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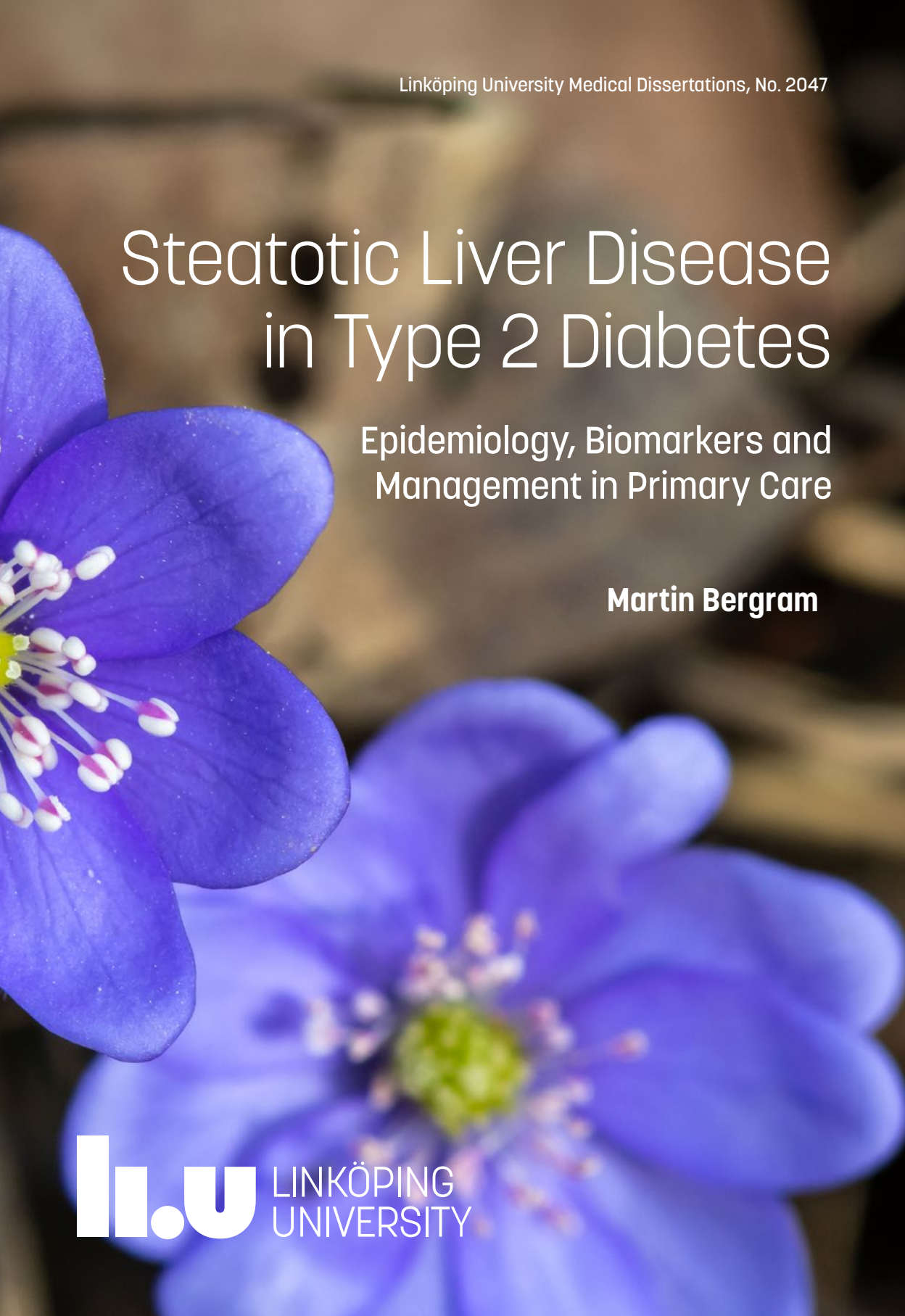
Steatotic Liver Disease in Type 2 Diabetes

Epidemiology, Biomarkers and Management in Primary Care

Martin Bergram



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Steatotic Liver Disease in Type 2 Diabetes:

Epidemiology, Biomarkers and Management in Primary Care

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"The more I garden, the less I know,

but the more pleasure I get from it."

- Monty Don

Abstract

Steatotic liver disease (SLD), which includes metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD), and alcohol-associated liver disease (ALD), affects up to 40% of the global population. Advanced fibrosis in SLD is more common in patients with type 2 diabetes (T2D) and is associated with a poorer prognosis. SLD is associated with other ectopic fat depositions and cardiac remodelling. Although MASLD is the most common chronic liver disease worldwide, evidence from Swedish primary care remains limited.

The relationship between MASLD and microvascular complications of T2D remains uncertain. Activin A has been linked to fibrogenesis, but its value as a biomarker for advanced fibrosis is unclear. Although interest in SLD screening among patients with T2D is increasing, its optimal design and cost-effectiveness remain unresolved.

This thesis examines the prevalence, clinical correlates, and management of MASLD, with or without advanced fibrosis, among patients with T2D in primary care. It also evaluates activin A as a biomarker for advanced fibrosis and assesses the cost-effectiveness of a screening and management algorithm for SLD.

Paper I was a retrospective primary care cohort study of patients with T2D, using medical record review and non-invasive algorithms to assess steatosis and advanced fibrosis risk. Papers II and IV analysed baseline data from a prospective primary care cohort in which patients with T2D underwent magnetic resonance imaging/spectroscopy and transient elastography to assess MASLD, with or without advanced fibrosis; Paper II also included medical record review of microvascular complications. Paper III used follow-up data from a cohort of participants with biopsy-proven MASLD to assess activin A levels and *PNPLA3* I148M genotype. Paper V used a lifetime microsimulation model to evaluate the costs and health outcomes of a SLD screening and management algorithm in primary care for patients with T2D.

In Paper I, 350 participants were included. Most had increased steatosis risk, 29–65% had increased risk of advanced fibrosis, and few had known steatosis. In Paper II, which included 308 participants with T2D, MASLD was not associated with a higher overall prevalence of microvascular complications. In Paper III, 41 participants were included; higher activin A levels were associated with advanced fibrosis and the *PNPLA3* I148M G/G genotype. In Paper IV, 59% of 308 participants had MASLD and 7% had suspected advanced fibrosis. MASLD was associated with obesity, ectopic fat deposition and distinct left ventricular characteristics. In Paper V, the ICER for screening and management compared with standard of care was EUR 128,072/QALY overall, ranging from EUR 5,168/QALY for ALD to EUR 157,489/QALY for MASLD.

In conclusion, MASLD is common among patients with T2D in Swedish primary care, although advanced disease appears uncommon and awareness of MASLD has historically been low. MASLD was not associated with an overall increase in microvascular complications, whereas obesity was associated with both MASLD and advanced fibrosis. Activin A showed potential as a biomarker for advanced fibrosis. The SLD screening and management algorithm were unlikely to be cost-effective overall, despite substantial variation between SLD subtypes.

Populärvetenskaplig sammanfattning

Över 3 miljarder människor världen över beräknas ha fettleversjukdom. De flesta vet inte om det, då sjukdomen oftast inte ger några symtom. För majoriteten är den inte farlig, men hos vissa kan den med tiden leda till allvarlig leversjukdom med risk för skrumplever och för tidig död. Risken är särskilt hög hos personer som dricker för mycket alkohol, men är också ökad hos personer med typ 2-diabetes.

Forskningen om fettleversjukdom har framför allt bedrivits inom specialistvården, men på senare år har sjukdomen fått ökad uppmärksamhet även inom primärvården. Samtidigt har studier från svenska vårdcentraler saknats. Eftersom patienter på vårdcentraler oftast är friskare än patienter som följs inom specialistvården är det osäkert om resultaten från specialistvården direkt kan överföras till primärvården. Fettleversjukdom vid typ 2-diabetes är kopplat till åderförkalkning, men sambandet med andra organskador vid typ 2-diabetes är ofullständigt känt. Eftersom sjukdomen är vanlig och potentiellt allvarlig har det föreslagits att vården aktivt ska leta efter fettleversjukdom hos patienter med typ 2-diabetes. Det är dock fortfarande oklart hur vården bäst ska göra detta och vad det skulle kosta.

I avhandlingen ingår fem vetenskapliga studier. I tre av studierna deltog patienter med typ 2-diabetes från vårdcentraler i Östergötland. Den första studien undersökte hur vårdcentralerna tidigare hade tagit hand om patienter med misstänkt fettleversjukdom och hur många patienter som hade ökad risk för sjukdomen Den andra studien undersökte hur vanlig fettleversjukdom var, hur många som hade tecken på allvarlig leversjukdom och hur fettet var fördelat i kroppen. För detta användes avancerade magnetkameraundersökningar. Den tredje studien undersökte om vissa organskador vid typ 2-diabetes var vanligare hos patienter som också hade fettleversjukdom. I en fjärde studie, från specialistvården, undersöktes om blodprovet activin A kan användas för att hitta patienter med allvarlig leversjukdom. Den femte studien undersökte hur en vårdmodell för att hitta och behandla fettleversjukdom på svenska vårdcentraler skulle kunna se ut. Modellen prövades sedan teoretiskt i ett datorprogram med simulerade patienter med typ 2-diabetes. Programmet användes för att beräkna vad vårdmodellen skulle kosta över tid och vilka hälsoeffekter den skulle kunna ge.

Studierna visade att kännedomen om fettleversjukdom historiskt har varit låg på vårdcentraler och att många patienter hade hög risk att ha sjukdomen. Bland patienter med typ 2-diabetes på vårdcentraler hade 60 % fettleversjukdom, men få hade sannolik allvarlig leversjukdom. Patienter som förutom typ 2-diabetes också hade fetma hade ökad risk för både fettleversjukdom och allvarlig leversjukdom. Patienter med fettleversjukdom hade också mer fett kring de inre organen. Däremot sågs ingen ökad risk för vissa organskador vid typ 2-diabetes hos patienter med fettleversjukdom. Blodprovet activin A var lovande som hjälpmedel för att hitta allvarlig leversjukdom, men mer forskning behövs. Vårdmodellen som prövades i datorprogrammet var dyr och gav små hälsoeffekter. Resultaten blev dock bättre när analysen avgränsades till patienter med typ 2-diabetes som också drack för mycket alkohol.

Sammanfattningsvis visar avhandlingen att fettleversjukdom är mycket vanlig bland patienter med typ 2-diabetes i primärvården, men att allvarlig leversjukdom är ovanlig. Resultaten talar för att vården bör rikta insatserna till de patienter som har högst risk för allvarlig leversjukdom, snarare än att hantera alla patienter på samma sätt.

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During the preparation of this thesis, Microsoft Copilot was used for language editing and proofreading to improve grammar and readability. All content was subsequently reviewed, edited, and approved by the author, who takes full responsibility for the final text.

List of papers

I. **Bergram M**, Nasr P, Iredahl F, Kechagias S, Rådholm K, Ekstedt M. Low awareness of non-alcoholic fatty liver disease in patients with type 2 diabetes in Swedish Primary Health Care. Scand J Gastroenterol. 2022 Jan;57(1):60-69. doi: 10.1080/00365521.2021.1984572. Epub 2021 Oct 7. PMID: 34618619.
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II. **Bergram M**, Kechagias S, Iredahl F, Balkhed W, Holmberg M, Dahlström N, Lundberg P, Nasr P, Ekstedt M, Rådholm K. Microvascular complications of type 2 diabetes with or without MASLD: the EPSOMIP study, a primary care cohort study. BMC Prim Care. 2025 Nov 11;26(1):354. doi: 10.1186/s12875-025-03096-2. PMID: 41219835; PMCID: PMC12604417.
Published open access under the CC BY license.

III. Jönsson C, **Bergram M**, Kechagias S, Nasr P, Ekstedt M. Activin A levels in metabolic dysfunction-associated steatotic liver disease associates with fibrosis and the *PNPLA3* I148M variant. Scand J Gastroenterol. 2024 Jun;59(6):737-741. doi: 10.1080/00365521.2024.2334804. Epub 2024 Apr 2. PMID: 38563432.
Published open access under the CC BY license.

IV. Balkhed W, **Bergram M**, Iredahl F, Holmberg M, Edin C, Carlhäll CJ, Ebbers T, Henriksson P, Simonsson C, Rådholm K, Cedersund G, Forsgren M, Leinhard OD, Jönsson C, Lundberg P, Kechagias S, Dahlström N, Nasr P, Ekstedt M. Evaluating the prevalence and severity of metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus in primary care. J Intern Med. 2025 Sep;298(3):173-187. doi: 10.1111/joim.20103. Epub 2025 Jun 16. PMID: 40518766; PMCID: PMC12374761.
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V. **Bergram M**, Klockhoff A, Rådholm K, Bendtsen M, Nasr P, Ekstedt M, Henriksson M. Cost-effectiveness of a Unified Screening and Treatment Algorithm for Steatotic Liver Disease in Patients with Type 2 Diabetes.
In manuscript.

Contributions

I. Designed and planned the project, collected data, served as a resource person for others involved in data collection, performed the statistical analyses, compiled the results, drafted the manuscript, was responsible for its revision, and handled correspondence with the journal.

II. Designed and planned the project. The study was partly based on data from the main study; I collected all additional data, performed the statistical analyses, compiled the results, drafted the manuscript, was responsible for its revision, and handled correspondence with the journal.

III. Contributed to the study design and project planning, processed previously collected data, performed statistical analyses, drafted parts of the manuscript, and contributed to manuscript revision.

IV. Contributed to project planning, was responsible for the primary care centre that included the largest number of participants, wrote supplementary ethics applications, participated in data collection, performed data quality control, and contributed to manuscript revision.

V. Designed and planned the project, collected all data for the model, constructed the screening algorithm and management strategy, was primarily responsible for the analysis and compilation of results, contributed to the model structure, drafted the manuscript, and was responsible for its revision.

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Introduction

A brief history of steatosis

As a physician working in a primary care centre, one manages many different types of diseases during a typical day. Thomas Addison was another physician with an interest in a broad spectrum of diseases. He worked in London during the first half of the nineteenth century. There, he described and made important discoveries concerning skin diseases, pernicious anaemia, appendicitis and pneumonia (1). He is best known as the first physician to describe adrenocortical insufficiency, now known as Addison's disease (1).

Thomas Addison was the first to describe fatty infiltration of the liver, or steatosis, in 1836 (2). Addison linked steatosis to alcohol and tuberculosis. As early as 1839, the first associations between steatosis and the development of liver fibrosis were made (3). In the mid-nineteenth century, researchers linked steatosis to a sedentary lifestyle and unhealthy diet (2). The association between steatosis and diabetes was first presented in 1938 (2). In the early 1980s, the terms non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) were introduced by Ludwig and Schaffner (2).

Although steatosis had been known for more than 150 years, clinical interest remained low around the turn of the millennium (3). Interest in NAFLD increased in the early 2000s, when the condition was shown to be extremely common, closely associated with the metabolic syndrome, and, in some forms, associated with increased mortality (4-6). Together with the later emergence of major interest in treatment, this has led to an exponential increase in the number of published articles over the past 20 years (3, 7).

Today, we know that steatosis is very common and can be seen in several different conditions (8). It has been estimated that 37.5% of the world's population has steatosis and that the prevalence in Europe is even higher, at 40.3% (9).

Steatotic liver disease

In 2023, the term steatotic liver disease (SLD) was introduced as an umbrella term for fat accumulation in the liver. SLD is defined by the presence of steatosis on biopsy or imaging (10, 11). As part of this nomenclature change, the terminology and diagnostic criteria for NAFLD and NASH were revised to metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). These changes were intended to better reflect the aetiology, reduce the risk of stigmatisation and address issues related to defining thresholds for alcohol consumption (11, 12). Despite the revised criteria, the new terms largely describe the same patient populations, and knowledge regarding NAFLD/NASH is considered applicable to MASLD/MASH (10, 13, 14).

For similar reasons, the official terminology for steatosis associated with excessive alcohol consumption became alcohol-associated liver disease (ALD) (the equivalent term alcohol-related liver disease is also widely used) and alcohol-associated steatohepatitis (ASH).

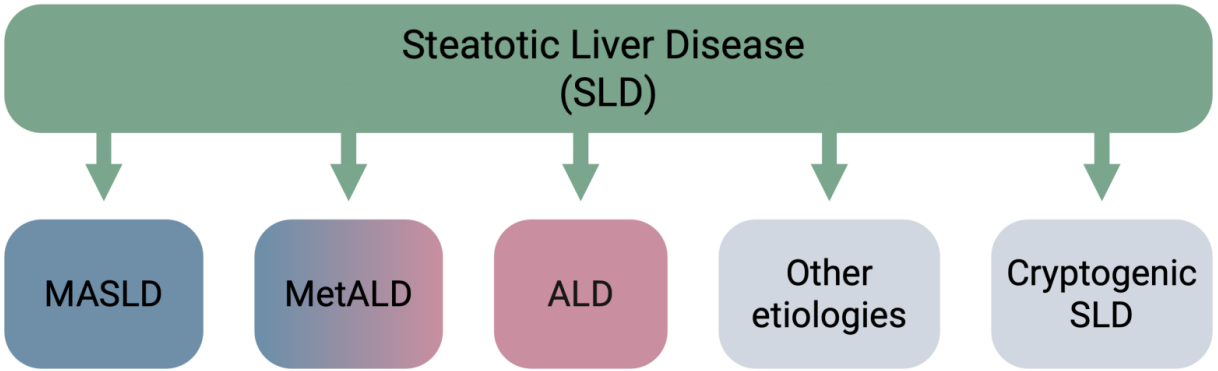
Historically, patients with both metabolic risk factors and increased alcohol intake did not fit into the previous classification. This gap in classification led to the introduction of the term metabolic dysfunction and alcohol-associated liver disease (MetALD) (Figure 1) (11).

SLD is very common in the population, and research interest in SLD has increased exponentially over time. However, only a minority of patients, particularly those with MASLD, develop severe liver disease. This has been described as the "steatotic liver disease burden paradox" (15). Why is severe liver disease so uncommon, relatively speaking, when so many people have steatosis? In view of this paradox, it has in recent years been questioned whether simple steatosis itself is a disease. Patients with simple steatosis have a very low risk of progression, usually experience no symptoms, and treatment of simple steatosis alone does not appear to affect prognosis (16). This raises the question of whether simple steatosis should instead be regarded as a risk factor for cardiometabolic dysfunction, with focus placed on what truly matters for the long-term prognosis in SLD: the presence of fibrosis and alcohol consumption (16)?

Next page (page nr 3)

Figure 1: SLD is an umbrella term that encompasses MASLD, MetALD, ALD, other less common aetiologies, and cryptogenic SLD.

Abbreviations: ALD, Alcohol-associated liver disease; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; SLD, Steatotic liver disease.


Steatotic Liver Disease
(SLD)
MASLD
MetALD
ALD
Other
etiologies
Cryptogenic
SLD

Metabolic dysfunction-associated steatotic liver disease

MASLD is the most common subtype of SLD, with an estimated global prevalence of up to 38% (17). MASLD has become increasingly prevalent over time, with a 142.7% increase between 1990 and 2023 and a further 42% increase projected by 2050 (17, 18).

In addition to the existence of steatosis, MASLD is defined by the presence of at least one of five cardiometabolic criteria and the absence of another aetiology for steatosis (11):

- Body mass index (BMI) ≥25 kg/m² or waist circumference >94 cm for men or >80 cm for women (different thresholds apply for some ethnicities)
- Fasting glucose ≥5.6 mmol/L or 2-hour post-load glucose levels ≥7.8 mmol/L or HbA1c ≥39 mmol/L, or known type 2 diabetes (T2D), or treatment for T2D
- Blood pressure ≥130/85 mmHg or specific antihypertensive drug treatment
- Plasma triglycerides ≥1.70 mmol/L or lipid-lowering treatment
- Plasma high-density lipoprotein (HDL) cholesterol ≤1.0 mmol/L for men and ≤1.3 mmol/L for women, or lipid-lowering treatment

In MASLD, hepatic triglyceride accumulation results from an imbalance between lipid acquisition and disposal. Increased intake of dietary carbohydrates, particularly mono- and disaccharides, promotes hepatic de novo lipogenesis, while obesity and insulin resistance further contribute to steatosis. Insulin resistance reduces glucose uptake in skeletal muscle and increases hepatic glucose availability, thereby promoting triglyceride synthesis in the liver. It also increases peripheral lipolysis, leading to greater delivery of free fatty acids to the liver. Together, these processes increase intrahepatic triglyceride accumulation in hepatocytes (19).

Genetic factors also contribute to steatosis by influencing hepatic triglyceride handling, including triglyceride export as very low-density lipoprotein (VLDL) and beta-oxidation. The best-established genetic risk variant is the I148M variant in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene. *PNPLA3* encodes an enzyme involved in hepatic triglyceride metabolism, and the I148M variant reduces its activity, thereby promoting triglyceride retention in hepatocytes. In addition to steatosis, this variant is associated with an increased risk of liver fibrosis and hepatocellular carcinoma (HCC) (19). The variant is common, being present in some form in approximately 45% of the global population (20).

Triglyceride accumulation in hepatocytes contributes to oxidative stress, which damages the cells. Cellular injury leads to inflammation, and macrophages in the liver acquire a pro-inflammatory profile that recruits additional immune cells from the bloodstream. Inflammatory mediators from visceral fat and altered gut microbiota, with increased production and uptake of endotoxins from the gut, also contribute to the inflammation. This condition, with the presence of steatosis and inflammation, is referred to as MASH. The *PNPLA3* I148M gene variant has also been associated with MASH (19).

Among patients with MASLD and simple steatosis, 15–40% progress to MASH (21). Patients may transition between these conditions, and 7% of patients with simple steatosis develop MASH annually, whereas 5% of patients with MASH resolve spontaneously (21). In a comparison between MASH and simple steatosis, fibrosis progresses approximately twice as fast in MASH as in simple steatosis (21, 22). In simple steatosis, 2–3% of patients develop

advanced fibrosis over a 20-year period, compared with MASH, where the corresponding figure is 25–30% (21).

Prognosis in MASLD is linked to the presence and stage of liver fibrosis (23). It is the fibrosis stage, and not the presence of steatosis or MASH, that is associated with increased mortality in MASLD (24). The 5-year risk of liver-related events (LRE) increases from 0.2% in fibrosis stage F0–F1 to 2.0% in F2 and 9.7% in F3–F4 (advanced fibrosis) (25). Compared with F0, F4 is associated with a 13-fold higher risk of LRE and an 11-fold higher risk of mortality (26). MASLD is associated with cardiovascular disease and cancer, and the most common cause of death in this patient group is cardiovascular (23, 27, 28). The risk of cardiovascular events is increased in MASLD, and the risk increases with fibrosis stage (29).

In MASLD, weight loss of ≥5% is associated with a reduction in steatosis, 7–10% improves MASH, and ≥10% may lead to regression of fibrosis (30). A Mediterranean-style diet, reduced intake of ultra-processed food, and avoidance of sugar-sweetened beverages are recommended (8). Regular physical activity is recommended, and smoking and harmful use of alcohol should be avoided (8). However, the long-term effects of these lifestyle changes are incompletely known (8).

Recently, two drugs have been approved in the USA and Europe for the treatment of MASH with significant fibrosis (≥F2). The first approved drug, resmetirom, is a thyroid hormone receptor agonist that is highly selective for the β1 subtype of the receptor, which is highly expressed in the liver. In MASH, the function of this receptor is impaired, leading to mitochondrial dysfunction and reduced β-oxidation, which is linked to increased fibrosis development (31). Resmetirom has shown effects both on resolution of MASH and on fibrosis regression (31).

The second approved drug is semaglutide, a glucagon-like peptide-1 (GLP-1) agonist with effects similar to those of endogenous incretins. Semaglutide has the same indication and comparable treatment effects as resmetirom (8, 32). The drug reduces appetite and increases satiety, resulting in substantial weight loss, which reduces steatosis and fibrosis and improves insulin resistances (8). However, neither of these two drugs is currently subsidised or has been launched for this indication on the Swedish market. At present, several drugs are under development, and additional treatments will be introduced in the coming years (33).

