adults in the United States: Analysis of the NHANES database. *BMC Gastroenterol* 2022;**22**:366. <https://doi.org/10.1186/s12876-022-02430-7>
 51. Graupera I, Thiele M, Serra-Burriel M, Caballeria L, Roulot D, Wong GL, et al.; Investigators of the LiverScreen Consortium. Low accuracy of FIB-4 and NAFLD fibrosis scores for screening for liver fibrosis in the population. *Clin Gastroenterol Hepatol* 2022;**20**:2567–2576.e6. <https://doi.org/10.1016/j.cgh.2021.12.034>
 52. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009;**7**:1104–1112. <https://doi.org/10.1016/j.cgh.2009.05.033>
 53. Gehrke N, Schattenberg JM. Metabolic inflammation-a role for hepatic inflammatory pathways as drivers of comorbidities in nonalcoholic fatty liver disease? *Gastroenterology* 2020;**158**:1929–1947.e6. <https://doi.org/10.1053/j.gastro.2020.02.020>
 54. Lv Q, Zhao H. The association of metabolic dysfunction-associated steatotic liver disease (MASLD) with the risk of myocardial infarction: A systematic review and meta-analysis. *Ann Med* 2024;**56**:2306192. <https://doi.org/10.1080/07853890.2024.2306192>
 55. Meyersohn NM, Mayrhofer T, Corey KE, Bittner DO, Staziaki PV, Szilveszter B, et al. Association of hepatic steatosis with major adverse cardiovascular events, independent of coronary artery disease. *Clin Gastroenterol Hepatol* 2021;**19**:1480–1488.e14. <https://doi.org/10.1016/j.cgh.2020.07.030>
 56. Simon TG, Roelstraete B, Hagström H, Sundström J, Ludvigsson JF. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: Results from a nationwide histology cohort. *Gut* 2022;**71**:1867–1875. <https://doi.org/10.1136/gutjnl-2021-325724>
 57. Song R, Li Z, Zhang Y, Tan J, Chen Z. Comparison of NAFLD, MAFLD and MASLD characteristics and mortality outcomes in United States adults. *Liver Int* 2024;**44**:1051–1060. <https://doi.org/10.1111/liv.15856>
 58. Xiao J, Ng CH, Chan KE, Fu C, Tay P, Yong JN, et al. Hepatic, extra-hepatic outcomes and causes of mortality in NAFLD – an umbrella overview of systematic review of meta-analysis. *J Clin Exp Hepatol* 2023;**13**:656–665. <https://doi.org/10.1016/j.jceh.2022.11.006>
 59. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR. Metabolic dysfunction-associated steatotic liver disease (MASLD): A state-of-the-art review. *J Obes Metab Syndr* 2023;**32**:197–213. <https://doi.org/10.7570/jomes23052>
 60. Nabi O, Lapidus N, Boursier J, de Ledinghen V, Kab S, Renuy A, et al. The NAFLD burden on mortality and morbidities in general population: A community-based longitudinal study (NASH-CO study). *Liver Int* 2023;**43**:2096–2106. <https://doi.org/10.1111/liv.15674>
 61. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015;**61**:1547–1554. <https://doi.org/10.1002/hep.27368>
 62. Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol* 2017;**67**:1265–1273. <https://doi.org/10.1016/j.jhep.2017.07.027>
 63. Byrne CD, Targher G. NAFLD: A multisystem disease. *J Hepatol* 2015;**62**:S47–S64. <https://doi.org/10.1016/j.jhep.2014.12.012>
 64. Tilg H, Adolph TE, Dudek M, Knolle P. Non-alcoholic fatty liver disease: The interplay between metabolism, microbes and immunity. *Nat Metab* 2021;**3**:1596–1607. <https://doi.org/10.1038/s42255-021-00501-9>
 65. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: The multiple parallel hits hypothesis. *Hepatology* 2010;**52**:1836–1846. <https://doi.org/10.1002/hep.24001>
 66. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, et al. Targeting cardiovascular inflammation: Next steps in clinical translation. *Eur Heart J* 2021;**42**:113–131. <https://doi.org/10.1093/eurheartj/ehaa099>
 67. Zhou XD, Targher G, Byrne CD, Somers V, Kim SU, Chahal CAA, et al. An international multidisciplinary consensus statement on MAFLD and the risk of CVD. *Hepatol Int* 2023;**17**:773–791. <https://doi.org/10.1007/s12072-023-10543-8>
 68. Pisetta C, Chillè C, Pelizzari G, Pigozzi MG, Salvetti M, Paini A, et al. Evaluation of cardiovascular risk in patient with primary non-alcoholic fatty liver disease. *High Blood Press Cardiovasc Prev* 2020;**27**:321–330. <https://doi.org/10.1007/s40292-020-00389-8>
 69. Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, Bugianesi E, et al. The EASL-Lancet Liver Commission: Protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet* 2022;**399**:61–116. [https://doi.org/10.1016/S0140-6736\(21\)01701-3](https://doi.org/10.1016/S0140-6736(21)01701-3)
 70. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al.; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med* 2024;**390**:497–509. <https://doi.org/10.1056/NEJMoa2309000>
 71. Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, et al.; 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med* 2024;**391**:311–319. <https://doi.org/10.1056/NEJMoa2401755>