Alcohol-associated liver disease

Alcohol has been used and misused by humanity for thousands of years. In writings attributed to Hippocrates, the father of medicine, different types of jaundice are described, including one resembling alcohol-related cirrhosis (34). During the Industrial Revolution, alcohol could be produced cheaply and in large quantities, and during this period the link between high alcohol consumption and liver disease became clearer (35). However, the toxicity of alcohol was long questioned, and until the mid-twentieth century liver disease was often attributed to malnutrition, which commonly coexisted with harmful alcohol use. It was not until the 1960s that Lieber demonstrated that alcohol is hepatotoxic, and during the 1970s ALD was defined as we know it today (36).

ALD describes a spectrum of liver disease manifestations caused by excessive or chronic alcohol consumption (37). The spectrum ranges from simple steatosis and ASH, through fibrosis development, to cirrhosis and HCC (37). Alcohol-associated hepatitis is an acute and severe manifestation of ALD that can occur at any stage of the underlying disease (37). The definition of excessive or chronic alcohol consumption is based on daily alcohol intake and the presence of cardiometabolic criteria. In the absence of cardiometabolic criteria, excessive alcohol consumption in ALD is defined as 20 g per day for women and 30 g per day for men. In the presence of cardiometabolic criteria, the corresponding thresholds are 50 g alcohol per day for women and 60 g per day for men (10). In ALD, the proportion of patients with cardiometabolic criteria is high (10, 27).

In the liver, alcohol increases de novo lipogenesis, reduces beta-oxidation, increases uptake of free fatty acids and reduces fat export. Peripheral lipolysis is also increased, resulting in greater influx of fatty acids to the liver (38). Together, these mechanisms promote steatosis. During the breakdown of alcohol in the liver, reactive oxygen species are formed, damaging or killing hepatocytes, while chronic alcohol exposure reduces the liver's capacity for regeneration (38). Alcohol consumption also contributes to changes in the gut microbiota and increased intestinal permeability, leading to increased uptake of endotoxins. The endotoxins, together with the direct tissue damage caused by alcohol, contribute to activation of immune cells in the liver, which in turn recruit additional immune cells (38). Alcohol is toxic to peripheral adipose tissue, and pro-inflammatory substances are formed that contribute to inflammation in the liver. Inflammation together with steatosis gives rise to ASH. In ALD, the *PNPLA3* I148M gene variant has also been linked to disease progression, including an increased risks of cirrhosis and HCC (39, 40).

ALD is estimated to account for approximately 6% of the SLD population, and in the general population 0.7–2% are estimated to be affected (37, 41-43). ALD has its highest prevalence and mortality in Europe, and its prevalence is increasing globally (40). Despite its relatively low prevalence, ALD is the most common cause of cirrhosis and liver-related mortality, and is the underlying aetiology in half of all liver transplantations in both Europe and the USA (40, 44).

Among the subclasses MASLD, MetALD and ALD, ALD is associated with the highest risk of decompensation in cirrhosis (10). Advanced fibrosis in ALD is linked to increased mortality, and ASH is associated with higher mortality and greater risks of cirrhosis and HCC compared with simple steatosis (45-47). Alcohol consumption generally affects prognosis in SLD, and ALD is associated with higher mortality and a higher risk of LRE, including HCC, than MASLD (48-50). Despite the high risk of LRE and death, the most common cause of death in ALD is cancer-related (27).

In ALD, the most important treatment is substantial reduction in alcohol consumption or complete abstinence (45, 46). A multidisciplinary approach is recommended (46). There is evidence that reduced alcohol consumption or abstinence can be achieved through brief interventions as well as through pharmacological options such as acamprosate, naltrexone and baclofen (10, 46, 51). Alcohol abstinence is associated with increased survival and a reduced risk of decompensation in patients with cirrhosis (52). Although treatment for alcohol use disorder (AUD) in ALD reduces mortality, it remains underused (51, 53). GLP-1 agonists may represent a possible future treatment in ALD, as studies have shown reduced alcohol

consumption as well as lower incidence and risk of relapse in AUD during treatment with GLP-1 agonists (54, 55).

Metabolic dysfunction and alcohol-associated liver disease

Historically, MASLD and ALD have been regarded as two biologically and clinically distinct diseases (56). However, the two conditions overlap substantially. They have similar pathophysiology, share genetic and epigenetic factors, and show similar histological features (10, 54). The difference between the diseases is an arbitrarily defined threshold for alcohol consumption (15, 57). Determining on which side of this threshold a patient falls is challenging (58). There are many barriers, at the patient, health care professional and system level, to identifying and treating harmful use of alcohol (40). Health care professionals may be reluctant to ask questions about alcohol consumption or may lack the time and resources to take a proper history. Patients may provide inaccurate information about their consumption because of stigma related to alcohol use, fear of negative consequences, or recall difficulties related to cognitive impairment associated with prolonged alcohol use or advanced liver disease (58, 59).

Several studies have shown that patients with chronic liver disease underreport their alcohol consumption when self-reported intake is compared with objective tests, and a substantial proportion of patients diagnosed with MASLD later develop ALD or AUD, suggesting possible misclassification (60-62). The proportion of patients with SLD who have liver disease linked to harmful use of alcohol is likely underestimated (27, 44). This has raised concerns that previous MASLD studies may have included patients with underreported alcohol consumption, potentially affecting estimates of prognosis and disease progression (27, 62, 63).

In patients with liver disease and metabolic risk factors, alcohol use appears to have an adverse synergistic effect on prognosis, even at moderate levels (15, 54, 58, 64). It is common for patients with harmful alcohol use to have metabolic risk factors (10). To reflect the clinical reality that many patients have alcohol consumption in a grey zone, and that many individuals with harmful alcohol use also have metabolic risk factors, the term MetALD was introduced in 2023 (11).

MetALD is a subtype of SLD that is characterised by steatosis, at least one cardiometabolic criterion (the same as MASLD) and a daily alcohol consumption between 20–50 g/day for women and 30–60 g/day for men (10). Assessment of weekly consumption can be performed using questionnaires such as The Alcohol Use Disorders Identification Test –Consumption (AUDIT-C) in combination with a clinical interview (54). Previous drinking patterns and the presence of binge drinking are likely to be important for the disease course, but current diagnostic criteria only take daily/weekly consumption into account (27, 58). Given the difficulties of estimating alcohol consumption by self-report, the use of objective biomarkers of alcohol consumption, such as phosphatidylethanol (PEth), is recommended (54). However, diagnostic criteria for which levels of PEth define the different subtypes in SLD are currently lacking (65). There is considerable interest in PEth and other biomarkers of alcohol consumption, and proposals have been made regarding which thresholds should distinguish the different subtypes (66).

The proportion of patients with MetALD among SLD populations has varied in previous studies, from 1.7% to 19% (54, 67). The prevalence ranges from 1.7% to 4.5% in the general population and has been reported as 5.6% in a primary care population (54). However, when the limitations of self-reported alcohol consumption are considered and SLD classification is instead based on proposed PEth thresholds, the proportion classified as MetALD has increased three- to fourfold in previous studies approaching 20% of the SLD population (68, 69). Difficulties in defining alcohol consumption may be one reason for the varying prevalence estimates, and the validity of the diagnosis has been questioned (70).

There are limited and conflicting data regarding prognosis in MetALD (71). The risk of LRE and all-cause mortality is higher than in MASLD, and the risks of HCC and fibrosis progression appear to lie between those observed in MASLD and ALD (49, 50, 54, 72). However, findings are inconsistent, with some studies reporting lower risks of cirrhosis and mortality in MetALD than in MASLD (15, 71). MetALD is associated with cardiovascular disease and cancer, and the most common cause of death is cardiovascular (27, 43).

Pathophysiologically, MetALD combines features of MASLD and ALD (54). Studies of histological findings in MetALD are lacking (58). Genetic variants in the *PNPLA3* gene also affect prognosis in MetALD (39). At present, there are no approved drugs specifically indicated for MetALD. Given its shared features with MASLD and ALD, it is plausible that treatments effective in these conditions may also be effective in MetALD (54).

Fibrosis, cirrhosis and hepatocellular carcinoma

Liver fibrosis is a wound-healing process in response to chronic liver injury. After transient injury, the necrotic or apoptotic cells are replaced by newly formed hepatocytes. With prolonged injury, this regenerative process becomes impaired. The hepatocytes are replaced by the proteins that make up the extracellular matrix, particularly various types of collagens. In advanced liver disease, the amount of extracellular matrix may be six times higher than in a healthy liver (73).

Fibrosis extent is traditionally classified histologically on a five-point scale, from F0 to F4. F0 corresponds to no fibrosis, F1 to mild fibrosis, F2 to moderate fibrosis, F3 to severe fibrosis and F4 to cirrhosis (74). Fibrosis stage ≥F2 is defined as significant fibrosis and stage ≥F3 as advanced fibrosis (10). In MASLD, significant fibrosis is associated with higher risks of LRE and all-cause mortality, and these risks become more pronounced in advanced fibrosis (26). In MASLD, cirrhosis is estimated to develop after approximately 20 years in patients with F2 and after 5 years in those with F3 (75). Fibrosis is an important prognostic factor in MASLD; the estimated time to development of decompensated cirrhosis decreases from 33 years in F0–F1 to 12 years in F3 and 6 years in established cirrhosis (14).

The association between fibrosis stage and prognosis has been studied extensively in MASLD, but fibrosis presence and progression are associated with both LRE and mortality across the entire SLD spectrum (10, 45). However, biopsy-based studies investigating the association between fibrosis and prognosis over time in ALD and MetALD remain scarce (76). In ALD, advanced fibrosis is linked to increased mortality and an increased risk of decompensation (15,

45, 76). Significant fibrosis in ALD is associated with an increased risk of LRE compared with F0–F1 (77). In MetALD, biopsy studies are largely lacking, but several studies have linked non-invasive tests (NITs) results suggestive of advanced fibrosis to a worse prognosis (50, 71, 78).

Cirrhosis represents the end stage of fibrosis development and of most chronic liver diseases, including MASLD, MetALD and ALD (79). It is a histological diagnosis characterised by extensive remodelling of the liver architecture. Inflammation and fibrogenesis have given rise to long fibrous septa surrounding regenerative hepatocyte nodules (79). Clinically, cirrhosis is divided into compensated and decompensated phases. Compensated cirrhosis is usually asymptomatic and relatively stable, whereas prognosis worsens when decompensation develops (79). Extensive parenchymal scarring, together with vascular changes, gives rise to portal hypertension, which contributes to the development of symptomatic disease (79). Median survival is 9–12 years in compensated cirrhosis, compared with approximately 2 years in decompensated cirrhosis (79, 80). The most common aetiologies of cirrhosis globally are ALD, MASLD and chronic hepatitis B and C (79).

Cirrhosis increases the risk of HCC, and 1–4% of patients with cirrhosis develop HCC each year (79). Given this increased risk, HCC surveillance twice yearly is recommended in patients with cirrhosis (79). The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used system for HCC staging and ranges from stage 0 to stage D (79). In BCLC stages 0–A, curative treatment may be possible with liver resection, ablation or liver transplantation (81, 82).

Ectopic fat deposition, the heart and sarcopenia in SLD

Excess energy in the body is stored as lipids. Under normal conditions, this occurs mainly in subcutaneous adipose tissue (83). However, it has been proposed that individuals have a limited capacity to how much lipid can store in the subcutaneous adipose tissue, and when this limit is exceeded, lipids begin to be stored elsewhere in the body (84, 85). Some lipids are stored in the visceral adipose tissue, but fat deposition can also occur in the liver, skeletal muscle (myosteatosis), pancreas, and cardiac and pericardial tissue (83). When lipids are stored in tissue other than subcutaneous or visceral adipose tissue, this is referred to as ectopic fat deposition (84). Obesity characterised by increased visceral and ectopic fat deposition is linked to the metabolic syndrome and insulin resistance and is associated with an increased risk of T2D and cardiovascular disease (83).

The association between visceral fat, coronary artery disease, and cardiovascular risk is well established, whereas the relationship between hepatic steatosis and cardiovascular risk is more complex (86). Numerous studies have examined the association between MASLD and cardiovascular disease, but meta-analyses have reported inconsistent findings regarding cardiovascular mortality (86-88). MASLD and cardiovascular disease share many metabolic factors, and it is difficult to disentangle the independent effect of steatosis itself (86). Studies examining liver fat content in relation to cardiovascular disease risk have reported an inverse association, suggesting that patients with high visceral adiposity but low liver fat may have a higher cardiovascular risk than those with both high visceral adiposity and high liver fat (89, 90). Myosteatosis is common in MASLD, occurs across the disease spectrum, and increases

with disease severity (91). In ALD, myosteatosis has mainly been studied in cirrhosis, where its prevalence appears similar to that in MASLD and is associated with poorer prognosis (92, 93).

MASLD has also been associated with heart failure with preserved ejection fraction (HFpEF). HFpEF is associated with the metabolic syndrome, and its prevalence is increasing (94). Echocardiographic features characteristic of HFpEF is associated with MASLD, while liver fibrosis in MASLD has been linked to poorer prognosis in patients with HFpEF. Observational studies also suggest that advanced fibrosis and cirrhosis are common in this patient group (94). MASLD has also been linked to ischaemic heart disease and arrhythmias (95).

The term sarcopenia was coined in the late 1980s and has evolved over time. The 2019 European definition includes loss of muscle mass, muscle strength and function, and is associated with reduced quality of life and increased mortality (96). Sarcopenia is associated with increased mortality in cirrhosis regardless of aetiology (97). In MASLD, concomitant sarcopenia is associated with a higher prevalence of advanced fibrosis and increased mortality (98). Whether this relationship is causal remains unclear, although several potential pathophysiological mechanisms may link the two conditions (98). In ALD, sarcopenia is common, but it has mainly been studied in severe disease, where it is linked to poorer prognosis (99).

The combination of sarcopenia and myosteatosis is referred to as adverse muscle composition (AMC). Patients with MASLD and concomitant AMC have a higher prevalence of T2D and coronary artery disease (100). AMC has also been linked to increased mortality in MASLD and is common in cirrhosis, where it has been associated with worse prognosis (91, 101).

Type 2 diabetes and SLD

Hepatic and peripheral insulin resistance are central to the pathogenesis of MASLD, but they also play a role in ALD, and many pathophysiological processes in ALD overlap with mechanisms related to insulin resistance (38, 102-104).

Liver disease is more common in patients with T2D. In a Swedish study from the National Diabetes Register (NDR), patients with T2D had a two- to threefold higher risk of severe liver disease, HCC, and liver-related mortality compared with matched controls (105). In a study of the Finnish general population, T2D was associated with an increased risk of LRE (106). Across the SLD spectrum, concurrent T2D is associated with an unfavourable prognosis, with faster fibrosis progression, a higher prevalence of steatohepatitis, an increased risk of HCC and other LRE, and increased mortality (8, 107-110).

MASLD is very common among patients with T2D, with an estimated global prevalence of 65%, which has increased over the past 30 years (107). T2D is associated with more severe MASLD. Among biopsy-assessed patients with MASLD and concomitant T2D, the prevalences of MASH, significant fibrosis, and advanced fibrosis are 66%, 41% and 15%, respectively (107). In MASLD, T2D is associated with faster development of decompensated cirrhosis, and the risk of decompensation increases with higher HbA1c (14). T2D is also associated with HCC;

patients with MASLD and T2D have a fivefold higher risk of developing HCC compared with patients with MASLD without T2D (14). In general, fibrosis progression is generally faster in MASLD when T2D is present (111).

The effect of metabolic risk factors on outcomes in ALD and MetALD has been studied to a much lesser extent (54). However, studies suggest that insulin resistance is the strongest predictor of liver fibrosis and ASH in ALD (112). In ALD, T2D is linked to liver-related mortality and the development of cirrhosis (103, 113). In a cohort of patients seeking care for AUD, T2D was associated with increased incidence of ALD and higher mortality (109). In MetALD, T2D is linked to an increased risk of significant fibrosis, advanced fibrosis, and cirrhosis (71, 108).

Approximately 60% of patients with MASLD have T2D or prediabetes (23). Patients with MASLD have at least twice the risk of developing T2D compared with patients without MASLD (8). T2D occurs in approximately 20% of patients with ALD (103, 114). In MetALD, the proportion with T2D is likely to fall between that seen in MASLD and ALD, although findings in the literature are conflicting (43, 71).

The association between MASLD and complications of T2D is incompletely understood. The risk of macrovascular complications and diabetic nephropathy is higher among patients with concomitant MASLD, whereas evidence for other microvascular complications is more uncertain (115, 116). In studies of the association between MASLD and retinopathy or neuropathy, risks have been reported as higher, lower, or unchanged (117-121). The association between diabetic foot ulcers and MASLD has been little studied, but available data suggest an increased risk (122, 123).

Non-invasive tests in SLD

Liver biopsy has long been the gold standard for diagnosing and staging liver disease, and much of our knowledge of prognosis in SLD comes from liver biopsy cohorts (14). However, the method has important limitations. Because a biopsy samples only a small part of the liver, and fibrosis may be heterogeneously distributed, its representativeness may be limited. In addition, interpretation is subject to interobserver variability among pathologists. Together with its invasive nature and risk of complications, these limitations have led to the role of liver biopsy as the gold standard being questioned in recent year (14, 124). Accordingly, increasing attention has shifted towards NITs. This paradigm shift is partly explained by evidence that NITs predict prognosis in SLD as well as, or better than, liver biopsy (14, 77, 78, 125).

NITs are non-biopsy-based tests mainly used to estimate the presence and severity of liver fibrosis (126). They can be divided into two main groups: serum-based tests, which often combine routine blood tests with anthropometric measurements and clinical history, and imaging-based tests (72). Serum-based tests can be further divided into simple point-of-care tests, such as FIB-4, which use inexpensive and well-established routine blood tests, and specialised tests that use patented, specifically developed markers, such as the Enhanced Liver Fibrosis (ELF) test (126). Imaging-based tests rely on diagnostic imaging techniques, but assessment is based on derived quantitative measures rather than visual image interpretation.

Fibrosis assessment instead relies on different types of elastography, such as vibration-controlled transient elastography (VCTE), in which ultrasound (US) or magnetic resonance (MR)-based data are used to measure liver stiffness (127). At present, numerous NITs are available for assessing steatosis and liver fibrosis, and NITs for diagnosing MASH are also under development (128, 129).

Fatty Liver Index

Several NITs, in the form of algorithms, are available for assessing the presence of steatosis (130-133). In general, these algorithms are used in screening studies and not clinically (134). They can detect steatosis with acceptable accuracy but cannot quantify hepatic fat content (135). The Fatty Liver Index (FLI) was one of the first and remains one of the most widely used algorithms (130, 135). FLI was developed in an Italian general population study. Participants with suspected liver disease, defined by elevated liver tests, underwent US to assess steatosis, and several blood tests and anthropometric data were collected. Using logistic regression, an algorithm was developed to predict US-detected steatosis using selected blood tests and anthropometric data. The algorithm includes BMI, waist circumference, triglycerides and gamma-glutamyl transferase (GGT), and uses lower and upper thresholds to classify patients as having low or high risk of steatosis. Since its introduction in 2006, FLI has been validated in several other populations, and the area under the receiver operating characteristic curve (AUROC) for detecting steatosis compared with liver biopsy is 0.83 (134). The algorithm has also been validated against magnetic resonance imaging proton density fat fraction (MRI-PDFF) (136).

FIB-4

Several algorithms are available for assessing the risk of liver fibrosis. The most widely used algorithm, and the one recommended in several guidelines, is FIB-4 (8, 137). FIB-4 was originally developed to assess significant fibrosis in patients with hepatitis C and human immunodeficiency virus coinfection (138). The algorithm was later validated against liver biopsy for detecting advanced fibrosis in a MASLD cohort and has since been used both in research and in clinical practice (10, 139). FIB-4 uses two thresholds to identify patients at low or high risk of advanced fibrosis, whereas further testing is recommended for patients who are not classified as low risk (10). FIB-4 includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count and age. Because age is included in the algorithm, and because the original study included patients aged 35–65 years, age-adjusted thresholds have been introduced (140). When the same threshold is applied to patients below and above 65 years of age, FIB-4 has low specificity in patients older than 65 years (141). FIB-4 should also be avoided in patients younger than 35 years, because its performance in this age group is poor (140).

Longitudinal changes in FIB-4 are clinically important in patients with known liver disease. FIB-4 increases with fibrosis stage, and rising FIB-4 values correlate with the development of cirrhosis and HCC in MASLD (128). Similar findings have been reported in the general population, where increasing or persistently high FIB-4 values over time are linked to LRE (142). However, the suitability of FIB-4 as a screening test has been questioned because it was originally developed in a high-risk specialist-care population (143).

In ALD, FIB-4 performs considerably worse than in MASLD, with a high false-positive rate, probably related to the direct effects of alcohol on AST levels and platelet count (57). Nevertheless, it is still recommended as a first-line test in ALD to exclude advanced fibrosis, followed by VCTE or the ELF-test when indicated (144, 145). For MetALD, the evidence base remains limited. However, FIB-4 performance appears similar to that in MASLD, and intermediate or high FIB-4 risk categories have been associated with decompensated cirrhosis and death in patients with MetALD (78).

Activin A

Several NITs are currently used clinically for fibrosis assessment and prognostication in SLD (10). In addition, research in the field is extensive, and many new NITs have been investigated in recent years (146, 147). One potential novel biomarker in SLD is the cytokine activin A. Activin A has been linked to inflammation and immune cell function, skin biology, fibrosis development in several organs, reproductive biology, stem cells, wound healing, sarcopenia, fasting and insulin resistance, among other processes (148-150). In addition to its association with MASLD, activin A has also been associated with HCC, cirrhosis in ALD and liver failure (148). During the development of liver fibrosis in MASLD and ALD, activin A probably contributes through activation of Kupffer cells, which in turn promote fibrogenesis via hepatic stellate cells (151, 152).

Studies have shown associations between elevated activin A levels and MASLD and MASH, and expression of genes related to activin A has been linked to the conditions (149, 153-155). In MASLD, activin A levels are higher in patients with advanced fibrosis than in those with lower fibrosis stages (152). In mouse models of chronic liver disease, inhibition of the activin A receptor has been shown to increase liver regeneration and interrupt fibrosis progression (156). However, findings from mouse models are conflicting, as overexpression of activin A has also been reported to improve disease (157). At present, the association between activin A and SLD remains incompletely understood, and whether activin A has clinical utility as a NIT remains uncertain.

Vibration-controlled transient elastography

In the early 2000s, several methods were developed to assess tissue elasticity, referred to in the liver as liver stiffness measurement (LSM). The first method to be used in chronic liver disease was VCTE (158). Initially, chronic hepatitis C was the main focus, but in 2007 the first study using VCTE to assess fibrosis stage in MASLD was published, followed by the first study in ALD in 2008 (158, 159). Shortly after the term MetALD was introduced, VCTE was also shown to be useful in this patient group (160).

VCTE was originally developed within the food industry to assess cheese maturation and is based on US technology (161). In this technique, a shear wave is induced through a probe and travels through the liver tissue, and its propagation is assessed by US. The stiffer the liver, the faster the shear wave travels through the tissue, and liver stiffness is expressed in kilopascals (kPa) (158). The patient is examined in the supine position; the examination takes approximately 5 minutes and causes no major discomfort. With VCTE, an area approximately 100 times larger than that assessed by liver biopsy is examined, providing a more representative assessment of the liver parenchyma (158). However, VCTE is not a perfect

technique, and in patients with obesity, or when the examination is performed by an inexperienced operator, the risk of false-positive results increases (162). Particularly in populations with a low prevalence of severe liver disease, such as primary care populations, agreement between repeated VCTE examinations can be low (163).

Elastography, including VCTE, is recommended in guidelines both to exclude and to predict advanced fibrosis in MASLD (8). VCTE performs at least as well as biopsy in predicting mortality and LRE in MASLD at thresholds of <10 kPa, 10–20 kPa and >20 kPa, corresponding approximately to F0–F2, F3 and F4, respectively (164). The introduction of pharmacological treatment for MASH with significant fibrosis has increased the need to identify patients with significant fibrosis using VCTE (31, 32). VCTE values of 8–15 kPa have been suggested to correspond to MASH with significant fibrosis and to represent an indication for treatment in MASLD (165).

In ALD, VCTE has good ability to exclude or confirm advanced fibrosis (166). LSM has strong prognostic value in ALD: compared with LSM <10 kPa, values of 10–15 kPa and >15 kPa are associated with 8- and 28-fold higher risks of LRE over time, respectively (77). In the study, VCTE predicted prognosis better than biopsy in ALD (77). Similar performance has been reported in other studies, in which increasing VCTE values over time have been linked to poorer prognosis (167). For MetALD, meta-analyses of VCTE performance are currently lacking, but individual studies suggest satisfactory results, and elevated LSM values are linked to increased risks of death and decompensated cirrhosis (78, 160).

Assessment of steatosis, the heart and body composition

Ultrasound

US has long been the standard method for detecting steatosis in clinical practice (168). The method can also detect other liver conditions, such as tumours and biliary tract abnormalities. It is non-invasive, inexpensive, well established, widely available, and well accepted by patients (168, 169). However, US has several clinical limitations. It reliably detects only moderate to severe steatosis, and mild steatosis is often missed, examination may be technically difficult in patients with severe obesity, the method is subjective and operator-dependent, and it cannot accurately quantify hepatic fat content (169-171). US assesses steatosis but does not provide fibrosis staging, although established cirrhosis may be detected during the examination (172).

Controlled attenuation parameter

In connection with VCTE, the controlled attenuation parameter (CAP) can also be measured (173). CAP measures the attenuation of the US signal as it passes through liver tissue. The greater the amount of fat present, the more the signal is attenuated, and the examination generates a numerical value expressed in dB/m (174). Advantages of CAP include that it can be performed simultaneously with conventional VCTE, has no adverse effects, is easy to perform, provides objective measurements with high reliability, examines a larger area than liver biopsy and, although the equipment is expensive to purchase, the examination itself is inexpensive (169, 170, 173, 175). Disadvantages include difficulties obtaining reliable

measurements in severe obesity, the inability to provide an exact quantification of hepatic fat content, and uncertainty regarding which thresholds should be used to define steatosis and its different grades (170, 176).

Magnetic resonance background

Multiple MR techniques are used in the assessment of SLD. The body consists mainly of water and fat, molecules that contain large numbers of hydrogen atoms. The nucleus of the hydrogen atom consists of a positively charged proton. This proton rotates around its axis, acts like a small compass needle, and can be influenced by magnetic fields (177). Under normal circumstances, the surrounding magnetic field is too weak for all the protons in the body to align in the same direction. In MR techniques, this property is used to align protons with the direction of a strong magnetic field, such as that generated by an MR scanner (177). In this strong magnetic field, the protons behave like tilted spinning tops: their axis of rotation all rotates around the direction of the magnetic field, a phenomenon known as precession. The speed of precession depends on the strength of the magnetic field, measured in tesla, and increases as field strength increases.

By transmitting a radiofrequency pulse adapted to the precession frequency of the protons, the protons absorb energy, are displaced from their alignment with the magnetic field, and begin to rotate in synchrony at another angle to the field (177). Often, the proton axis is displaced by 90 degrees from the direction of the magnetic field, although this varies between methods and is referred to as the flip angle. When the pulse ceases, the protons return towards alignment with the magnetic field. As they do so, they emit the absorbed energy in the form of radio waves. This signal is then captured by antennas in the MR scanner.

Different tissues contain protons in different molecular environments. In water molecules, oxygen attracts the electron of the hydrogen atom, making the proton more exposed to the surrounding magnetic field than in fat molecules, where carbon atoms have less tendency to attract electrons. These differences influence how long it takes for protons to return towards alignment with the magnetic field and are used in MR techniques to distinguish between tissues. Two time-related aspects are mainly used, referred to as T1 and T2 relaxation (177). T1 relaxation describes the time it takes for protons to return towards alignment with the magnetic field, whereas T2 relaxation describes how quickly their synchronised rotation decays, resulting in decreasing signal strength.

To localise where in the magnetic field the different radio signals originate, gradient coils are used in the MR scanner (177). These smaller magnetic coils rapidly switch on and off, altering the magnetic field and making it possible to determine the origin of the signals. By combining information about the signal from the tissue with information about where the signal originates, MRI data can be used to create a greyscale image of the examined area.

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS) uses the same underlying principles as MRI, but instead of producing images, it analyses the chemical content within a specific measurement volume, referred to as a voxel. When examining the liver, this voxel is placed in the liver parenchyma, avoiding large blood vessels and bile ducts. Using specific radiofrequency pulse sequences, such as Stimulated Echo Acquisition Mode (STEAM), in

combination with magnetic gradients generated by smaller coils, a signal reflecting the chemical content within this voxel can be obtained (178). By making use of the fact that protons are shielded differently from the magnetic field in different molecular environments, the signal can be divided into frequency components corresponding to different substances, such as water or triglycerides. This phenomenon is referred to as chemical shift (178). To interpret these frequency components, they are processed using mathematical algorithms, such as AMARES, and presented graphically as curves. By calculating the area under each curve, a measure is obtained of the number of protons in the voxel that are bound to water or fat.

Whereas MRI uses T1 and T2 relaxation to distinguish between tissues, in ^{1}H-MRS these effects need to be corrected for (178). Because protons in fat and water take different amounts of time to return towards alignment with the magnetic field, a sufficiently long interval is needed between repeated measurements to allow all protons to recover. This interval is expressed as the repetition time (TR) (178). Signal strength is also affected by when the emitted radio signals are measured, and this differs between water and fat. By acquiring repeated measurements, it is possible to extrapolate the signal to the time when the radiofrequency pulse was emitted, allowing this difference between water and fat to be corrected for (178). This is expressed as the echo time (TE). In fat molecules, hydrogen and carbon atoms are very close together, meaning that the protons affect each other through chemical bonds and produce complex attenuation of the echo. These are known as J-coupling effects, which need to be corrected for when measuring fat. By keeping the time between the final pulses in the STEAM sequence short, known as the mixing time (TM), there is insufficient time for J-coupling effects to influence the echo to any substantial extent (178).

Once these factors have been accounted for, measures of the proportions of fat and water in the voxel can be obtained, and PDFF can be calculated and expressed as a percentage (178). PDFF is calculated as the proportion of protons bound to fat relative to the total number of protons bound to water and fat in the examined voxel.

PDFF can also be calculated using MRI, but ^{1}H-MRS-PDFF is more sensitive to small amounts of fat and is considered the gold standard for quantifying hepatic triglyceride content (8, 176). Because ^{1}H-MRS-PDFF is expensive, requires specially trained personnel, specialised equipment and considerable time, and measures only a limited area of the liver, it is not commonly used in clinical practice and is mainly used in research (176).

Cardiac magnetic resonance imaging

The human heart normally beats 50-100 times per minute. Capturing this with MRI is therefore a challenge. In cardiac MRI, this is addressed by acquiring multiple images over several heartbeats and synchronising them with the cardiac cycle using electrocardiographic gating (179). By acquiring many images in succession, a cine sequence can be reconstructed, providing a moving image of the beating heart. Using radiofrequency pulse sequences such as balanced steady-state free precession (bSSFP), high contrast between the myocardium and flowing blood can be achieved despite rapid image acquisition (179). By keeping TR very short, using a flip angle lower than 90 degrees and a short time to echo registration, these rapid images can be acquired (179). By using post-processing algorithms to reconstruct missing image data, the amount of acquired image data can be reduced, further shortening acquisition time (179, 180). After image reconstruction and processing, cardiac MRI data can be analysed

using software such as Segment (Medviso AB, Lund, Sweden) to obtain automated cardiac measurements (181).

Body composition magnetic resonance imaging

Body composition MRI is used to assess tissue composition, particularly the distribution of adipose tissue. In contrast to ^{1}H-MRS, which measures fat content within only a small region of interest, body composition MRI provides a whole-body assessment of fat distribution. The examination is performed using the Dixon method, which, like ^{1}H-MRS, makes use of chemical shift (178). Because fat and water signals differ, images can be acquired at two different echo times, generating data that can be reconstructed into separate water and fat images. In Dixon methods acquiring more than two echoes, referred to as multi-echo Dixon, MRI-PDFF can also be calculated, for example in the liver (178). Body composition MRI images can then be automatically processed and analysed using software such as AMRA Researcher (AMRA Medical AB, Linköping, Sweden) to quantify measures such as fat-free muscle volume (FFMV) and visceral adipose tissue (VAT) volume (182).

Screening for SLD

Wilson and Jungner's ten criteria for screening were published in a World Health Organization report in 1968 (183). Although these criteria were published almost 60 years ago, they are still used, despite not fully reflecting the complexity of contemporary health care (184). Johansen et al. have discussed screening for SLD in relation to Wilson and Jungner's criteria, supplemented by newer criteria that better address contemporary screening challenges (72). They conclude that screening for SLD is promising, as it may enable early intervention. They further suggest that a holistic approach could reduce the risk of severe liver disease and provide broader health benefits. However, they also acknowledge that the long-term effects of screening remain unclear, as randomised studies with long-term follow-up are lacking. Screening will probably need to be adapted to local conditions and existing health care structures in different countries and health care systems (72).

Studies of screening

Several studies have examined screening for SLD, mainly focusing on MASLD and ALD (72). Most studies have focused on MASLD in patients with T2D, and assessment using FIB-4 or VCTE has been the most used approach, although routine liver tests, non-FIB-4 algorithms, MRI, MR elastography (MRE), liver biopsy, and US have also been used (163, 185-189). These studies have reported promising results, but study designs are heterogeneous, and a key limitation is the lack of a uniform definition of advanced disease (185). In a recent Swedish study, VCTE was offered alongside routine retinal photography in patients with T2D (163). The examination was accepted by a large proportion of participants, suggesting that this may be a feasible strategy for MASLD screening, although a high proportion of false-positive results was noted (163). Similar VCTE-based screening for SLD has also been conducted in the general population in Denmark (190).

Results have recently been reported from the LiverScreen study, in which 30,000 individuals from the general population in nine European countries underwent VCTE-based screening for liver fibrosis in SLD (191). After hepatological assessment, approximately 1.6% of the population were found to have previously undetected chronic liver disease with fibrosis. MASLD was by far the most common aetiology (73%), although MetALD (15%) and ALD (5%) also contributed. Participants with T2D, obesity, and harmful alcohol use had significantly higher odds of liver fibrosis than participants without these risk factors (191). A high proportion of VCTE false-positive results was also noted in this study (191). Several studies of similar or larger size are currently underway (192, 193).

Cost-effectiveness studies of SLD screening, including studies that also incorporate subsequent treatment, have been conducted. Studies of screening cost-effectiveness have reported varying results (194-201). When treatment has been included, some studies have suggested cost-effectiveness in specific scenarios, but these analyses are assumption-based and context-dependent, and the results should therefore be interpreted with caution (200, 202-204).

Current screening practice

In 2016, European guidelines were published that recommended that patients with T2D be screened for MASLD with advanced fibrosis, and this recommendation has remained in place since then (135, 205). Despite this recommendation, no systematic screening programme for advanced fibrosis in T2D is well-established in clinical practice, either internationally or in Sweden, a gap that has been linked to high costs and limited preparedness within health care organisations (206-209). In Sweden, the Swedish Society of Gastroenterology recommends that patients with obesity and T2D be screened with FIB-4 for advanced fibrosis, but no corresponding recommendation is included in the Swedish national guidelines for T2D care (168, 210). A review of regional primary care guidelines for T2D from Region Skåne, Region Östergötland, and Region Stockholm found no clear recommendation for systematic MASLD screening (211-213). Internationally, regular screening with FIB-4 for MASLD with fibrosis is recommended in American T2D guidelines (214). However, studies indicate that this recommendation has not been fully implemented in clinical practice (215).

SLD in primary care

SLD includes diseases that have historically been managed in specialist care. However, these diseases are very common, and MASLD is often encountered in primary care. In Chapter 13 of the Swedish Health and Medical Services Act, the basic assignment of primary care is described as follows (216):

- *"provide the health and medical care services required to meet commonly occurring physical and mental health care needs"*
- *"provide preventive interventions based on both the needs of the population and the individual needs and circumstances of the patient"*
- *"provide rehabilitative interventions based on the patient's individual needs and circumstances"*

- *"coordinate different interventions for the patient in cases where it is most appropriate for the coordination to take place within primary care"*

Management and potential screening of SLD align well with these responsibilities. It has also been proposed that simple steatosis should be regarded as a risk factor for liver and cardiovascular disease rather than a disease in itself (16). Primary care has extensive experience of managing other risk factors, such as hypertension and hypercholesterolaemia. Against this background, it is difficult to argue that SLD, particularly MASLD, should not be managed in primary care, given its high prevalence (17, 209).

Prevalence in primary care

In a meta-analysis of MASLD prevalence in T2D, the prevalence was 60% in a subgroup analysis of general population studies (217). In the overall meta-analysis, 36% of participants had significant fibrosis and 15% had advanced fibrosis, but no subgroup analyses were performed for general population or primary care settings. The authors noted substantial heterogeneity between studies, and many studies were conducted in specialist care settings, raising the possibility of selection bias. A VCTE- and CAP-based study of the US general population reported prevalences of 32.4% for MASLD, 2.2% for MetALD, and 1.3% for ALD (218). Among individuals with SLD, the proportions with LSM >8 kPa, >12 kPa, and >15 kPa were 17–27%, 5–20%, and 4–13%, respectively, depending on SLD subtype.

Awareness in primary care

Although SLD is commonly observed in general population studies, the proportion of individuals with a recorded diagnosis is low, suggesting substantial underdiagnosis (219). In a Swedish national registry study, the recorded prevalence of MASLD and ALD in 2019 was 0.02% and 0.05%, respectively (220). However, primary care was not included in the study. In a large European primary care registry study, the prevalence of a recorded MASLD diagnosis was 1.9% in 2014 (221). Despite the high expected global prevalence of MASLD, only 6% of affected individuals are reported to be diagnosed (222).

Difficulties in managing MASLD with concomitant T2D among primary care healthcare professionals in Australia have been investigated qualitatively (223). The study found that other health problems were often prioritised over MASLD, partly because the risk of complications was perceived to be low, healthcare professionals were concerned about overwhelming patients with information, consultations were constrained by time, and tests for advanced fibrosis were perceived as unavailable. A similar study conducted in the UK reported comparable findings (224). In a European study, awareness of MASLD guidelines and clearly established liver care pathways was investigated both quantitatively and qualitatively among physicians, approximately 25% of whom worked in primary care (225). One third of respondents were unaware of the guidelines. Among American general practitioners, awareness of the importance of fibrosis in MASLD was high, but few were aware of or used FIB-4 (226). Similar findings have also been reported from primary care in the Netherlands and Australia (227, 228).

At present, barriers exist at multiple levels, including among patients, within primary care and among policymakers, limiting the effective management of liver disease in primary care (209). In MASLD, underdiagnosis appears to be substantial, and awareness in primary care remains

limited. However, this may be changing. The incidence of recorded MASLD and ALD diagnoses is increasing over time in Sweden (220). This may reflect increased morbidity but may also be related to increased awareness within health care. In recent years, the role of primary care in MASLD has also been more clearly defined (209, 229, 230). The increasing attention given to MASLD in recent years, not least because of emerging pharmacological treatment options, has prompted discussion of a potential paradigm shift in the field (209, 219).

Limitations of evidence from specialist care

Most evidence on SLD comes from specialist care settings, which may limit its generalisability to primary care. For example, data on advanced fibrosis in patients with T2D are available only to a limited extent from primary care (231). Similarly, much of current understanding of the natural history of MASLD is based on biopsy cohorts, which largely consist of patients managed in specialist care (14). These patients are likely to have more advanced liver disease and may therefore not be representative of the broader MASLD population. If prevalence estimates of advanced fibrosis in T2D from specialist care studies were generalisable to the broader primary care population, a large proportion of patients would be expected to develop cirrhosis over time. However, this pattern is not reflected in clinical practice, which is supported by NDR data on the occurrence of cirrhosis in patients with T2D in Sweden (231). A further limitation is that most NITs have been developed in specialist care settings, and their performance in primary care populations remains uncertain (14).

Health economics and modelling

Health care, like society more broadly, is constrained by available resources. Budgets are limited, and as new treatment methods are introduced, priorities need to be set. According to a decision by the Swedish Parliament, prioritisation in health care should be based on three principles, one of which is the cost-effectiveness principle (232). Cost-effectiveness is therefore central to the allocation of limited resources, and health economic studies provide a tool for assessing cost-effectiveness.

To draw conclusions about cost-effectiveness, data on health-related outcomes and costs must be collected. Health care includes many different patient groups and interventions, which are difficult to compare directly. Health-related outcome measures, such as quality-adjusted life years (QALYs), have therefore been developed. A QALY is a measure that combines survival with health-related quality of life (233). One QALY corresponds to one year lived in full health-related quality of life. To calculate QALYs, a measure of health-related quality of life in the form of a QALY weight is needed. These weights can be estimated in different ways (234). Direct estimates use methods based on hypothetical scenarios, although these can be abstract and difficult for study participants to assess. More commonly, indirect methods are used, in which quality of life is estimated using questionnaires such as EQ-5D or SF-36. The questions in these instruments describe different aspects of health-related quality of life, and each participant's responses generate a specific health-state profile. This profile can then be translated into a corresponding QALY weight using a tariff (234). The tariffs have been created through population studies in which individuals have compared quality-of-life questionnaires with a direct estimation method.

In addition to health-related outcomes, costs need to be estimated in a health economic analysis. The analytical perspective determines which costs are included. From a health care perspective, costs typically include direct medical costs, such as diagnostics, visits, hospital care and treatment, all of which directly affect the health care budget. From a societal perspective, the analysis may also include indirect costs, most commonly productivity losses due to morbidity or premature mortality (234).

Once effects and costs have been estimated, the health economic analysis can be performed. In a cost-effectiveness analysis, an incremental cost-effectiveness ratio (ICER) is usually presented to compare different alternatives (235). For example, drug treatment A can be compared with drug treatment B. The costs and health effects associated with the two treatments over time are compared. With the incremental cost and health effects can the ICER be calculated and expressed as cost per QALY gained.

How, then, should one assess whether an intervention is cost-effective? If a new treatment is both cheaper and more effective, the assessment is straightforward, the new treatment is cost-effective. A new treatment that is both more expensive and less effective is also easy to evaluate, it is not cost-effective. The assessment becomes more complex when a treatment is more effective but also more expensive, or slightly less effective but substantially cheaper. These different combinations can be visualised using the cost-effectiveness plane (234). This is a coordinate system with incremental effect on the x-axis and incremental cost on the y-axis. The axes divide the plane into four quadrants, named after the points of the compass. Treatments that are cheaper and more effective fall in the south-eastern quadrant, those that are more expensive and less effective in the north-western quadrant, those that are more expensive but more effective in the north-eastern quadrant, and those that are cheaper but less effective in the south-western quadrant.

To assess whether treatments in the north-eastern and south-western quadrants are cost-effective, a threshold value can be used. This threshold reflects what society, or the health care system, is willing to pay to gain one QALY. In some countries, such as the United Kingdom, the threshold value is officially specified, whereas in Sweden there is no entirely official value, although established practice exists. In Sweden, the practice used by the Dental and Pharmaceutical Benefits Agency (TLV) when assessing reimbursement of new drugs is often applied. The threshold value ranges from SEK 500,000 to SEK 1,000,000 per QALY, depending on disease severity, compassionate considerations or rarity (236). In the cost-effectiveness plane, the threshold value can be drawn as a straight line, illustrating whether an ICER in the north-eastern or south-western quadrant lies within the range considered cost-effective. The threshold value can also be used to calculate net health benefit (NHB), another way of expressing costs and health effects that takes the opportunity cost of money into account (235). A positive NHB means that the intervention provides a net health gain for the health care system, whereas a negative NHB means that the cost of the intervention displaces other, more cost-effective care.

For an ICER to be useful, the relevant time horizon must be considered (234). Sometimes the outcomes of interest occur far in the future and cannot feasibly be evaluated in a clinical study. In such cases, modelling studies may be an alternative. Different types of models are used for different purposes. When modelling long-term processes in chronic, slowly progressive diseases such as SLD, Markov models are commonly used. In a Markov model, a cohort is

modelled over time (233). The model includes relevant health states for disease and death. Individuals in the cohort start in one state, and in each model cycle, usually one year, they have a certain probability of remaining in that state or moving to another state. Each state is associated with a cost and a QALY weight. The cohort is followed for a specified period or until all individuals have died, providing an estimate of the costs and health effects associated with the intervention and the comparator.

A Markov model has no memory, and in each cycle each individual can only be in one state. If information is needed about which states an individual has previously occupied, additional states must be created to reflect this. For conditions that require more complex modelling, a Markov model can become difficult to manage. This can instead be addressed using microsimulation, in which each individual is simulated separately. The model retains information about where the individual has been in previous cycles, and individual characteristics can affect the probability of moving between states. The disadvantage is that the model becomes computationally intensive and requires substantial computing power. Another challenge is that detailed individual-level data are needed to obtain the full benefit of the simulation. If such data are lacking, theoretical assumptions may be required, which can reduce credibility. In addition, coding a microsimulation is complex, making external review challenging, and coding errors may have far-reaching effects that are difficult to detect (237).

Models are always based, to a greater or lesser extent, on assumptions that may vary in accuracy. To account for this uncertainty, sensitivity analyses are performed. In a one-way sensitivity analysis, one variable is changed and the effect on the result is examined. To take a more comprehensive approach to model uncertainty, a probabilistic sensitivity analysis (PSA) can be performed (233). In a PSA, probability distributions are assigned to each variable, with different types of distributions used depending on the variable type (233). Values are then repeatedly drawn from these distributions, generating a corresponding number of ICERs. These ICERs can, for example, be plotted in the cost-effectiveness plane, providing a visualisation of the spread of results and the probability that the intervention is cost-effective.

Aim

The overall aim of this doctoral project is to investigate, in primary care, the prevalence and management of MASLD among patients with concurrent T2D, and to examine how the prevalence of diabetes complications varies according to the presence of MASLD. The project also aims to evaluate novel biomarkers for liver fibrosis and to assess whether a screening and management algorithm for SLD among patients with T2D in primary care is cost-effective.

Research questions in Papers I-V

I.

- How many patients with T2D in Swedish primary care have known MASLD?
- What is the likely prevalence of MASLD, with or without advanced fibrosis, in this patient group?
- How are patients with MASLD and concurrent T2D managed within Swedish primary care?

II.

- Are there differences in the prevalence of microvascular diabetes complications and diabetic foot ulcers between patients with T2D and concurrent MASLD and those with only T2D?
- Are there differences in the prevalence of microvascular diabetes complications and diabetic foot ulcers in patients with T2D between those with MASLD and concurrent advanced fibrosis and those without advanced fibrosis?

III.

- Are plasma activin A levels different in patients with biopsy-proven MASLD with advanced fibrosis compared with patients without advanced fibrosis?
- Are plasma activin A levels different among patients homozygous for the *PNPLA3* I148M variant compared with patients who are heterozygous or wild type?

IV.

- How common is MASLD among patients with T2D within Swedish primary care?
- How common is advanced fibrosis in MASLD within the patient group?
- What distinguishes patients with T2D and concurrent MASLD with advanced fibrosis from those without advanced fibrosis?
- How do MR-based biomarkers differ between patients with and without MASLD, and how are they associated with advanced fibrosis?

V.

- How could a unified SLD screening and management strategy for Swedish primary care patients with T2D be designed?

- What would the introduction of a unified SLD screening and management strategy, compared with standard of care, entail in terms of lifetime costs and health benefits within primary and specialised care?
- Is it cost-effective to introduce a unified SLD screening and management strategy for patients with T2D within Swedish primary care?

Methods

Study designs and populations, Papers I-V

Table 1 provides an overview of the study designs and populations included in Papers I-V.

Paper I: retrospective cohort study

The study population in Paper I consisted of 350 randomly selected participants with T2D listed at five primary care centres in Östergötland during 2018–2019. All patients with a T2D diagnosis (ICD-10 E11.0–E11.9) recorded in the electronic medical record and listed at one of the participating primary care centres were eligible for random selection. The inclusion criteria were a diagnosis of T2D and age ≥18 years at inclusion. The exclusion criteria were acute or chronic liver disease other than NAFLD and harmful alcohol use, defined as any of the following: AUDIT-C score ≥4 for men or ≥3 for women, PEth >0.30 μmol/L, carbohydrate-deficient transferrin (CDT) ≥2.5%, and/or medical record information suggestive of AUD.

Papers II and IV: prospective cohort study with cross-sectional data from inclusion

The study population in Papers II and IV consisted of participants from the Evaluating Prevalence and Severity of MASLD in Primary care (EPSOMIP) study (238). A total of 308 participants were included during 2019–2023 during annual T2D follow-up at seven primary care centres in Östergötland. Participants could also be invited by randomly distributed invitation letters sent to patients on waiting lists for annual T2D follow-up. Eligible participants were required to have a T2D diagnosis according to current guidelines and to be aged 35–75 years. The exclusion criteria were contraindications to MRI (pacemaker, iron-containing implants, claustrophobia, extreme obesity, and/or pregnancy), AUD, previously diagnosed liver cirrhosis, or primary liver disease other than MASLD.

A total of 345 participants accepted further examination at hospital outpatient clinics in Linköping or Norrköping, of whom 308 were ultimately included. Reasons for non-inclusion among those who accepted further examination included previous liver disease, MRI contraindications, or AUD identified retrospectively; harmful alcohol use or another liver disease detected during further examination; or inability to estimate either ^{1}H-MRS-PDFF or CAP. Papers II and IV were based on cross-sectional baseline data from the prospective cohort study. In Paper II, a retrospective medical record review was also performed for included participants.

Paper III: prospective cohort study with cross-sectional data from follow-up

The study population in Paper III consisted of 41 participants with MASLD. These participants had undergone liver biopsy on clinical indication between 1988 and 1993 because of elevated liver tests, and MASLD was established based on this biopsy. In total, 129 patients were

included in the original prospective cohort. Between 2003 and 2005, participants from the original cohort who were still alive were invited to a follow-up visit (4). Of the original 129 participants, 41 underwent follow-up liver biopsy and provided a plasma sample at the same visit.

Paper V: Cost-effectiveness analysis and validation of a screening algorithm

Paper V was a cost-effectiveness analysis using a microsimulation model, and no new data were collected. However, the screening and management algorithm was validated in the EPSOMIP cohort among patients with available PEth.

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Table 1: Overview of studies in thesis

Abbreviations: AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; ELISA, enzyme-linked immunosorbent assay; FIB-4, Fibrosis-4 index; ^{1}H-MRS-PDFF, proton magnetic resonance spectroscopy-proton density fat fraction; ICER, incremental cost-effectiveness ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, magnetic resonance imaging; NHB, net health benefit; *PNPLA3*, patatin-like phospholipase domain-containing protein 3; QALY, quality-adjusted life year; SOC, standard of care; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

Table 1: Overview of studies

Study	Design	Population	Data collection & measurements	Outcome	Statistical analysis
I	Retrospective cohort study	N = 350 Participants with T2D in primary care.	• Medical records review • Steatosis and advanced fibrosis algorithms • Imaging results and management	• Probable prevalence of steatosis and advanced fibrosis • Clinical documentation and management of confirmed steatosis	• Kolmogorov-Smirnov test • Student's t-test • Mann-Whitney U test • Chi-square test
II	Cross-sectional data from cohort study + retrospective medical records review	N = 308 Participants with T2D in primary care	• Medical records review • See study IV	• Prevalence of MASLD and advanced fibrosis • Prevalence of microvascular complications of T2D • Association between MASLD and microvascular complications of T2D	• Student's t-test • Mann-Whitney U test • Kruskal-Wallis test • Fisher's exact test • Directed acyclic graph • Logistic regression • Variance inflation factor
III	Cross-sectional data from prospective cohort study	N = 41 Participants with biopsy-proven MASLD in specialist care	• Liver biopsy • ELISA • *PNPLA3* I148M genotyping	• Plasma Activin A levels in relation to histological fibrosis stage and *PNPLA3* genotype • Diagnostic accuracy of Activin A compared to FIB-4	• Mann-Whitney U test • Kruskal-Wallis test • Logistic regression • AUROC
IV	Cross-sectional data from prospective cohort study	N = 308 Participants with T2D in primary care	• Blood samples • VCTE with CAP • ^{1}H-MRS-PDFF • Body composition MRI • Cardiac MRI • Liver biopsy	• Prevalence and predictors of MASLD and advanced fibrosis • Ectopic fat and muscle composition • Cardiac morphology	• Chi-square test • Mann-Whitney U test • Kruskal-Wallis test • Logistic regression
V	Cost-effectiveness analysis using microsimulation model	N = 28,109 Simulated T2D cohort	• Prevalence, natural history, mortality, test, treatment, cost and utility parameters from published literature • Validation in cohort study IV	• Costs, QALYs and outcomes of screening vs SOC • ICER and NHB • One-way and probabilistic sensitivity analysis	• Parameter estimation by method of moments and numerical optimization

Methods included in Papers I-IV

Medical record review

Medical record review was used as a method in Papers I and II. In Paper I, a retrospective medical record review was conducted using the electronic medical record system Cambio COSMIC (Cambio Healthcare Systems AB, Stockholm, Sweden), which was used by all participating primary care centres. The participants' medical records were reviewed for the period 2008–2019. The review was performed by four resident physicians, two specialist physicians, and one medical student using written instructions and a standardised form. The extracted data were then compiled by the first author. Sex, age, diabetes-related data, diabetes treatment, anthropometric data, information on comorbidities, medication use, lifestyle factors, and results from retinal photography were collected. Reports from imaging examinations that included the liver (US, computed tomography (CT), or MRI) were reviewed for information on steatosis and referral indication. Laboratory data from the date of T2D diagnosis onwards were included. If multiple measurement points were available, the most recent values were recorded. Variables used to calculate algorithms for steatosis and advanced fibrosis had to have been recorded within a 6-month interval.

In Paper II, available electronic medical records were reviewed from 2008 until study inclusion, no later than 2023. All participating primary care centres used the same electronic medical record system, Cambio COSMIC version 3.8.0 (Cambio Healthcare Systems AB, Stockholm, Sweden). Only microvascular complications occurring after T2D onset were included. The participants' diagnosis lists and medical record notes from primary care and T2D-related specialist clinics were reviewed. Laboratory data and results from retinal and neurophysiological examinations were reviewed. For definition of microvascular complications of T2D collected see Paper II supplementary table 1. All medical record reviews were performed by the first author.

AUDIT-C questionnaire

In Papers I, II, and IV, the Swedish version of the AUDIT-C questionnaire was used to assess alcohol consumption (239). The questionnaire includes three questions:

1. How often do you drink alcohol?

2. How many "standard drinks" do you drink on a typical day when you drink alcohol?

3. How often do you drink six such "standard drinks" or more on one occasion?

The response options generate an overall score. In Paper I, participants with an AUDIT-C score ≥3 for women or ≥4 for men identified during medical record review were excluded because of probable harmful alcohol use (240). In Papers II and IV, questions 1 and 2 were used instead to calculate weekly alcohol consumption. Participants with weekly alcohol consumption ≥210 g for men or ≥140 g for women could not be classified as having MASLD.

Algorithms for steatosis

In Paper I, four algorithms for hepatic steatosis were calculated to estimate the likely prevalence of steatosis in the population. All variables included in each algorithm had to have been recorded within a 6-month period for that algorithm to be calculated. The algorithms were calculated in accordance with previous studies, and the following cut-offs were used:

- FLI (130): FLI <30 was considered low risk and FLI ≥60 high risk of MASLD.

- Hepatic Steatosis Index (HSI) (133): HSI <30 was considered low risk and HSI ≥36 high risk of MASLD.

- NAFLD Liver Fat Score (NAFLD-LFS) (131): NAFLD-LFS ≤−0.640 was considered low risk and >−0.640 high risk of MASLD.

- NAFLD ridge score (132): NAFLD ridge score <0.24 was considered low risk and >0.44 high risk of MASLD.

Algorithms for advanced fibrosis

In Papers I and IV, the FIB-4 and NAFLD Fibrosis Score (NFS) algorithms were calculated to assess the risk of advanced fibrosis. In Paper III, only FIB-4 was calculated. In Paper I, all variables included in each algorithm had to have been recorded within a 6-month period for that algorithm to be calculated. The algorithms were calculated for patients with steatosis according to imaging and/or intermediate to high risk of steatosis according to at least one steatosis algorithm.

In Paper IV, the algorithms were calculated using data from inclusion, whereas in Paper III they were calculated using data from follow-up. In Paper III, the numerical FIB-4 value was used, and no cut-off was applied. The algorithms were calculated in accordance with previous studies, using the following cut-offs:

- FIB-4 (138, 139)

  Paper I: FIB-4 <1.3 was considered low risk of advanced fibrosis in patients aged <65 years, and FIB-4 <2.0 was considered low risk in patients aged ≥65 years. FIB-4 ≥3.25 was considered high risk of advanced fibrosis regardless of age.

  Paper IV: FIB-4 <1.3 was considered low risk of advanced fibrosis, and FIB-4 ≥2.67 was considered high risk of advanced fibrosis.

- NFS (241, 242)

  Paper I: NFS <−1.455 was considered low risk of advanced fibrosis in patients aged <65 years, and NFS <0.12 was considered low risk in patients aged ≥65 years. NFS ≥0.676 was considered high risk of advanced fibrosis regardless of age.

  Paper IV: NFS <−1.44 was considered low risk of advanced fibrosis, and NFS ≥0.676 was considered high risk of advanced fibrosis.

Activin A

In Paper III, activin A was measured in plasma samples that had been stored in a biobank since collection in 2003–2005 (4). Activin A concentration (pg/mL) was analysed using a sandwich enzyme-linked immunosorbent assay (ELISA) kit #DAC00B (R&D Systems, Minneapolis, MN, USA), in accordance with the manufacturer's instructions. Control set #QC22 from the same manufacturer was used for quality control of the assay.

PNPLA3 I148M genotyping

In Paper III, data on the *PNPLA3* I148M genotype from a previous study of the cohort were used (4, 243). In this variant, isoleucine at position 148 in the PNPLA3 protein is replaced by methionine. In the previous study, participants were classified as wild type, heterozygous or homozygous for the variant. DNA was extracted from liver biopsy samples, and genotype was determined using PCR, followed by restriction enzyme digestion of the amplicon and subsequent analysis by agarose gel electrophoresis (243).

VCTE & CAP

In Papers II and IV, advanced fibrosis was assessed using VCTE (FibroScan®, Echosens, Paris, France). The examinations were performed by certified research nurses in accordance with current recommendations. Participants had fasted for at least three hours before the examination. The examinations were performed using the M probe; in some cases, the XL probe was used following a recommendation from the automated software. A valid examination required at least 10 valid shear wave measurements, and at least 80% of shear waves had to yield valid measurements. Measurements with excessive variability were excluded, and the IQR had to be ≤30% of the median. Advanced fibrosis was defined as VCTE-derived LSM ≥10 kPa. In Paper IV, the proportions of participants with LSM ≥8 kPa and ≥15 kPa were also presented. CAP was measured during VCTE, and CAP ≥248 dB/m was used as the cut-off for steatosis in participants without available ^{1}H-MRS-PDFF.

^{1}H-MRS-PDFF

In Papers II and IV, ^{1}H-MRS-PDFF was used to quantify hepatic fat content. The examination was performed using a 1.5-tesla MR scanner (Philips Achieva dStream, Philips Healthcare, Amsterdam, the Netherlands). A multi-echo STEAM pulse sequence with TM = 12 ms was used, with a pause in the sequence to minimise measurement error from J-coupling. To prevent previous pulse sequences from interfering with the measurement, TR was set to 3200 ms. At each echo time, one data acquisition was performed (NSA = 1), and the flip angle was 90°. Measurements were performed at six echo times: TE = 10, 15, 20, 25, 30 and 35 ms, enabling calculation of the proportions of fat and water in the tissue. ^{1}H-MRS was performed in a 30 × 30 × 30 mm voxel in the liver parenchyma, avoiding large vessels. The examination was performed twice consecutively, and PDFF was reported as the mean value of the two measurements. ^{1}H-MRS data were analysed in the jMRUI software using the AMARES algorithm to calculate the area under the curves for the water and fat peaks in the spectrum to quantify the amounts (244, 245). The six echo times were used to correct the curves in the spectrum for T2 relaxation. PDFF was calculated as follows: fat/(fat + water) × 100. In Papers II and IV, MASLD was defined as ^{1}H-MRS-PDFF ≥5%.

Cardiac magnetic resonance imaging

In Paper IV, cardiac MRI data were used. During the examination, short-axis images were acquired to calculate cardiac volumes and wall thickness. Multiple images were acquired during the cardiac cycle to construct a cine sequence. A bSSFP sequence was used to obtain high contrast between the myocardium and intracardiac blood. To minimise motion artefacts during cardiac motion, a short TR of 2.9 ms and TE of 1.4 ms were used, together with a flip angle of 60°. Image acquisition was further accelerated using a compressed sensing factor of 3. The acquired spatial resolution was 2.0 × 2.0–2.6 × 8.0 mm and was increased during image reconstruction to 0.9 × 0.9 × 8.0 mm. Images were acquired every 34 ms, and the cine sequence was reconstructed to 30 frames per cardiac cycle. Segment Research version 12067b (Medviso AB, Lund, Sweden) was used to assess left ventricular morphology and global systolic function (181). The software automatically delineated the endocardial and epicardial myocardial borders. Myocardial mass, end-diastolic volume, stroke volume, and ejection fraction were calculated. Left ventricular concentricity was calculated as myocardial mass divided by end-diastolic volume. Myocardial mass, end-diastolic volume, and stroke volume were normalised to body surface area using Mosteller's formula (246).

Dual- and multi-echo Dixon magnetic resonance imaging

In Paper IV, dual-echo and multi-echo Dixon MRI data were used to analyse body composition. Using AMRA Researcher software (AMRA Medical AB, Linköping, Sweden), fat-free muscle volume (FFMV), muscle fat infiltration (MFI), VAT, abdominal subcutaneous adipose tissue (ASAT), and liver PDFF were calculated (182). In the software, automatic image calibration was performed, followed by registration of adipose and muscle tissue regions. Quality control was then performed by trained personnel at AMRA, followed by quantification of fat and muscle volumes. Based on expected muscle mass according to sex and BMI in a reference population, an FFMV z-score was calculated, and MFI was adjusted for sex differences based on a reference population. Low muscle volume was defined as an FFMV z-score below the 25th percentile of the reference population, and myosteatosis as MFI above the 75th percentile of the reference population (100). Participants with both low muscle volume according to the FFMV z-score and myosteatosis according to MFI were considered to have AMC.

Liver biopsy

In Papers II and IV, liver biopsy data from the EPSOMIP study were used. Patients with VCTE ≥8 kPa were recommended to undergo biopsy in Papers II and IV. All biopsies were performed percutaneously under US guidance, using a 1.6 mm BioPince needle, and were reviewed by an experienced liver pathologist. In Paper III, biopsies were performed in the same way, but all biopsies were reviewed by two experienced liver pathologists who were blinded to patient characteristics. Further assessment was otherwise performed in a similar manner to Papers II and IV.

The biopsies were assessed according to the Kleiner scoring system, in which steatosis, lobular inflammation, hepatocellular ballooning and fibrosis are assessed semi-quantitatively (74). The presence of MASH was assessed using the MASH-FLIP algorithm (247). In this algorithm, patients with steatosis, hepatocellular ballooning and lobular inflammation of any grade are classified as having MASH.

Methods included in Paper V

The screening algorithm

For Paper V, the following screening algorithm was constructed and evaluated. Patients with T2D are followed up twice yearly in primary care (210). Every third year, screening is performed during a routine visit. Screening starts at 35 years of age and stops at 75 years of age. In patients younger than 35 years, FIB-4 has reduced diagnostic performance, while the likelihood of severe liver disease is low (140, 174). Patients with a healthy liver who are older than 75 years have a low risk of developing advanced liver disease during their remaining lifetime, and the risk of false-positive results when using FIB-4 is high (141, 248).

The screening algorithm consists of two steps, with initial testing using FIB-4 in primary care. Patients who are not classified as being at low risk of liver disease are subsequently referred for VCTE in specialist care to identify those at low risk of liver disease, those with significant fibrosis, and those with cirrhosis. The proposed algorithm is based on screening algorithms from guidelines and previous studies (189, 205, 249). Age-adjusted FIB-4 thresholds (<1.3 below 65 years of age and <2.0 above 65 years of age) have been studied to exclude advanced fibrosis, but the American Diabetes Association also recommends these thresholds to exclude significant fibrosis (214).

Patients who are not classified as being at low risk of liver disease according to FIB-4 are further evaluated with VCTE in specialist care. In patients with probable significant fibrosis (8–15 kPa) or cirrhosis (≥15 kPa), blood tests are performed to exclude liver diseases other than MASLD, MetALD or ALD (Figure 2). The proportion of patients with another aetiology in a Swedish primary care context is considered sufficiently low for these diagnoses to be disregarded in the model (250). During blood testing, PEth is also assessed to identify patients with MASLD (<0.05 μmol/L), MetALD (0.05–0.30 μmol/L) or ALD (>0.30 μmol/L) (69).

In the model, patients who develop decompensated cirrhosis are expected to be detected immediately, given the presence of clear symptoms (201). Patients who develop HCC may also be detected incidentally (201).

Management after screening

Patients with probable significant fibrosis are followed in specialist care with annual physician visits and VCTE assessments. Semaglutide is used for MASLD, semaglutide in combination with baclofen for MetALD, and baclofen for ALD (32, 165, 251). If patients with significant fibrosis on VCTE later meet VCTE criteria for cirrhosis, they are transferred to cirrhosis follow-up.

Patients with probable cirrhosis according to VCTE are followed in specialist care. Follow-up includes two annual visits, VCTE, and twice-yearly HCC surveillance with US and alpha-fetoprotein (252). Patients with suspected HCC undergo confirmatory CT (201). Patients with MetALD or ALD who are followed for cirrhosis are started on baclofen. Patients who were started on semaglutide because of probable significant fibrosis remain on this treatment. Treatment with baclofen or semaglutide is discontinued if HCC develops (Figure 3).

In the model, HCC can be detected either incidentally or through HCC surveillance. Patients who have undergone liver transplantation and patients under follow-up after curative HCC treatment who develop recurrent HCC are assumed to be detected immediately because of close follow-up. HCC stages A–D were modelled in accordance with the BCLC classification (81). HCC treatment is based on simplified stage-specific recommendations and Swedish registry data (82, 253). Patients with HCC stage A receive curative treatment in the form of liver transplantation or resection/ablation. Curative treatment is associated with perioperative mortality risk. In HCC stage B, palliative treatment consists of transcatheter arterial chemoembolization (TACE); in stage C, palliative systemic treatment consists of atezolizumab plus bevacizumab; and in stage D, best supportive care (BSC) is provided. After curative treatment, follow-up CT is performed for five years (254). During palliative treatment with TACE and atezolizumab plus bevacizumab, regular CT examinations are performed as follow-up (254, 255). After curative treatment, recurrence risk is modelled annually for five years, and treatment after recurrence is based on simplified assumptions from previous studies (254, 256, 257).

Among patients with decompensated cirrhosis, a proportion become eligible for liver transplantation, which is also associated with perioperative mortality risk (201, 258). After liver transplantation, patients undergo regular follow-up and receive standard immunosuppressive treatment in accordance with Swedish national guidelines (259). After liver transplantation, the risk of redeveloping SLD returns to the baseline risk associated with diabetes and current alcohol consumption (Figure 4).

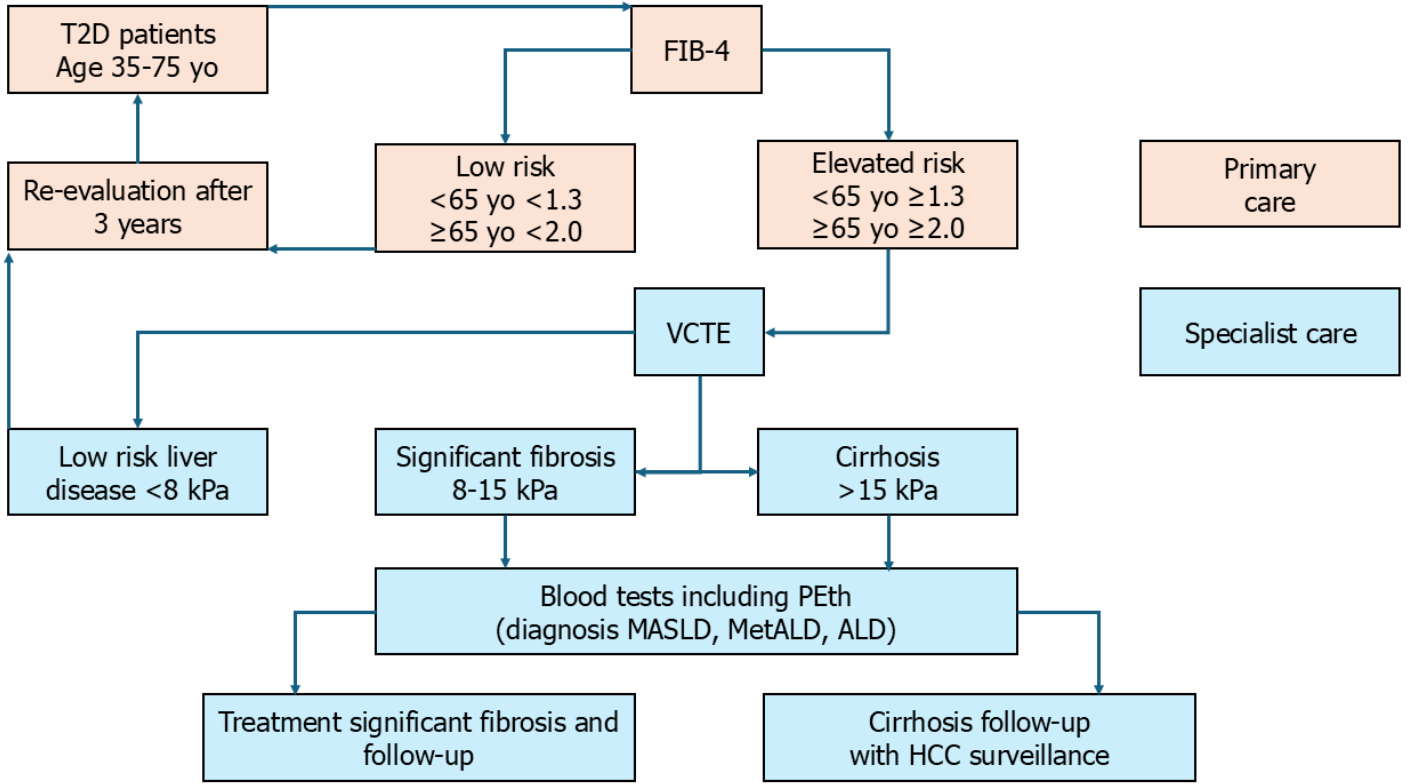
Next pages (pages nr 34-36)

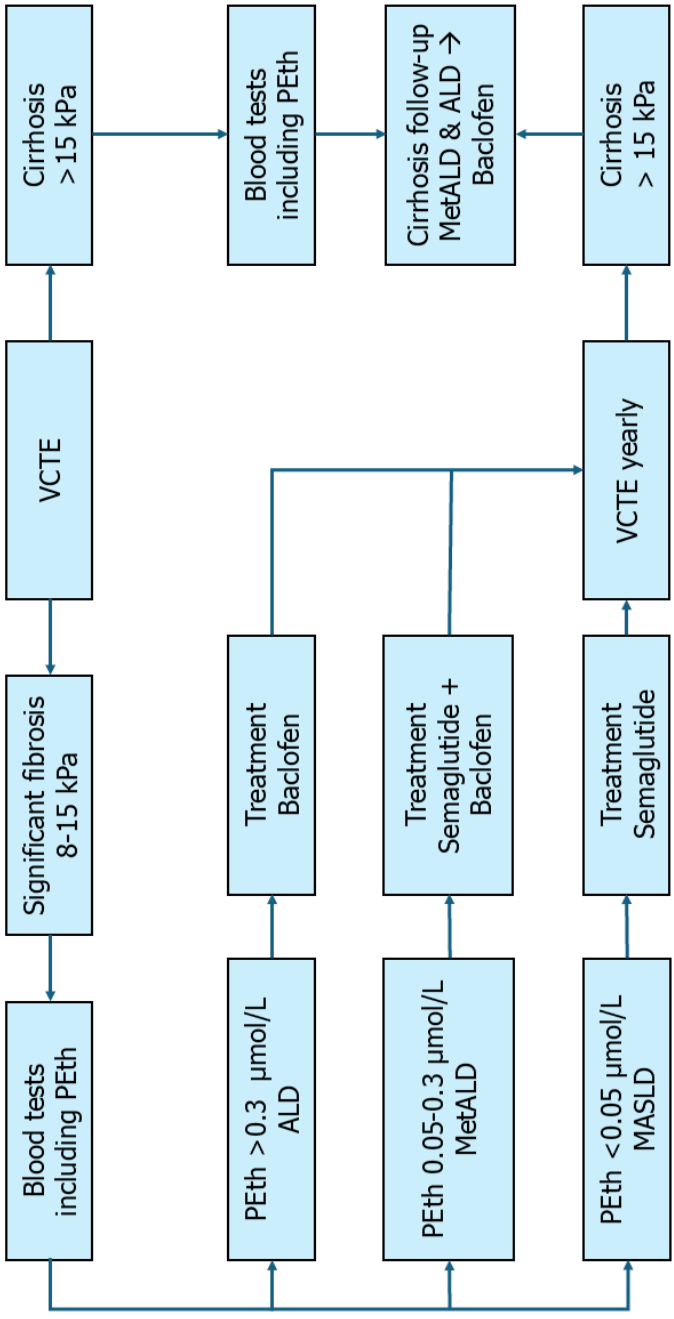
Figure 2: Structure of screening of significant fibrosis in MASLD, MetALD and ALD among patients with T2D in primary care.

Figure 3: Follow-up significant fibrosis and cirrhosis including treatment in MASLD, MetALD and ALD.

Figure 4: HCC surveillance in cirrhosis, HCC treatment and liver transplantation.

Abbreviations: ALD, Alcohol-associated liver disease; BSC, Best supportive care; CT, computed tomography; FIB-4, Fibrosis 4 index; HCC, Hepatocellular carcinoma: kPa, kilopascal: MASLD, Metabolic dysfunction-associated steatotic liver disease: MetALD, Metabolic dysfunction and alcohol-associated liver disease: PEth, Phosphatidylethanol: TACE; Transcatheter arterial chemoembolization; T2D, Type 2 diabetes: VCTE, Vibration-controlled transient elastography: yo; Years old**.**


T2D patients
Age 35-75 yo
FIB-4
Re-evaluation after
3 years
Low risk
<65 yo <1.3
≥65 yo <2.0
Elevated risk
<65 yo ≥1.3
≥65 yo ≥2.0
Primary
care
VCTE
Specialist care
Low risk liver
disease <8 kPa
Significant fibrosis
8-15 kPa
Cirrhosis
>15 kPa
Blood tests including PEth
(diagnosis MASLD, MetALD, ALD)
Treatment significant fibrosis and
follow-up
Cirrhosis follow-up
with HCC surveillance


Blood tests including PEth
Significant fibrosis 8-15 kPa
VCTE
Cirrhosis >15 kPa
PEth >0.3 µmol/L ALD
Treatment Baclofen
Blood tests including PEth
PEth 0.05-0.3 µmol/L MetALD
Treatment Semaglutide + Baclofen
Cirrhosis follow-up MetALD & ALD → Baclofen
PEth <0.05 µmol/L MASLD
Treatment Semaglutide
VCTE yearly
Cirrhosis > 15 kPa

Cirrhosis follow-up
HCC surveillance
CT Liver
HCC
Curative treatment
Non-curative treatment
BSC
Atezolizumab + Bevacizumab
TACE
HCC follow up
Decompensated cirrhosis
Liver transplant
Accidental discovery HCC
Liver transplant follow-up

Standard of care

The current screening and management algorithm was compared with standard of care (SOC), defined as two annual diabetes follow-up visits in primary care, incidental detection of HCC, and immediate detection of decompensated cirrhosis (201, 210). In patients with HCC or decompensated cirrhosis, treatment was assumed to follow the same approach as in the screening algorithm.

Health economic analysis

To estimate the health care costs and health effects of the screening algorithm, the proposed screening strategy was compared with SOC over a lifetime horizon. The different SLD subtypes progress at varying rates, but even in ALD, cirrhosis usually takes several decades to develop (14, 54, 260). Because the study examines the entire spectrum of SLD, a lifetime horizon was considered appropriate. The analysis was conducted from a health care perspective.

Health effects were measured in QALYs. Health care costs included diagnostics, primary and specialist care visits, inpatient care, and treatment. Costs and QALYs were discounted by 3% in accordance with TLV recommendations (261). Costs were expressed in EUR, inflation-adjusted using the consumer price index, and reported in 2026 prices. The results of the analysis were presented as an ICER, expressed in EUR/QALY, comparing costs and health gains between screening and SOC. NHB was calculated using a threshold value of EUR 50,000/QALY. In addition, we presented life years gained, the proportions of patients developing decompensated cirrhosis, developing HCC, undergoing HCC treatment, undergoing liver transplantation, and receiving treatment, as well as 5- to 40-year mortality for the screening and SOC alternatives.

Microsimulation

To examine costs and health outcomes over time for the screening and management algorithm, a microsimulation model of the natural history of SLD was used. The model was implemented in Python, and outputs from the simulation formed the basis of the health economic analysis. The simulation included a large number of hypothetical individuals, each with unique characteristics, and individual disease trajectories were determined by transition probabilities and risk factors. In each annual model cycle, each individual had probabilities of developing SLD or progressing or regressing between SLD stages depending on baseline status. HCC and decompensated cirrhosis could also develop as complications. In addition to T2D- and age-adjusted mortality risk, individuals also had mortality risks related to SLD severity and complications. Each individual's current health state, together with its associated costs and health effects, contributed to accumulated costs and QALYs over the time horizon.

In addition to T2D with a healthy liver, SLD was modelled using the following stages: MASL (simple steatosis), MASH F0 (steatohepatitis without fibrosis), MASH F1 (steatohepatitis with mild fibrosis), MASH F2 (steatohepatitis with significant fibrosis), MASH F3 (steatohepatitis with advanced fibrosis), and MASH F4 (cirrhosis). HCC stage A could develop from all SLD stages and could progress to HCC stages B, C, and D. All HCC stages could also be in combination with decompensated cirrhosis. Decompensated cirrhosis could develop from MASH F3 and MASH F4. Alcohol consumption category (low, intermediate, or high) determined SLD subtype (MASLD, MetALD, or ALD) once SLD had developed. The risks of

developing SLD, MASH F4, HCC, decompensated cirrhosis, and death were adjusted in individuals with intermediate or high alcohol consumption (Figure 5) (49, 50).

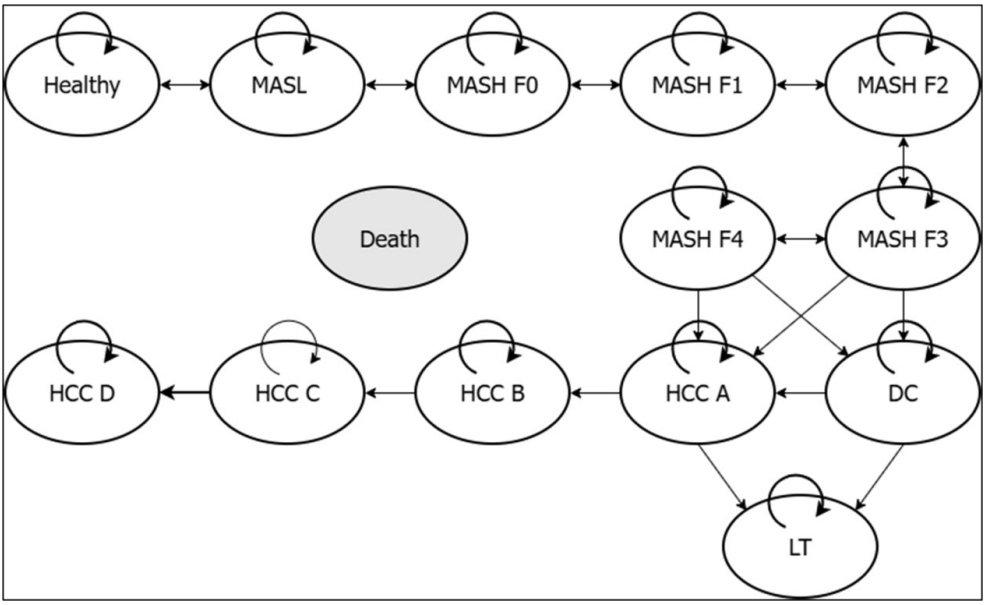


Figure 5: Model structure for MASLD. Equivalent health states for MetALD and ALD. All HCC stages could also be in combination with DC. The model also accounts for low probabilities of progressing or regressing more than one stage per year. Possibility to progress to death from all health states.

Abbreviations: ALD; Alcohol-associated liver disease, DC; Decompensated cirrhosis, HCC; Hepatocellular carcinoma, LT; Liver transplantation, MASH; Metabolic dysfunction-associated steatohepatitis, MASL; Metabolic dysfunction-associated steatotic liver, MASLD; Metabolic dysfunction-associated steatotic liver disease, MetALD; Metabolic dysfunction and alcohol-associated liver disease.

Model parameters

- **Steatotic liver disease subtypes and alcohol consumption**

The baseline distribution of SLD and healthy liver in the simulation was based on a American cross-sectional study published in 2024 (262). In that study, participants were recruited from primary care or the general population. Participants were aged 40–75 years and had overweight or obesity. Approximately 30% had T2D. Steatosis was assessed using MRI-PDFF, and SLD subtypes were defined based on daily alcohol consumption, AUDIT score, or the presence of AUD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Based on the occurrence of MASLD and MetALD in the study, the proportion of individuals with a healthy liver who had low or intermediate alcohol consumption was assumed. Because high alcohol consumption is associated with a very high risk of developing simple steatosis, no simulated individual with a healthy liver was assigned high alcohol consumption at baseline (46, 263). However, a proportion of individuals could transition to high alcohol consumption in each cycle, and this transition probability was estimated from the incidence of ALD in the general population in Denmark (109).

The fibrosis stage distribution was derived from a American general population study published in 2025 (218). Approximately 50% of participants had prediabetes or T2D. SLD was defined using CAP, and subclassification into SLD subtypes was based on daily alcohol consumption. The proportions with F2, F3, and F4 fibrosis were estimated using VCTE. Because the distribution from simple steatosis to F1 was not presented for any subtype, this distribution was assumed. This assumption was based on the prevalence of MASH among patients with T2D reported in a meta-analysis, the prevalence of ASH in ALD reported in a systematic review, and the stage distribution used in a previous modelling study of MASLD in T2D (Table 2) (195, 217, 264). The proportions of simple steatosis, MASH F0, and MASH F1 were assumed to be the same in MetALD as in MASLD.

- **Natural history parameters**

The risk of developing MASLD among individuals with low alcohol consumption was obtained from a previous modelling study of MASLD in T2D (265). This risk was modified for individuals with intermediate alcohol consumption based on a study of the impact of alcohol consumption on MASLD (266). All individuals who transitioned to high alcohol consumption during a model cycle were assumed to develop simple steatosis (46). The risks of progression and regression in the MASLD disease model were obtained from previous modelling studies of MASLD and a systematic review of disease progression in MASLD (21, 200, 201, 267). The risks of progression and regression in MetALD and ALD were based on MASLD but adjusted using estimates for more severe disease states, including MASH F4, decompensated cirrhosis, and HCC, obtained from a meta-analysis of longitudinal outcomes in MASLD and MetALD and a retrospective cohort study of patients with SLD (49, 50). The risks of progression and regression in HCC were obtained from a previous modelling study of HCC and a cohort study (268, 269).

Table 2: Cohort at baseline	
	Proportions
Subtype	
MASLD	0.673
MetALD	0.048
ALD	0.026
No liver disease	0.253
SLD stage	
MASL	0.515
MASH F0	0.046
MASH F1	0.096
MASH F2	0.195
MASH F3	0.074
MASH F4	0.074
MetALD SS	0.515
MetALD MASH F0	0.070
MetALD MASH F1	0.147
MetALD MASH F2	0.177
MetALD MASH F3	0.050
MetALD MASH F4	0.041
ALD SS	0.318
ASH F0	0.025
ASH F1	0.053
ASH F2	0.271
ASH F3	0.202
ASH F4	0.132

Table 2: Distribution of healthy and SLD subtypes with corresponding stage in cohort at baseline

Abbreviations: ALD, Alcohol-associated liver disease; ASH, Alcohol-associated steatohepatitis; F0-F3, Fibrosis grade 0-3: F4, cirrhosis; MASH, Metabolic dysfunction and alcohol-associated steatohepatitis; MASL, Metabolic dysfunction-associated steatotic liver; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, Metabolic dysfunction and alcohol-associated liver disease; SLD, Steatotic liver disease; SS, Simple steatosis.

- **Mortality**

In the model, mortality was adjusted for age and the presence of T2D. Age-specific mortality was obtained from Statistics Sweden, and excess mortality associated with T2D was based on a Swedish NDR study comparing patients with T2D with matched controls (270, 271). The age distribution of the simulated cohort was derived from 2024 national data on patients with T2D in Swedish primary care (272). Mortality was then further adjusted according to the presence and severity of SLD, using estimates from a Swedish MASLD cohort and a previous modelling study (201, 273). In MetALD and ALD, mortality was adjusted using estimates from an American retrospective cohort study of SLD (Table 3) (50). Mortality in undetected HCC and after liver transplantation was obtained from a previous modelling study (201).

- **Tests**

Sensitivity and specificity of FIB-4 for detecting significant fibrosis in MASLD and MetALD were obtained from a meta-analysis of FIB-4 performance in MASLD, a Korean retrospective cohort study of diagnostic performance in MetALD, and a Danish screening study of SLD in the general population and among individuals with risk factors for MASLD and ALD (145, 274, 275). For ALD, sensitivity and specificity for detecting significant fibrosis were based on the same Danish screening study. For advanced fibrosis (including cirrhosis), FIB-4 diagnostic performance was obtained from a European cohort study for MASLD and a Danish cohort study for MetALD and ALD (Table 3) (78, 140).

Sensitivity and specificity of VCTE for detecting significant fibrosis in MASLD and MetALD, using a threshold of ≥8 kPa, were based on a meta-analysis of fibrosis assessment in chronic liver disease and a French cross-sectional study in ALD (159, 276). For cirrhosis, using thresholds of ≥8 kPa and ≥15 kPa, cross-sectional data from a European multicentre study were used (277). Patients with true cirrhosis who tested false negative using the ≥15 kPa threshold were then assessed using the ≥8 kPa threshold; those who tested positive at this lower threshold were followed as having significant fibrosis rather than cirrhosis.

The probability of incidental HCC detection at onset was obtained from a previous modelling study (201). Sensitivity and specificity for detecting HCC stage A during cirrhosis surveillance were based on a meta-analysis, whereas for HCC stages B–D it was assumed that all cases would be detected (278). During follow-up after liver transplantation or curative HCC treatment, it was also assumed that all recurrences would be detected, given the close follow-up.

- **Treatment effects**

The treatment effect of semaglutide in the model was obtained from a global multicentre randomised controlled trial (RCT) in patients with biopsy-confirmed MASH F2–F3 (32). Semaglutide was assumed to have an effect in MASH F0–F3 (279, 280). During treatment, MASH resolution occurred in 28.7% of treated individuals in the model, resulting in a 50% reduction in the rate of fibrosis progression. This assumption was based on the RCT and a meta-analysis comparing MASL and MASH regarding fibrosis progression (Table 3) (22). Additionally, half of the patients that had MASH resolution regressed by one fibrosis stage (32). The effect in MetALD was assumed to be the same as in MASLD (54).

In the model, brief intervention combined with baclofen treatment for MetALD and ALD was assumed to result in long-term abstinence in 70% of treated individuals. This estimate was based on an Italian RCT of baclofen treatment in patients with liver cirrhosis and AUD, and a Danish study in which lifestyle advice regarding alcohol consumption was provided in connection with screening for SLD in the general population (Table 3) (190, 251). The effect was considered reasonable given that approximately 50% of patients with alcohol-associated cirrhosis become abstinent in the long term according to a meta-analysis (52). In patients who became abstinent in the long term, risk of severe disease states and mortality in MetALD and ALD were assumed to decrease to the same level as in MASLD, whereas quality of life was assumed to increase to the same level as in MASLD. These assumptions were based on results from meta-analyses of long-term abstinence in alcohol-associated cirrhosis and the risk of developing cirrhosis (52, 281).

Patients with true cirrhosis who were followed for cirrhosis were assumed to have a lower risk of decompensation. This was considered reasonable given the structured care provided, including surveillance and treatment of oesophageal varices (201, 252).

In the model, HCC stage A could be treated curatively with resection/ablation or liver transplantation. The proportions undergoing each treatment were simplified based on a Swedish registry study and current international guidelines (82, 253). Both treatments were associated with perioperative mortality and altered mortality over time. These estimates were obtained from a previous modelling study of MASLD/HCC, a French retrospective cohort study of survival after liver resection, an American registry study of early mortality after liver transplantation, and data from the Swedish national care programme for HCC (201, 254, 257, 258). The treatments were also associated with a risk of recurrence based on data from the Swedish national care programme, the French retrospective cohort study, and a meta-analysis of recurrence risk after liver transplantation (256). In the event of recurrence after liver transplantation, the patient was treated with BSC. If recurrence occurred after resection/ablation, there was a probability of repeat resection/ablation, palliative treatment with atezolizumab and bevacizumab, or BSC, based on the Swedish national care programme and the French retrospective cohort study (254, 257).

Treatment choices for HCC stages B–D were palliative and were simplified based on a Swedish registry study and current international guidelines (82, 253). In HCC stage B, TACE was given, and post-treatment mortality was based on a Swedish registry study (282). In HCC stage C, treatment consisted of atezolizumab and bevacizumab, whereas in HCC stage D, treatment consisted of BSC. Subsequent mortality for both stages was obtained from a previous modelling study of MASLD/HCC (201). All HCC treatment was assumed to be the same and to have the same effect regardless of the underlying SLD subtype. In liver transplantation for decompensated cirrhosis, perioperative and subsequent mortality were assumed to be the same as for liver transplantation for HCC stage A and were based on the same sources (201, 258).

- **Costs**

Costs in the model were based on the current health state and treatment. Follow-up components were based, as far as possible, on current Swedish clinical guidelines (210, 252, 254, 259). Individual cost estimates were obtained from different sources; for a comprehensive

overview, see the Supplementary material and Supplementary figures and tables from Paper V. For example, costs for inpatient and outpatient care were estimated using Diagnosis-Related Group (DRG) codes from the South-Eastern Health Care Region, whereas costs for laboratory tests and diagnostic imaging were derived from current Swedish regional price lists (Table 3) (283-285). Drug costs were based on price data from Swedish pharmacies and procurement agreements (286-288).

Table 3: Selected input parameters

Parameter	
Alcohol consumption and risk SLD	**Annual risk**
Low (PEth <0.05 µmol/L)	0.04
Moderate (PEth 0.05–0.30 µmol/L)	0.07
High (PEth >0.30 µmol/L)	1.00
Mortality	**HR**
MASLD	1.0 (reference)
MetALD	1.08
ALD	1.42
FIB-4	**Sensitivity/specificity**
MASLD SF <65 yo	0.65/0.74
MASLD SF >65 yo	0.39/0.84
MASLD AF	0.77/0.70
VCTE	**Sensitivity/specificity**
MASLD SF (>8 kPa)	0.76/0.73
MASLD cirrhosis (>15 kPa)	0.67/0.90
Treatment	**Proportions**
Semaglutide - MASH resolution	0.29
Semaglutide - Fibrosis regression	0.14
Baclofen + Brief intervention - Abstinence	0.70
Cost	**EUR**
FIB-4	22
VCTE	169
Semaglutide (annual)	2,600
Baclofen (annual)	99

Previous page (page nr43)

Table 3: Selected input parameters

Abbreviations: AF, Advanced fibrosis; ALD, Alcohol-associated liver disease; FIB-4, Fibrosis 4 index; kPa, Kilopascal; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, Metabolic dysfunction and alcohol-associated liver disease; PEth, Phosphatidylethanol; SF, Significant fibrosis; VCTE, Vibration-controlled transient elastography.

- **Quality of life**

In the model, age-specific quality-of-life weights were obtained from a study of the general Swedish population (289). Because all simulated individuals had T2D, these weights were further adjusted based on data from a previous modelling study of MASLD (267). Health-state-specific quality-of-life weights were obtained from a previous modelling study of MASLD and were assumed to be the same in MetALD and ALD (201). An additional adjustment was applied for high alcohol consumption based on a American study of quality of life in AUD (290). Quality-of-life weights for undetected HCC, HCC treatment, and the post-liver-transplantation state were obtained from a previous modelling study of MASLD and were assumed to be the same regardless of the underlying SLD subtype (201). In the model, we assumed that screening or follow-up itself, as well as treatment with semaglutide, baclofen, or brief intervention, did not affect quality of life. Previous RCTs of semaglutide and baclofen have not shown adverse effects on quality of life (291, 292). A previous study of quality of life in patients screened for MASLD found predominantly positive effects of screening (222).

Analysis

The simulated cohort included 28,109 hypothetical individuals, corresponding to one-tenth of the Swedish adult primary care population aged 35–75 years with T2D (272). In the base-case analysis, 5,000 model simulations were performed, with values sampled from the probability distributions assigned to model parameters, as described in the section on probabilistic sensitivity analysis. Outcomes from the base-case analysis are presented as means across these simulations. Cost-effectiveness outcomes for the screening and SOC alternatives are presented as mean values per individual. Outcomes for specific SLD subtypes and for individuals without SLD were based on classification at death or at the end of the 60-year simulation horizon, and this approach was applied in both base-case and sensitivity analyses.

- **One-way sensitivity analyses**

To examine how individual parameters affected the ICER, one-way sensitivity analyses were performed. In each analysis, 500 simulations were conducted to limit computational demand, and results were presented as mean values. The following analyses were performed:

- Exclusion of FIB-4 and direct use of VCTE:
  FIB-4 has been questioned as a screening tool in ALD (275, 293, 294). VCTE has been used in screening studies in T2D but has also been questioned (163). In this analysis, VCTE was used instead of FIB-4 every third year.

- Adjustment of F0–F3 progression rates by SLD subtype:
  In recent years, prognostic data for MASLD have been questioned (44). Studies have shown that even moderate alcohol consumption in MASLD increases the risk of severe liver disease (266). An unexpectedly high proportion of patients initially classified as having MASLD later develop ALD or AUD (62). When objective measures of alcohol consumption are used, the proportion with MetALD and ALD increases significantly in SLD cohorts (62, 68). In view of these concerns, fibrosis progression rates were lowered by 25% for MASLD, increased by 25% for MetALD, and increased by 50% for ALD in the analysis.

- Modification of baseline SLD subtype and alcohol consumption distributions based on PEth in the general population:
  This analysis was performed to further examine the effect of underreported alcohol consumption (62, 68). The baseline proportions of MASLD, MetALD, and ALD were adjusted according to the PEth distribution observed in the general Norwegian population, in which 70% had low, 25% intermediate, and 5% high alcohol consumption (295). The proportions with low or intermediate alcohol consumption among those with a healthy liver were also adjusted.

- Adjustment of the treatment effect of semaglutide in MASLD and MetALD:
  To examine the effect of semaglutide, the effect on fibrosis regression was either removed or doubled in two separate analyses.

- Adjustment of the treatment effect of baclofen on long-term abstinence:
  The effect of baclofen was obtained from a small RCT with short follow-up, and its long-term effect is uncertain (251, 296). Three scenario analyses were conducted in which the assumed effect of baclofen on long-term abstinence was varied: no effect, long-term abstinence in 25% of treated individuals, and long-term abstinence in 50% of treated individuals.

- **Probabilistic sensitivity analysis**

To perform the PSA, probability distributions were assigned to variables for which measures of dispersion were available. Variables lacking measures of dispersion were used deterministically. The beta distribution was used for most parameters throughout the analysis. Probability distributions were parameterised using the method of moments when the mean and measure of dispersion suggested a symmetric distribution. Using this method, the shape parameters of the beta distribution, α and β, can be calculated from the mean and variance. If the relationship between the mean and measure of dispersion suggested asymmetry, the beta distribution was parameterised using numerical optimisation. In this approach, different combinations of α and β values are tested to identify the beta distribution that best matches the specified mean and measure of dispersion. The PSA was performed by sampling from the probability distributions assigned to the model parameters, and 5,000 individual simulations were performed. The resulting 5,000 paired incremental costs and health effects were then plotted in the cost-effectiveness plane with a threshold line of EUR 50,000/QALY to visualise the proportion of simulations indicating cost-effectiveness.

- **Validity**

To assess model validity, model outputs were compared with data from EPSOMIP. The baseline distribution of SLD subtypes and alcohol consumption in the model was compared with corresponding distributions in the EPSOMIP cohort. In the EPSOMIP cohort, steatosis was defined as described above, but data from participants excluded because of harmful alcohol use were also included in this comparison. SLD subtypes were defined using previously proposed PEth thresholds (69). The first step of the screening algorithm, FIB-4, was evaluated using FIB-4, VCTE and PEth data from the EPSOMIP cohort. Sensitivity, specificity, PPV, and NPV were calculated for significant fibrosis and cirrhosis as a combined outcome

Statistical methods Paper I-IV

Descriptive statistics

Throughout the papers, normally distributed continuous variables are presented as means with standard deviations, whereas non-normally distributed continuous variables are presented as medians with interquartile ranges (IQRs). In Paper I, the Kolmogorov–Smirnov test was used to assess whether variables were normally distributed. Categorical data are presented as numbers and percentages. When data were missing in pairwise comparisons, pairwise exclusion was applied without imputation.

Hypothesis testing and group comparisons

For normally distributed continuous variables, the independent-samples Student's t-test was used for comparisons between two groups. For skewed distributions, the Mann–Whitney U test was used for comparisons between two groups, including comparisons of ordinal variables. For comparisons between more than two groups, the Kruskal–Wallis test was used for non-normally distributed continuous variables. When p <0.10, Mann–Whitney U tests were performed between individual groups. For categorical data, the chi-square test was used, or Fisher's exact test when group sizes were small. When p <0.10, chi-square tests were performed between individual groups.

Regression analysis and modelling

Univariate and multivariate binary logistic regression analyses were performed to examine associations and identify independent predictors of clinical outcomes. Variables were first explored in univariate analyses, resulting in crude odds ratios (cORs), and selected variables were then added stepwise in multivariate analyses to calculate adjusted odds ratios (aORs). In Paper II, collinearity diagnostics were performed using the variance inflation factor (VIF) to exclude problematic multicollinearity in the adjusted models. To identify variables suitable for inclusion in multivariate regression analysis and to examine potential biasing paths, a directed acyclic graph (DAG) was constructed in Paper II.

Diagnostic performance

In Paper III, the performance of activin A as a biomarker for advanced fibrosis in MASLD was explored using receiver operating characteristic (ROC) curves. The biomarker's sensitivity and specificity at different thresholds were visualised in a curve, and the area under the receiver operating characteristic curve (AUROC) was calculated to quantify the diagnostic ability of activin A to classify advanced fibrosis. The AUROC was also calculated for FIB-4 to enable comparison between activin A and FIB-4.

Software and significance level

Statistical analyses were performed using IBM SPSS Statistics versions 26 and 29 (IBM Corp., Armonk, NY, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA). Graphs were constructed using these programs and GraphPad Prism version 9.1.2 (GraphPad Software, Boston, MA, USA). The DAG was constructed using the web-based tool DAGitty (www.dagitty.net, Radboud University, Nijmegen, The Netherlands). In all papers, the statistical significance level was set at a two-sided *p*-value of 0.05.

Ethical considerations

Paper I

In Paper I, a retrospective medical record review was conducted in which sensitive personal data were collected. When participants were included, they were assigned a study number. The study number could be linked to the participant's personal identity number using a separate code key, which was stored in paper form in a locked safe accessible only to authorised persons. All participant data were pseudonymised after collection and analysed at group level. The study was approved by the Regional Ethical Review Board in Linköping (registration number: 2018/365–31).

However, participants were not asked whether they wished to participate in the study, which raises ethical concerns despite approval by the ethics board. Another ethical aspect is that many cases of steatosis were noted in radiology reports, and in most cases the medical record contained no information indicating that this had led to further action. Some of these participants may have benefited from further evaluation of steatosis. A similar issue applies to the calculated algorithms for advanced fibrosis. High FIB-4 values, for example, would usually lead to further investigation in specialist care in clinical practice. Contacting participants to inform them about previously unaddressed steatosis and an increased risk of advanced liver disease according to FIB-4 would also raise ethical concerns. Participants had not been asked to participate or given informed consent, and information about possible disease could cause anxiety and may not have been information they wished to receive. Furthermore, direct contact with participants in the event of potentially serious findings had not been discussed in the ethics application.

Papers II and IV

These papers are based on the EPSOMIP study, a prospective cohort study in which patients were included from primary care. EPSOMIP was conducted in accordance with the ethical principles of the Declaration of Helsinki. Before the study was conducted, the study protocol had been published, and the study had been registered as a clinical trial at ClinicalTrials.gov (NCT03864510) (238). The EPSOMIP study was approved by the Regional Ethical Review Board in Östergötland (2018/176-31 and 2018/494-32).

At inclusion, participants received oral and written information about the study. It was clearly stated that participation was voluntary and that participants could withdraw from the study at any time without giving a reason. Participants were given the opportunity to ask questions about the study design and what participation would entail. They then provided written informed consent to participate in the study. At inclusion, each participant was assigned a study number. The study number could be linked to the personal identity number using a separate code key, which was stored in paper form in a locked safe accessible only to authorised persons. All participant data were pseudonymised after collection and analysed at group level.

The likely knowledge gains from EPSOMIP were considered to outweigh the risks to study participants. Blood sampling causes minimal discomfort in most cases, and the amount of blood drawn, 90 mL, is a negligible volume. MRI and VCTE are harmless methods if the exclusion criteria are followed. Participants with signs of advanced fibrosis were offered liver biopsy, which was the most invasive procedure in the study and is associated with a risk of complications. However, when standard clinical routines are followed, complications are very rare. Liver biopsy was offered only to participants who would have had a clinical indication for the procedure in routine care, and undergoing biopsy was not required for study participation. No complications occurred among the few participants who underwent liver biopsy in the study.

In Paper II, a medical record review was conducted. Reviewing participants' medical records may constitute an intrusion into privacy, but at inclusion, participants consented to the research group accessing their medical records.

For individual participants in EPSOMIP, there were potential benefits in the form of possible detection of MASLD and its complications, as well as other diseases. Participants in whom simple steatosis was detected could gain increased motivation for lifestyle changes, which may improve the disease and reduce the risk of complications. Participants who already had severe liver disease were given the opportunity for follow-up and, if needed, treatment. Participants without MASLD probably gained increased awareness and knowledge of MASLD, which may lead to greater motivation for lifestyle changes. The project may also have increased knowledge and awareness of MASLD at the participating primary care centres.

Paper III

The analysis was based on previously collected data and biobanked samples. In the original study, written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Ethical Review Board in Linköping, Sweden (reference number 2002-454) (4). Measurement of activin A currently has no established clinical significance, and the results were therefore not expected to affect participants' clinical management.

Paper V

No new participant-level data were collected for this study, and no participants were recruited. The model was based on data from multiple previous studies with ethical approval and published in peer-reviewed sources. Published and unpublished EPSOMIP data were used for validation. Ethical considerations related to the use of EPSOMIP data are described above.

Results

Paper I

After application of the exclusion criteria, a total of 350 participants were included. Among participants, 44% were women, median age was 71 years (IQR 17), and median BMI was 28.9 kg/m² (IQR 6.4). The median duration of T2D was 9 years (IQR 9), and 83% were receiving pharmacological treatment for T2D.

The number of participants for whom steatosis algorithms could be calculated ranged from 7 for NAFLD-LFS to 175 for HSI. The proportion classified as having intermediate to high risk of steatosis ranged from approximately 70% for NAFLD-LFS to 95% for the other steatosis algorithms (HSI, FLI, and NAFLD Ridge Score) (Figure 6). In total, at least one steatosis algorithm could be calculated for 220 participants. Of these, 89% were classified as high risk, 9% as intermediate risk, and 2% as low risk of steatosis in at least one algorithm. Agreement between the steatosis algorithms, among the 125 participants who could be assessed using two or three algorithms, was 65–70%.

For advanced fibrosis algorithms, 134 participants could be assessed using NFS and 190 using FIB-4, and the proportion classified as having intermediate to high risk of advanced fibrosis ranged from 29% for FIB-4 to 64% for NFS (Figure 6). In total, at least one advanced fibrosis algorithm could be calculated for 191 participants. Of these, 22% were classified as high risk, 34% as intermediate risk, and 44% as low risk of advanced fibrosis in at least one algorithm. Agreement between the advanced fibrosis algorithms, among the 132 participants who could be assessed using both algorithms, was 45%.

Among the 132 participants who had undergone diagnostic imaging including the liver, 34 (26%) had signs of steatosis. This finding was documented in the medical record in 18 cases (53%), and in 4 of these, some form of further action had been taken because of suspected steatosis (Figure 7).

To estimate the proportion that would require further assessment in specialist care if algorithms were used for primary care screening, HSI and FIB-4 were combined. Participants at high risk of steatosis according to HSI were further assessed using FIB-4, and those classified as having intermediate to high risk of advanced fibrosis were considered eligible for referral. This approach resulted in 15% of the total number of assessable participants being referred to specialist care, corresponding to 22% of those at high risk of steatosis according to HSI.

Participants classified as having intermediate to high risk of advanced fibrosis by at least one algorithm were compared with those consistently classified as low risk across all algorithms. The intermediate-to-high-risk group had significantly higher weight, waist-to-height ratio, and GGT levels, and higher proportions had hypertension, arrhythmias, angina pectoris, and malignancy. Among women, those with intermediate to high risk had significantly larger waist circumference than those at low risk (Table 4).

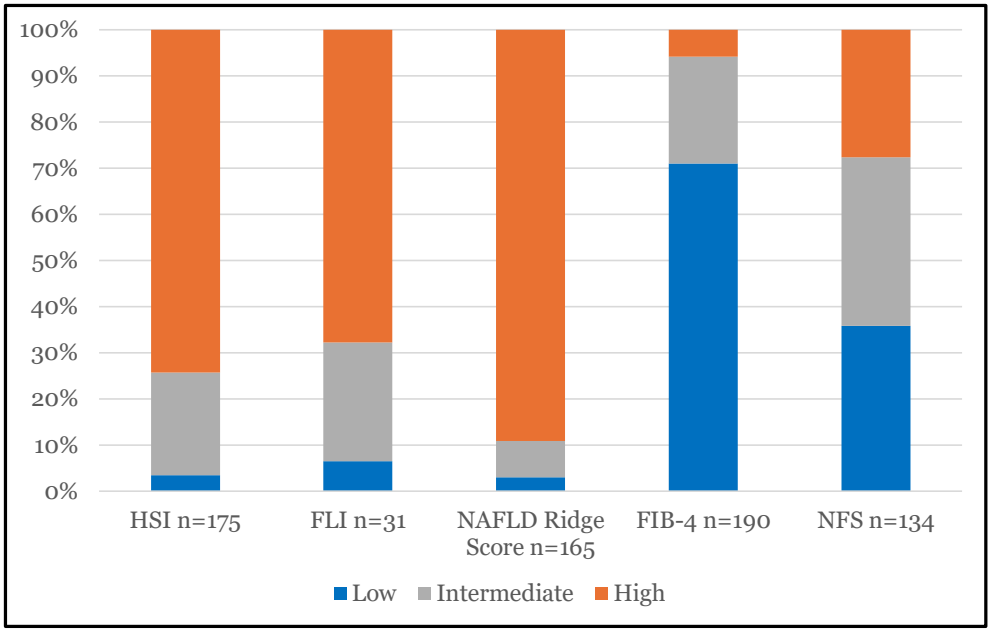


Figure 6: Number of assessable participants and risk category according to steatosis and advanced fibrosis algorithms (HIS, FLI, NAFLD Ridge Score, FIB-4 and NFS). Steatosis algorithm NAFLD-LFS excluded due to low number of assessable participants (n=7)

Abbreviations: FIB-4, Fibrosis 4 Index; FLI, Fatty Liver Index; HSI, Hepatic Steatosis index; NAFLD, Non-alcoholic fatty liver disease; NAFLD-LFS, NAFLD Liver Fat Score; NFS, NAFLD Fibrosis Score.

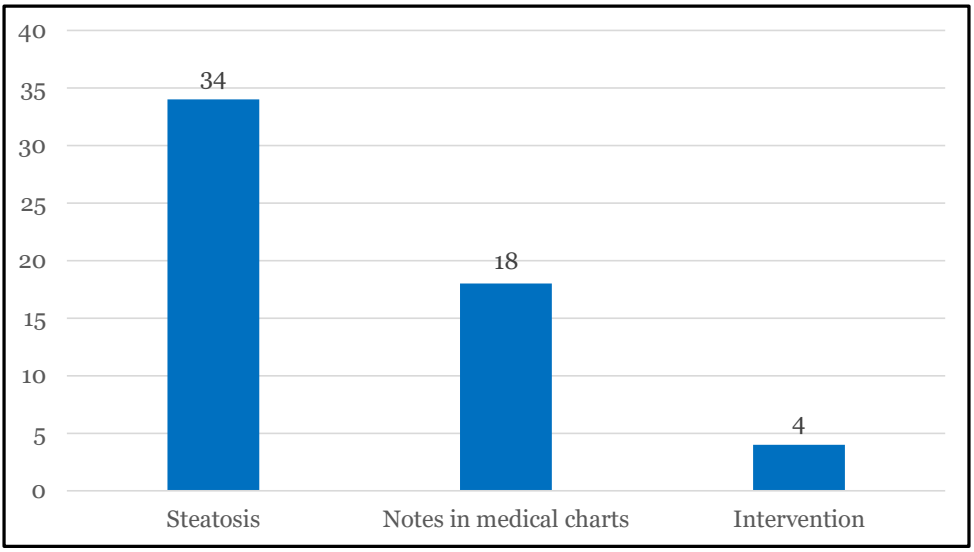


Figure 7: Results of liver imaging and subsequent clinical management among participants with imaging-confirmed steatosis. Overall, 132 participants (38%) had undergone liver imaging, and steatosis was detected in 34 (26%) of assessable participants.

Table 4: Baseline characteristics by fibrosis risk category			
	High/Intermediate	**Low**	***p***
N	106	85	
Age	74 (21)	72 (13)	0.538
Sex (women)	44 (42 %)	39 (46 %)	0.545
Waist circumference (cm)			
- Women	109 (15)	99 (14)	**0.014**
- Men	107 (17)	99 (18)	0.096
Weight (kg)	89 (19.9)	79 (22.2)	**0.022**
Waist-to-height-ratio	0.63 (0.08)	0.58 (0.08)	**0.021**
GGT (µkat/L)	0.85 (0.86)	0.50 (0.62)	**0.002**
Cholesterol (mmol/L)	4.4 (1.3)	3.9 (1.1)	0.628
LDL-Cholesterol (mmol/L)	2.4 (1.0)	2.2 (0.6)	0.613
Triglycerides (mmol/L)	1.5 (0.9)	1.3 (0.8)	0.065
Creatinine (µmol/L)	89 (41)	80 (24)	0.066
Diabetes duration (years)	10 (10)	9 (9)	0.875
Diabetes treatment			
- Nonpharmacological	21 (20%)	10 (12%)	0.134
- Oral antidiabetic	67 (64%)	62 (73%)	0.180
- Insulin	40 (38%)	32 (38%)	0.990
Presence of retinopathy	43 (41%)	30 (35%)	0.384
Hypertension	101 (95%)	63 (74%)	**<0.001**
Heart failure	19 (18%)	8 (9%)	0.093
Cardiac arrhythmia	34 (32%)	12 (14%)	**0.004**
Angina pectoris	26 (25%)	11 (13%)	**0.044**
Malignancy	31 (29%)	14 (16%)	**0.039**

Table 4: Baseline characteristics by fibrosis risk category. Fibrosis risk was assessed using FIB-4 or NFS in all participants with known steatosis or intermediate to high risk for steatosis in algorithms. Continuous variables are presented as median (IQR) and compared using the Mann–Whitney U test. Categorical variables are presented as n (%) and compared using the chi-square test. Significance level $p < 0.05$. Bold values indicate significant differences.

Abbreviations: GGT, gamma-glutamyl transferase; FIB-4, Fibrosis 4 Index; NFS, NAFLD Fibrosis Score; LDL, low-density lipoprotein

Paper II

A total of 308 participants were included in the cohort. In total, 181 (59%) had MASLD, and 7% of the total cohort (11% of those with MASLD) had suspected advanced fibrosis. The median duration of T2D in the entire cohort was 7 years (IQR 10). Overall, 151 participants (49%) had one or more microvascular diabetes complications, 64 (20%) had neuropathy, 60 (19%) had retinopathy of any grade, and 59 (19%) had chronic kidney disease (CKD). Diabetic foot ulcers were uncommon, occurring in 13 participants (4%) (Figure 8).

There were no significant differences in the prevalence of neuropathy, retinopathy, albuminuria, reduced MDRD-estimated GFR, CKD, diabetic foot ulcers, or a composite of all complications when comparing participants without MASLD, those with simple steatosis, and those with advanced fibrosis (Table 5). There were no significant differences in ^{1}H-MRS-PDFF or VCTE-derived LSM between participants with and without one or more microvascular diabetes complications. However, CAP was significantly higher among participants with one or more microvascular diabetes complications than among those without such complications (287 ± 61 vs 272 ± 64; p=0.046). In binary logistic regression, MASLD, defined as simple steatosis or advanced fibrosis, was not associated with the presence of any microvascular diabetes complication. In the same analysis, higher age (aOR 1.05, 95% CI 1.01–1.08) and longer duration of T2D (aOR 1.08, 95% CI 1.03–1.13) were associated with the presence of complications.

In total, 23 participants underwent liver biopsy, of whom 5 had advanced fibrosis. MASH was present in 4 biopsies. Among biopsied participants, Kleiner fibrosis stage differed significantly between those with and without one or more microvascular diabetes complications, with a higher fibrosis stage among participants with complications (median 2.0 [IQR 1] vs 0.5 [IQR 1]; p=0.008). In binary logistic regression analysis, Kleiner fibrosis stage at biopsy was associated with the presence of any microvascular diabetes complication both before and after adjustment for age and sex (aOR 3.68, 95% CI 1.12–12.06). Across all regression analyses, VIF values ranged from 1.003 to 1.360, indicating no evidence of problematic multicollinearity.

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Figure 8: STROBE flow diagram of participants with type 2 diabetes, stratified by MASLD status and prevalent microvascular complications. A total of 308 participants were included in the study, of whom 151 had at least one microvascular complication.

Abbreviations: CAP, controlled attenuation parameter; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; wk, week.

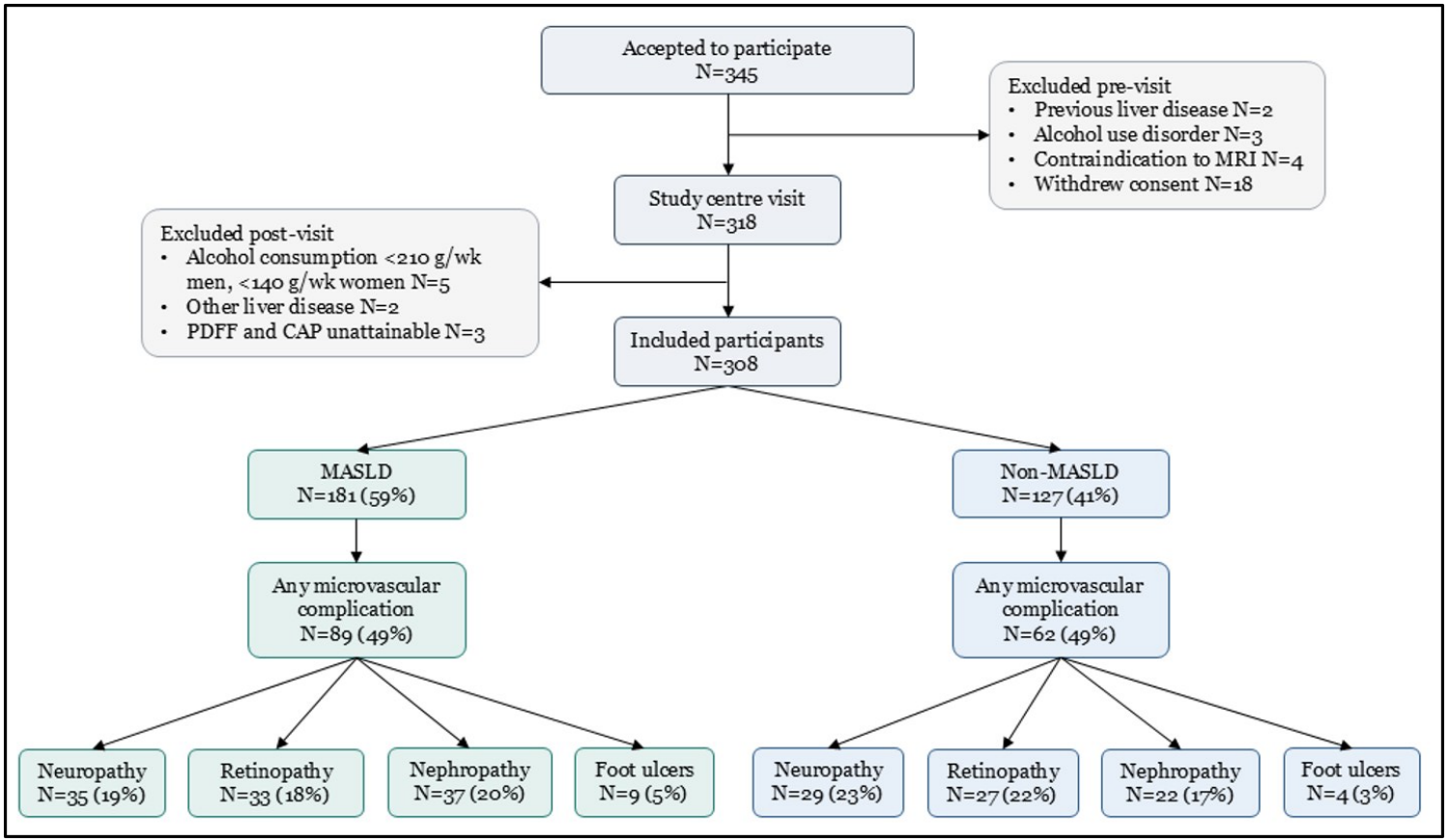

Accepted to participate
N=345
Excluded pre-visit
• Previous liver disease N=2
• Alcohol use disorder N=3
• Contraindication to MRI N=4
• Withdrew consent N=18
Study centre visit
N=318
Excluded post-visit
• Alcohol consumption <210 g/wk men, <140 g/wk women N=5
• Other liver disease N=2
• PDFF and CAP unattainable N=3
Included participants
N=308
MASLD
N=181 (59%)
Non-MASLD
N=127 (41%)
Any microvascular complication
N=89 (49%)
Any microvascular complication
N=62 (49%)
Neuropathy
N=35 (19%)
Retinopathy
N=33 (18%)
Nephropathy
N=37 (20%)
Foot ulcers
N=9 (5%)
Neuropathy
N=29 (23%)
Retinopathy
N=27 (22%)
Nephropathy
N=22 (17%)
Foot ulcers
N=4 (3%)

Table 5: T2D characteristics of participants

	Non-MASLD	Simple steatosis	Advanced fibrosis	*p*
N	127	161	20	
Duration (years)	7 (IQR 3-13)	7 (IQR 3-12)	5 (IQR 2-11)	n.s.
HbA1c (mmol/mol)	48 (IQR 43-54)	50 (IQR 46-58)	51 (IQR 44-59)	**0.021**
Current T2D treatment				
Pharmacological treatment	110 (87%)	133 (83%)	18 (90%)	n.s.
Metformin	93 (73%)	126 (79%)	16 (80%)	n.s.
Pioglitazon	1 (1%)	0 (0%)	0 (0%)	n.s.
DPP4 inhibitors	3 (3%)	2 (1%)	0 (0%)	n.s.
Insulin	23 (19%)	37 (24%)	5 (25%)	n.s.
Sulfonylurea	12 (10%)	14 (9%)	1 (5%)	n.s.
GLP-1 RAs	5 (4%)	13 (8%)	1 (5%)	n.s.
SGLT2 inhibitors	35 (29%)	41 (26%)	10 (50%)	n.s.
Microvascular complications				
Neuropathy	29 (23%)	31 (20%)	4 (20%)	n.s.
Retinopathy	27 (22%)	27 (17%)	6 (32%)	n.s.
Albuminuria	19 (15%)	30 (20%)	4 (20%)	n.s.
MDRD GFR<60	8 (6%)	6 (4%)	2 (10%)	n.s.
Albuminuria or MDRD GFR<60	22 (17%)	31 (20%)	6 (30%)	n.s.
Foot ulcers	4 (3%)	9 (6%)	0 (0%)	n.s.
Any microvascular complication	62 (49%)	76 (48%)	13 (65%)	n.s.

Table 5: Characteristics related to T2D in participants with non-MASLD and MASLD (subdivided into simple steatosis and advanced fibrosis). For categorical variables, data are presented as the number of participants (percentage). For continuous variables, data are presented as median (IQR with interquartile range). Overall *p*-values were calculated to compare differences between groups. For categorical variables, comparisons were made using Fisher's exact test. For continuous variables, the Kruskal–Wallias test was used. Significance level $p < 0.05$. Bold values indicate statistically significant differences.

Abbreviations: DDP4, dipeptidyl peptidase 4; GFR, glomerular filtration rate; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; MASLD, metabolic dysfunction-associated steatotic liver disease; MDRD, modification of diet in renal disease; n.s., not significant; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

Paper III

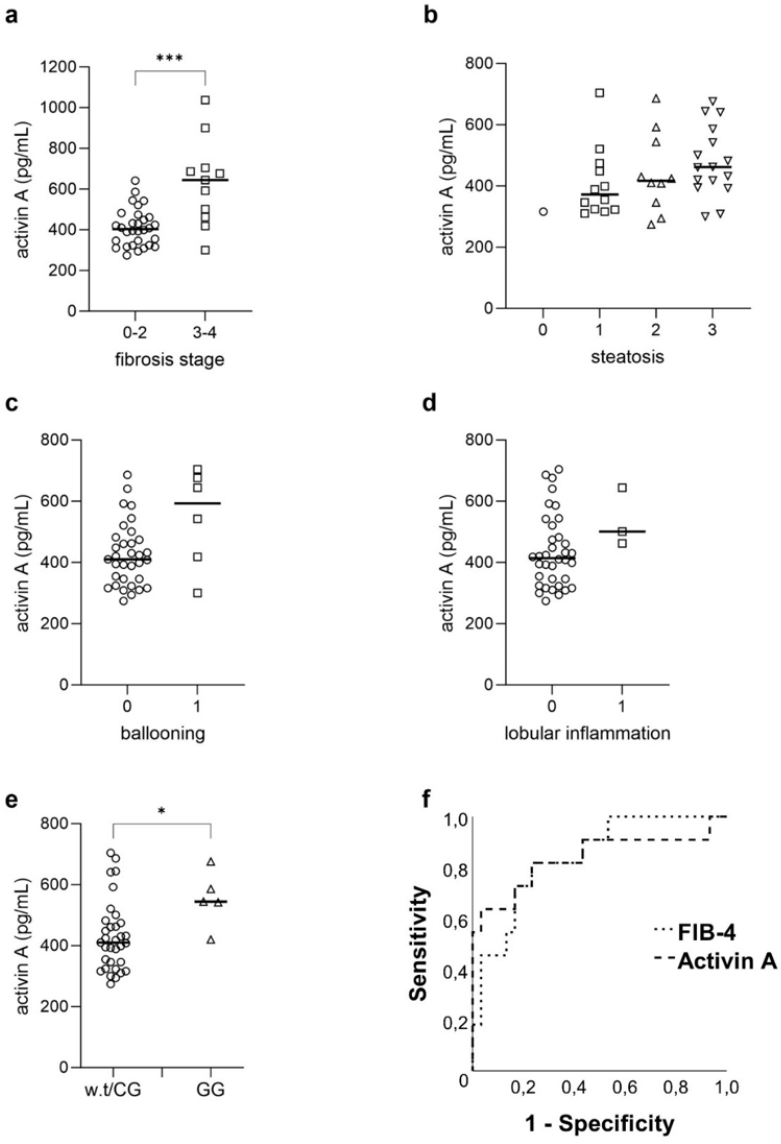
In total, plasma samples from 41 participants with MASLD were analysed. The mean age was 69 years, and the mean BMI was 28.1 kg/m². Seventy-seven per cent of participants were men, and 66% had T2D. Advanced fibrosis was present on liver biopsy in 11 participants (27%). In the analysis of *PNPLA3* alleles, 15 participants were wild type, 18 were heterozygous C/G and five were homozygous G/G. Plasma activin A levels were significantly higher in participants with advanced fibrosis on liver biopsy ($p<0.001$). No significant differences in activin A levels were observed across different grades of steatosis, lobular inflammation or hepatocellular ballooning on liver biopsy. However, activin A levels differed significantly between *PNPLA3* wild type and C/G compared with G/G, with higher levels observed in the G/G group ($p<0.05$) (Figure 9). In univariate and multivariate logistic regression analyses with selected covariates, only activin A level was significantly associated with the presence of advanced fibrosis on liver biopsy, both in crude and adjusted analyses ($p=0.003$) (Table 6). To examine the diagnostic performance of activin A, it was compared with FIB-4 for classification of advanced fibrosis on liver biopsy. The AUROC was 0.836 for activin A and 0.839 for FIB-4, indicating high diagnostic accuracy for both tests (Figure 9).

Table 6: Univariate and multivariate logistic regression analysis. Evaluation of predictors of advanced fibrosis in MASLD.

	Model 1			Model 2		
Variable	**cOR**	**95 % CI**	**p**	**aOR**	**95 % CI**	***p***
Activin A	1.011	1.004-1.019	**0.003**	1.021	1.007-1.035	**0.003**
PNLPA3 (G/G)	0.781	0.076-8.041	0.836	0.120	0.002-8.153	0.324
Gender (male)	0.812	0.168-3.915	0.795	4.903	0.246-97.687	0.298
Age (years)	1.046	0.973-1.125	0.220	0.220	0.801-1.039	0.166
BMI (kg/m²)	0.982	0.841-1.146	0.813	1.214	0.828-1.781	0.321
T2D	1.778	0.391-8.085	0.457	2.438	0.186-30.568	0.504

Table 6: Predictors of advanced fibrosis in MASLD were evaluated using univariate and multivariate logistic regression analyses. Model 1 represents the crude, unadjusted associations, and Model 2 includes adjustment for all variables entered in the univariate analyses. Significance level $p < 0.05$. Bold values indicate significant differences.

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; cOR, crude odds ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; *PNPLA3*, patatin-like phospholipase domain-containing protein 3; T2D, type 2 diabetes; 95 % Cl, 95% confidence interval.


a
activin A (pg/mL)
1200
1000
800
600
400
200
0
***
0-2
3-4
fibrosis stage
b
activin A (pg/mL)
800
600
400
200
0
0
1
2
3
steatosis
c
activin A (pg/mL)
800
600
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200
0
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1
ballooning
d
activin A (pg/mL)
800
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0
0
1
lobular inflammation
e
activin A (pg/mL)
800
600
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*
w.t/CG
GG
f
Sensitivity
1,0
0,8
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0,2
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1 - Specificity
FIB-4
Activin A

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Figure 9: Circulating plasma levels of activin A in participants according to the (a) fibrosis stage, (b) steatosis grade, (c) ballooning grade and (d) lobular inflammation grade. (e) Circulating plasma levels of activin A in participants with *PNPLA3* wild type (w.t) or heterozygote C/G allele compared to participants with the homozygote G/G allele (n = 5). Data are presented as individual values and medians. Between group comparison using Mann-Whitney U-test or Kruskal-Wallis test. (f) ROC curve demonstrating the performance of FIB-4 and activin A in detecting the presence of advanced fibrosis. Activin A AUROC = 0.836 and FIB-4 AUROC = 0.839. Significance level $p < 0.05$.

* for $p < 0.05$, *** for $p < 0.001$.

Abbreviations: Area under the receiver operating characteristic curve, AUROC; FIB-4, Fibosis-4; Patatin-like phospholipase domain-containing protein 3, *PNPLA3*; Receiver operating characteristic, ROC.

Figure originally by Activin A levels in metabolic dysfunction-associated steatotic liver disease associates with fibrosis and the *PNPLA3* I148M variant. Jönsson, C. et al. 2024. *Scandinavian Journal of Gastroenterology*, *59*(6), 737–741. (https://doi.org/10.1080/00365521.2024.2334804). Licensed under CC BY 4.0. (297)

Paper IV

Of the 345 invited participants, 37 were excluded because exclusion criteria emerged or consent was withdrawn (Figure 10). Among the 308 included participants, 114 (37%) were women and the mean age was 63.9 years (± 8.1). The mean duration of T2D was 8.7 years (± 6.8), mean HbA1c was 51.8 mmol/mol (± 11.6), and mean BMI was 29.5 kg/m² (± 4.6). ^{1}H-MRS-PDFF was available for 282 participants, and 154 of these had ^{1}H-MRS-PDFF ≥5%. Twenty-six participants did not undergo ^{1}H-MRS/MRI, and in these cases the presence of steatosis was based on CAP (CAP ≥248 dB/m). Of these, 25 of 26 were classified as having steatosis according to CAP. Two participants had suspected advanced fibrosis according to VCTE (≥10 kPa) in combination with PDFF <5% but were nevertheless assessed as having MASLD. Overall, 181 of 308 participants (59%) were assessed as having MASLD (Table 7).

When participants with and without MASLD were compared, MASLD was clearly associated with obesity and abdominal obesity. Participants with MASLD had significantly higher BMI, a higher prevalence of obesity, larger waist circumference, and higher waist-to-hip ratio. Liver enzyme levels were significantly higher in participants with MASLD than in those without MASLD. Markers of insulin resistance were also significantly higher among participants with MASLD, including fasting glucose, HbA1c, insulin, C-peptide, homeostatic model assessment of insulin resistance (HOMA-IR), and triglycerides (Table 7).

In total, 20 participants (7%) had suspected advanced fibrosis according to VCTE (≥10 kPa). In univariable logistic regression analysis, higher BMI, AST, ALT, GGT, fasting insulin, HOMA-IR, C-peptide and ASAT were associated with suspected advanced fibrosis. In multivariable analysis adjusted for age and sex, all predictors remained significant. However, when additional predictors with $p<0.1$ in univariable analyses were added to the model, after

excluding variables with substantial collinearity, only obesity and AST remained significant predictors of suspected advanced fibrosis. Among participants with MASLD, 11% had suspected advanced fibrosis, and when participants with MASLD and suspected advanced fibrosis were compared with those with simple steatosis, the former group had significantly higher BMI, a higher prevalence of obesity, larger waist circumference, and higher AST and GGT (Table 8).

When body composition data were compared between participants without MASLD, those with MASLD and simple steatosis, and those with MASLD and suspected advanced fibrosis, there were significant differences in ASAT and VAT, with lower volumes in participants without MASLD. Sex-adjusted MFI differed significantly between groups, with higher MFI in participants with MASLD and simple steatosis compared with participants without MASLD. No significant differences were observed in FFMV z-score or the presence of AMC between groups (Table 8).

When cardiac MRI data (n=211) were compared between participants without MASLD, those with MASLD and simple steatosis, and those with MASLD and suspected advanced fibrosis, significant between-group differences were observed in left ventricular (LV) stroke volume index, LV mass index, LV concentricity, and LV end-diastolic volume. Details are shown in Table 8.

Participants with obesity had a significantly higher prevalence of MASLD than those without obesity (81% vs 42%; $p<0.001$), as well as a higher prevalence of MASLD with suspected advanced fibrosis (13% vs 2%; $p<0.001$). MASLD was also significantly more common among participants with overweight than among those with normal weight (22% vs 5%; $p<0.001$) (Figure 11).

PEth values and VCTE-derived LSM were available for 300 participants. Of these, 76% had low or undetectable PEth (<0.05 μmol/L), 20% had moderately elevated PEth (0.05–0.30 μmol/L), and 5% had markedly elevated PEth (>0.30 μmol/L). The proportion of participants with elevated PEth did not differ significantly between those with and without suspected advanced fibrosis.

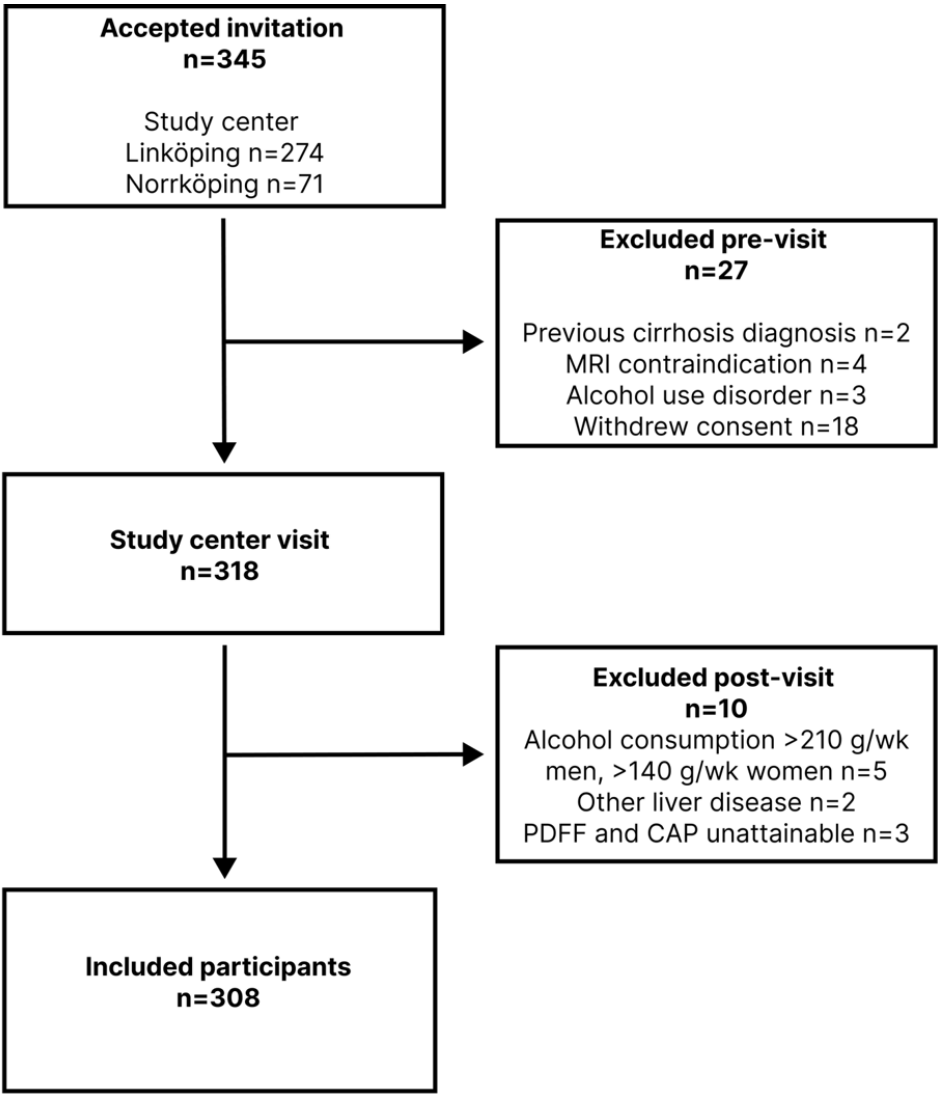

Figure 10: Flow chart of inclusion and exclusion of participants.

Abbreviations: Controlled attenuated parameter, CAP; Magnetic resonance imaging, MRI; Proton density fat fraction, PDFF.

Figure originally by Evaluating the prevalence and severity of metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus in primary care. Balkhed, W. et. 2025. *J Intern Med*. 2025; 298: 173–187. (https://doi.org/10.1111/joim.20103) Licensed under CC BY 4.0.

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Table 7: Characteristics of all included participants and divided into MASLD and non-MASLD. Parameters are expressed as mean (±SD) or n (%). *P*-values are calculated comparing MASLD with non-MASLD groups. Continuous variables were tested using Mann-Whitney U-test and categorical variables using Chi-square test. Significance level $p < 0.05$. Bold values indicate significant differences. a n=299, b n=240 and c n=234.

Table 8: Characteristics of non-MASLD, MASLD with simple steatosis and MASLD with suspected advanced fibrosis. Parameters are presented as mean (±SD) or n (%). Continuous variables were compared using the Kruskal–Wallis test, followed by pairwise comparisons with Mann–Whitney U test. Categorical variables were compared using the chi-square test, with the same test used for pairwise comparisons. Overall *p* value reported. If $p < 0.10$, pairwise comparisons were performed. The significance level was set at $p < 0.05$. Bold values indicate statistically significant differences. a n = 295, b n = 238, c n = 233.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMC, adverse muscle composition; ASAT, abdominal subcutaneous adipose tissue; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; FFMV, fat-free muscle volume; FIB-4, fibrosis-4; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; INR, international normalized ratio; LDL, low-density lipoprotein; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVSV, left ventricular stroke volume; MASLD, metabolic dysfunction-associated steatotic liver disease; MFI, muscle fat infiltration; MRI, magnetic resonance imaging; NFS, NAFLD fibrosis score; PDFF, proton density fat fraction; SD, standard deviation; T2D, type 2 diabetes; VAT, visceral adipose tissue; VCTE, vibration-controlled transient elastography.

Table 7: Characteristics of MASLD and non-MASLD participants				
Parameter	**All**	**Non-MASLD**	**MASLD**	***p***
N	308	127	181	
Demographic and clinical				
Sex (women)	114 (37%)	47 (37%)	67 (37%)	.399
Age (yrs)	63.9 ± 8.1	64.3 ± 7.7	63.5 ± 8.3	.451
Time since T2D diagnosis (yrs)	8.7 ± 6.8	8.8 ± 7.0	8.5 ± 6.7	.839
BMI (kg/m²)	29.5 ± 4.6	27.4 ± 4.1	31.1 ± 4.4	**<.001**
Overweight (25-30 kg/m²)	121 (39%)	60 (48%)	61 (34%)	**.014**
Obesity (≥ 30 kg/m²)	135 (44%)	26 (21%)	109 (60%)	**<.001**
Waist circumference (cm)	105.6 ± 12.6	99.8 ± 11.8	109.7 ± 11.6	**<.001**
Waist to hip ratio	1.0 ± 0.1	0.97 ± 0.08	1.01 ± 0.07	**<.001**
Alcohol (g/w)	28.7 ± 34.1	25.6 ± 29.0	31.0 ± 37.2	.539
Hypertension	202 (66%)	77 (61%)	125 (69%)	.125
Systolic BP (mm Hg)	131.5 ± 15.1	130.8 ± 15.0	131.9 ± 15.2	.378
Diastolic BP (mm Hg)	78.5 ± 10.7	77.3 ± 9.8	79.5 ± 11.3	.099
Manifest CVD	74 (24%)	29 (23%)	45 (25%)	.991
Dyslipidaemia	244 (79%)	103 (81%)	141 (78%)	.495
Metabolic syndrome [a]	276 (92%)	112 (90%)	164 (94%)	.370
Glucose lowering therapy				
Lifestyle modification	30 (10%)	13 (10%)	17 (9%)	.941
Oral medication	213 (69%)	91 (72%)	122 (67%)	.427
Insulin treatment	65 (21%)	23 (18%)	42 (23%)	.281
Combination therapy	120 (39%)	44 (35%)	76 (42%)	.193
Statins	226 (73%)	99 (78%)	127 (70%)	.128
Biochemical				
INR	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	**.007**
Platelet count (10⁹/L)	230.0 ± 56.8	229.6 ± 54.5	230.3 ± 58.5	.892
AST (U/L)	25.3 ± 7.9	23.6 ± 6.5	26.5 ± 8.5	**.004**
ALT (U/L)	29.7 ± 15.7	23.9 ± 8.9	33.8 ± 18.0	**<.001**
GGT (U/L)	37.1 ± 61.3	23.3 ± 22.8	46.8 ± 76.2	**<.001**
Bilirubin (µmol/L)	9.3 ± 4.6	8.6 ± 4.0	9.8 ± 4.9	**.021**
ALP (U/L)	69.6 ± 22.9	68.8 ± 18.3	70.3 ± 25.6	.992
Albumin (g/L)	41.4 ± 4.5	41.6 ± 3.4	41.2 ± 5.1	.850
fP-Glucose (mg/dL)	140.0 ± 32.9	134.0 ± 29.1	144.2 ± 34.6	**.001**
HbA1c (mmol/mol)	51.8 ± 11.6	49.8 ± 10.2	53.3 ± 12.4	**.006**
Creatinine (µmol/L)	74.5 ± 19.6	74.1 ± 22.6	74.8 ± 17.3	.376
Cholesterol (mmol/L)	4.0 ± 1.1	4.0 ± 1.1	4.0 ± 1.1	.701
Triglycerides (mmol/L)	1.5 ± 1.3	1.1 ± 0.5	1.8 ± 1.6	**<.001**
LDL (mmol/L)	2.0 ± 0.8	2.0 ± 0.8	2.0 ± 0.8	.734
HDL (mmol/L)	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	**<.001**
hsCRP (mg/L)	2.5 ± 5.9	1.9 ± 3.6	2.9 ± 7.0	**<.001**
f-Insulin (mIE/L) [b]	16.0 ± 10.4	10.1 ± 5.3	20.4 ± 11.1	**<.001**
f-C-peptide (nmol/L)	1.1 ± 0.5	0.8 ± 0.4	1.2 ± 0.5	**<.001**
HOMA-IR [c]	5.5 ± 4.2	3.2 ± 1.8	7.1 ± 4.6	**<.001**
Hepatic imaging/elastography				
PDFF *n*=282	8.3 ± 7.3	2.5 ± 1.2	12.9 ± 6.8	**<.001**
VCTE *n*=304	6.0 ± 4.0	4.9 ± 1.4	6.8 ± 5.0	**<.001**
≥ 8 kPa	43 (14%)	2 (1.6%)	41 (23%)	
≥ 10 kPa	20 (6.6%)		20 (11%)	
≥ 15 kPa	5 (1.6%)		5 (2.8%)	

Table 8: Characteristics of non-MASLD, MASLD with simple steatosis and MASLD with suspected advanced fibrosis

Parameter	Non-MASLD (1)	MASLD (2) (VCTE < 10kPa)	VCTE (3) (VCTE ≥ 10 kPa)				
N	124	160	20				
Demographic and clinical				***p***	*1vs.2*	*1vs.3*	*2vs.3*
Sex (women)	46 (37%)	61 (38%)	6 (30%)	.778			
Age (years)	64.4 ± 7.6	63.9 ± 7.7	60.8 ± 11.9	.491			
Time since diagnosis (years)	8.7 ± 7.0	8.7 ± 6.6	7.3 ± 7.3	.529			
BMI (kg/m²)	27.3 ± 4.0	30.7 ± 4.0	34.2 ± 5.6	**<.001**	**<.001**	**<.001**	**.004**
Overweight (25-30 kg/m²)	59 (48%)	59 (37%)	2 (10%)	**.003**	.061	**.001**	**.017**
Obesity (≥ 30 kg/m²)	24 (19%)	91 (57%)	17 (85%)	**<.001**	**<.001**	**<.001**	**.015**
Waist circumference (cm)	99.4 ± 11.4	108.7 ± 11.1	117.4 ± 13.4	**<.001**	**<.001**	**<.001**	**.002**
Waist to hip ratio	0.97 ± 0.08	1.01 ± 0.07	1.03 ± 0.08	**<.001**	**<.001**	**.018**	.439
Alcohol (g/w)	25.8 ± 29.2	30.8 ± 35.9	34.1 ± 49.3	.814			
Hypertension	76 (61%)	111 (69%)	13 (65%)	.362			
Systolic BP (mm Hg)	130.7 ± 15.2	131.9 ± 15.3	133.3 ± 13.9	.552			
Diastolic BP (mm Hg)	77.3 ± 9.9	79.0 ± 11.0	83.6 ± 12.5	.095	.195	**.039**	.171
Manifest CVD	27 (22%)	34 (21%)	6 (30%)	.670			
Dyslipidaemia	100 (81%)	125 (78%)	15 (75%)	.791			
Metabolic syndrome [a]	109 (90%)	144 (94%)	19 (95%)	.563			
Glucose lowering therapy							
Lifestyle modification	13 (10%)	17 (11%)	2 (10%)	.996			
Oral medication	89 (72%)	109 (68%)	13 (65%)	.728			
Insulin treatment	22 (18%)	36 (23%)	5 (25%)	.549			
Combination therapy	43 (35%)	65 (41%)	10 (50%)	.338			
Statin treatment	96 (77%)	112 (70%)	14 (70%)	.358			
FIB-4	1.47 ± 0.55	1.37 ± 0.51	1.67 ± 0.82	.072	.146	.147	**.048**
FIB-4 < 1.30	59 (48%)	81 (51%)	6 (30%)	.198			
FIB-4 1.30-2.67	59 (48%)	75 (47%)	13 (65%)	.325			
FIB-4 ≥ 2.67	5 (4%)	2 (1%)	1 (5%)	.280			
NAFLD Fibrosis Score	-0.31 ± 0.89	-0.21 ± 0.94	0.28 ± 1.12	**.043**	.364	**.012**	**.039**
NFS < -1.44	9 (7%)	15 (9%)	1 (5%)	.699			
NFS -1.44-0.672	97 (80%)	117 (74%)	12 (60%)	.148			
NFS ≥ 0.672	16 (13%)	26 (16%)	7 (35%)	**.049**	.438	**.014**	**.044**
Biochemical							
INR	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.1	**.010**	**.004**	.921	.141
Platelet count (10⁹/L)	230.9 ± 54.2	232.7 ± 58.5	212.4 ± 58.2	.403			
AST (U/L)	23.6 ± 6.6	25.5 ± 7.3	34.1 ± 13.1	**<.001**	**.029**	**<.001**	**.008**
ALT (U/L)	23.7 ± 8.7	32.5 ± 16.3	44.0 ± 26.9	**<.001**	**<.001**	**<.001**	.079
GGT (U/L)	23.3 ± 23.1	43.5 ± 64.7	75.1 ± 137.9	**<.001**	**<.001**	**<.001**	**.017**
Bilirubin (µmol/L)	8.7 ± 4.0	9.6 ± 4.8	11.2 ± 6.0	**.048**	**.032**	.089	.415
ALP (U/L)	68.6 ± 18.4	69.9 ± 26.5	74.5 ± 16.2	.205			
Albumin (g/L)	41.7 ± 3.3	41.4 ± 4.4	39.8 ± 9.2	.888			
fP-Glucose (mg/dL)	133.9 ± 29.3	144.6 ± 35.4	144.1 ± 27.1	**.003**	**.001**	.061	.837
HbA1c (mmol/moL)	49.7 ± 10.3	53.3 ± 12.5	52.6 ± 12.3	**.020**	**.005**	.293	.811
Creatinine (µmol/L)	74.6 ± 22.5	74.7 ± 16.8	75.1 ± 22.1	.599			
Cholesterol (mmol/L)	4.0 ± 1.2	4.0 ± 1.0	4.0 ± 1.0	.776			
f-Triglycerides (mmol/l)	1.1 ± 0.5	1.8 ± 1.7	1.6 ± 0.7	**<.001**	**<.001**	**<.001**	.741
LDL (mmol/L)	2.0 ± 0.9	1.9 ± 0.8	2.2 ± 0.9	.585			
HDL (mmol/L)	1.4 ± 0.4	1.3 ± 0.4	1.1 ± 0.3	**<.001**	**<.001**	**<.001**	.103
hsCRP (mg/L)	1.9 ± 3.6	2.7 ± 7.0	4.4 ± 7.8	**<.001**	**<.001**	**<.001**	**.037**
f-Insulin (mIE/L) [b]	10.1 ± 5.4	19.8 ± 9.9	24.7 ± 18.5	**<.001**	**<.001**	**<.001**	.487
f-C-peptide (nmol/)	0.8 ± 0.4	1.2 ± 0.5	1.3 ± 0.5	**<.001**	**<.001**	**<.001**	.402
HOMA-IR [c]	3.3 ± 1.8	6.9 ± 4.2	9.1 ± 7.2	**<.001**	**<.001**	**<.001**	.464
Imaging							
Hepatic (*n*=278)							
PDFF (%)	2.5 ± 1.2	12.9 ± 6.7	13.2 ± 8.3	**<.001**	**<.001**	**<.001**	.925
Body composition (*n*=280)							
ASAT (L)	7.32 ± 3.33	9.00 ± 3.41	11.20 ± 4.98	**<.001**	**<.001**	**.005**	.122
VAT (L)	4.72 ± 2.22	7.20 ± 2.44	7.32 ± 2.34	**<.001**	**<.001**	**<.001**	.670
Sex-adjusted MFI (pp)	-0.82 ± 2.04	-0.21 ± 1.96	-1.01 ± 1.37	**.036**	**.014**	.944	.210
FFMV Z-score (SD)	-0.09 ± 1.09	-0.02 ± 1.02	0.00 ± 1.30	.858			
High MFI	37 (30%)	54 (38%)	4 (31%)	.430			
Low FFMV Z-score	35 (29%)	43 (30%)	6 (46%)	.442			
AMC	14 (12%)	25 (17%)	4 (31%)	.133			
Cardiac MRI (*n*=211)							
LVMi (g/m²)	50.0 ± 9.5	48.3 ± 9.3	44.9 ± 6.3	.079	.162	**.036**	.203
LVEDVi (mL/m²)	71.2 ± 15.5	65.0 ± 13.8	61.2 ± 9.9	**.002**	**.003**	**.014**	.385
LVEF (%)	58.4 ± 7.0	58.4 ± 6.9	60.5 ± 6.2	.424			
LVSVi (mL/m²)	41.2 ± 8.3	37.6 ± 7.0	37.0 ± 7.3	**.008**	**.004**	.107	.678
LV concentricity (g/mL)	0.71 ± 0.09	0.76 ± 0.12	0.74 ± 0.12	**.011**	**.003**	.214	.882

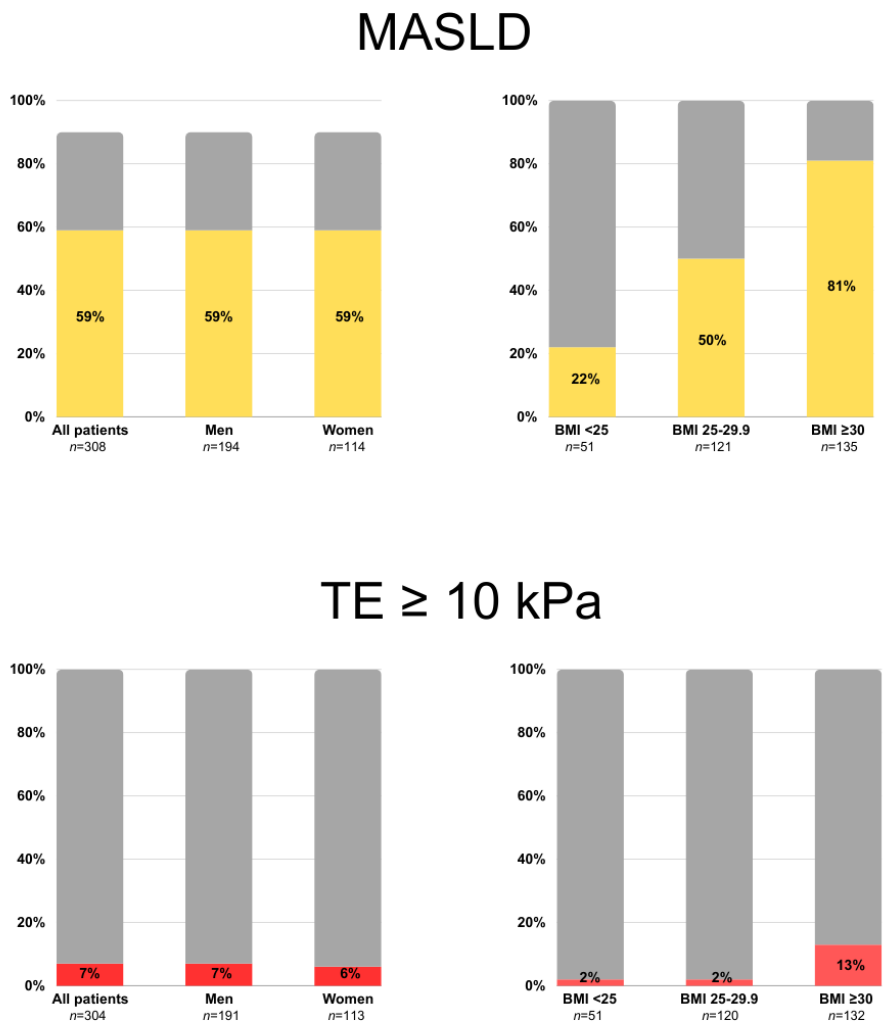

Figure 11: Prevalence of MASLD and suspected advanced fibrosis (TE ≥ 10 kPa) in all participants and by sex, overweight, and obesity status.

Abbreviations: BMI, Body mass index; kPa, kilo Pascal; Transient elastography, TE; MASLD, Metabolic dysfunction-associated steatotic liver disease.

Figure originally by Evaluating the prevalence and severity of metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus in primary care. Balkhed, W. et. 2025. *J Intern Med*. 2025; 298: 173–187. (https://doi.org/10.1111/joim.20103) Licensed under CC BY 4.0.

(250)

Paper V

When a screening and management algorithm for significant fibrosis in SLD was compared with SOC, screening led to an incremental cost of EUR 8,237 and a gain of 0.0643 QALYs per patient over a lifetime horizon. This resulted in an ICER of EUR 128,072/QALY and an NHB of −0.1004 at a cost-effectiveness threshold of EUR 50,000/QALY. This ICER substantially exceeds the usual willingness-to-pay threshold applied by Swedish authorities. However, when ICERs were examined by SLD subtype, considerable heterogeneity was observed. The highest ICER was observed for MASLD, at EUR 157,490/QALY, with an NHB of −0.1213. The ICER for MetALD was EUR 71,975/QALY, with an NHB of −0.0573, and the lowest ICER was observed for ALD, at EUR 5,168/QALY, with a positive NHB of 0.3924 (Table 9).

In the screening strategy, 23% of individuals were treated in specialist care with semaglutide or baclofen, resulting in 8% fewer cases of cirrhosis (143 fewer cases among 28,109 individuals), 17% fewer cases of decompensated cirrhosis (160 fewer cases), and 2% fewer cases of HCC (2 fewer cases). No or only marginal differences were observed in the proportion undergoing liver transplantation or in mortality between the screening and SOC alternatives. The greatest effects of screening and treatment were seen in the ALD subgroup, with reductions of 20% in cirrhosis, 30% in decompensated cirrhosis, and 11% in HCC compared with SOC. Approximately 13% of individuals without SLD received treatment with semaglutide, indicating a substantial false-positive proportion (Table 10).

EPSOMIP data were examined for SLD subtypes defined using previously proposed PEth thresholds (69). Among EPSOMIP participants with complete data on FIB-4, VCTE, PEth, and ^{1}H-MRS-PDFF, the prevalences of MASLD, MetALD, and ALD were 38.7%, 11.0%, and 4.6%, respectively. Compared with the data used in the model, SLD was less common in EPSOMIP (54% vs 67%), and the proportion classified as MetALD or ALD among those with SLD was approximately three times higher. When the screening algorithm was applied to EPSOMIP data, the sensitivity, specificity, PPV, and NPV of FIB-4, for significant fibrosis and cirrhosis as combined outcome, were 52.9%, 77.7%, 24.7%, and 92.3%, respectively.

Results from the one-way sensitivity analyses, expressed as NHB, are shown in Table 11. Across these sensitivity analyses, positive NHB was observed only for ALD.

In the PSA, the distribution of 5,000 simulations was examined. When these simulations were plotted in the cost-effectiveness plane, most fell in the north-eastern quadrant, but at a willingness-to-pay threshold of EUR 50,000/QALY, only 10 of 5,000 simulations fell below the threshold line (Figure 12). When the willingness-to-pay threshold was increased to EUR 100,000/QALY, 1,526 of 5,000 simulations fell below the threshold line. These results suggest that SLD screening is unlikely to be cost-effective at willingness-to-pay thresholds of either EUR 50,000 or EUR 100,000/QALY.

Table 9: Cost-effectiveness outcomes

	n	Δ Costs (mean)	Δ QALY (mean)	ICER	NHB
MASLD	22,492	8,886	0.0564	157,490	-0.1213
MetALD	1,562	9,385	0.1304	71,975	-0.0573
ALD	749	2,262	0.4377	5,168	0.3924
No SLD	3,306	4,630	0.0025	1,862,811	-0.0901
Total	28,109	8,237	0.0643	128,072	-0.1004

Table 9: All results are presented from a lifetime horizon. Outcomes are expressed as mean per patient. Subtype-specific and No SLD outcomes are based on classification at the time of death or simulation end (60 years). Net Health Benefit (NHB) was calculated using a threshold of EUR 50,000. All values mean of 5,000 simulations.

Abbreviations: ALD, Alcohol-associated liver disease; ICER Incremental cost-effectiveness ratio; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, Metabolic dysfunction and alcohol-associated liver disease; NHB, Net health benefit; QALY, Quality-adjusted life years; SLD, Steatotic liver disease.

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Table 10: Clinical outcomes and cost-effectiveness outcomes. All results are presented from a lifetime horizon, except for mortality. All values represent the total count per 28,109 patients except for QALY, costs, NHB and life years which is expressed as mean per patient. Subtype-specific and No SLD outcomes are based on classification at the time of death or simulation end (60 years). NHB was calculated using a threshold of EUR 50,000. All values mean 5,000 simulations.

Abbreviations: ALD, Alcohol-associated liver disease; CC, Compensated cirrhosis; DC, Decompensated cirrhosis; EUR, euro; HCC, Hepatocellular carcinoma; LT, Liver transplantation; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, Metabolic dysfunction and alcohol-associated liver disease; NCT, Non curative treatment; NHB, Net Health Benefit; OCT, Other curative treatment; QALY, Quality adjusted life years; SLD, Steatotic liver disease; SOC, Standard of care.

Table 10: Clinical outcomes and cost-effectiveness outcomes

	SOC					Screening				
	Total	**MASLD**	**MetALD**	**ALD**	**No SLD**	**Total**	**MASLD**	**MetALD**	**ALD**	**No SLD**
Cohort at start (n)	28,109	18,917	1,349	731	7,112	28,109	18,917	1,349	731	7,112
Net change over time (n)	0	3,575	212	18	-3,806	0	3,575	212	18	-3,806
Semaglutide (n)	42	39	3	0	0	6,278	5,452	399	1	425
Baclofen (n)	5	0	3	1	0	668	0	399	249	19
CC (n)	1,846	1,575	143	127	0	1,703	1,464	125	115	0
DC (n)	929	737	78	114	0	766	628	58	80	0
HCC (n)	860	740	67	53	0	843	734	62	47	0
OCT HCC (n)	69	61	5	3	0	78	69	6	4	0
NCT HCC (n)	37	31	3	3	0	35	30	3	3	0
LT (n)	52	43	4	4	0	52	44	4	4	0
5-year mortality (n)	2,566	1,901	146	137	382	2514	1870	139	123	382
10-year mortality (n)	6,668	5,027	384	313	943	6554	4954	369	288	943
20-year mortality (n)	16,212	12,535	921	564	2,191	16,101	12,457	906	546	2,193
30-year mortality (n)	23,161	18,231	1,301	684	2,945	23,106	18,191	1,291	676	2,947
40-year mortality (n)	26,575	21,143	1,485	733	3,214	26,554	21,128	1,479	730	3,217
QALY	11.11	11.33	10.94	7.94	10.43	11.17	11.38	11.07	8.38	10.43
Cost (EUR)	5,862	6,001	5,881	4,967	5,108	14,099	14,888	15,266	7,229	9,738
NHB	10.99	11.21	10.82	7.84	10.32	10.89	11.08	10.76	8.24	10.23
Life years		19.22	18.37	13.75	16.30		19.31	18.61	14.50	16.30

Table 11: One-way sensitivity analysis				
	Total	**MASLD**	**MetALD**	**ALD**
Base case scenario	-0.1004	-0.1213	-0.0573	**0.3924**
First line VCTE	-0.2110	-0.2430	-0.1426	**0.5422**
Fibrosis progression adjustment	-0.1030	-0.1239	-0.0614	**0.3919**
Modified alcohol consumption	-0.0823	-0.1204	-0.0594	**0.3865**
Baclofen 0% abstinence	-0.1148	-0.1215	-0.1172	-0.0179
Baclofen 25% abstinence	-0.1096	-0.1214	-0.0848	**0.1348**
Baclofen 50% abstinence	-0.1036	-0.1191	-0.0732	**0.2766**
Semaglutid regression 0 stages	-0.1209	-0.1454	-0.0870	**0.4098**
Semaglutid regression 2 stages	-0.0778	-0.0936	-0.0301	**0.3928**

Table 11: One-way sensitivity analysis. All results expressed as NHB when comparing screening to a standard of care no screening alternative. Subtype-specific outcomes are based on classification at the time of death or simulation end (60 years). NHB was calculated using a threshold of EUR 50,000. Positive NHB are presented in bold.

Abbreviations: ALD, Alcohol-associated liver disease; MASLD, Metabolic dysfunction-associated steatotic liver disease; MetALD, Metabolic dysfunction and alcohol-associated liver disease; NHB, Net Health Benefit; VCTE, Vibration-controlled transient elastography.

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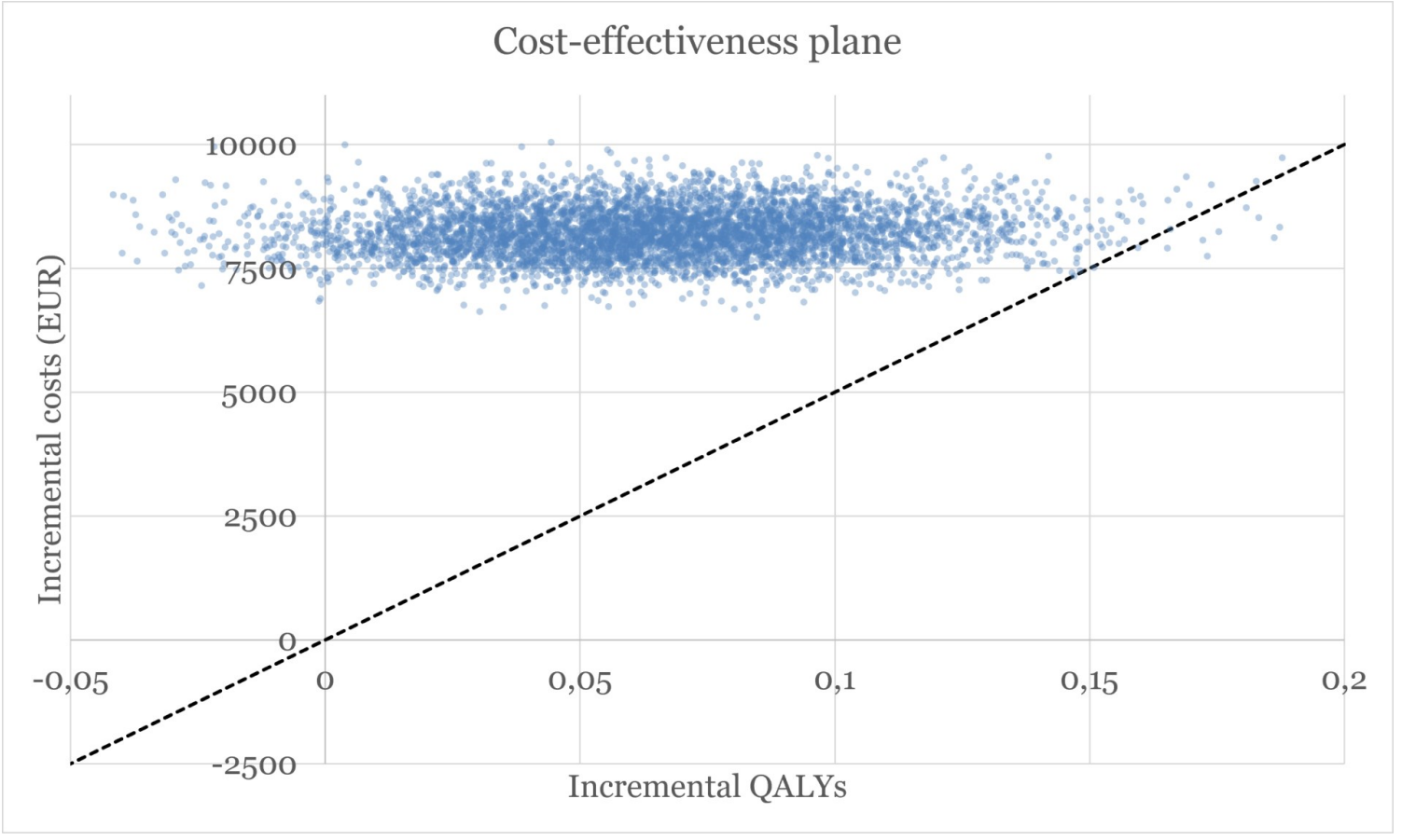
Figure 12: Probabilistic sensitivity analysis. Cost-effectiveness plane plotting incremental costs (vertical axis) against incremental QALYs (horizontal axis) for screening compared to standard of care. Points below the black line (threshold at EUR 50,000/QALY) are likely to be cost-effective.

Abbreviations: EUR, euro; QALY, Quality-adjusted life years.


Cost-effectiveness plane
10000
7500
5000
2500
0
-2500
Incremental costs (EUR)
-0,05
0
0,05
0,1
0,15
0,2
Incremental QALYs

Discussion

Paper I

In Paper I, a very high proportion of participants were classified as having intermediate to high risk of steatosis by the algorithms, which is consistent with previous studies (298). Among participants who had undergone diagnostic imaging, however, steatosis was detected in only 26%, and this was documented in the medical record in only approximately half of cases and resulted in further action in only a few cases. Later studies have shown that steatosis detected by diagnostic imaging rarely results in a MASLD diagnosis in primary care (299). This may indicate low awareness of MASLD in Swedish primary care, although the medical record review covered the period 2008–2019. Low awareness has also been reported in primary care studies from other parts of the world during the same period and later (221, 226-228). Reasons for the under-recognition of MASLD, including in primary care, have been investigated in recent years (223-225).

Among participants assessed with FIB-4, 29% were classified as having intermediate to high risk of advanced fibrosis, which is broadly consistent with previous primary care findings (221, 300). The associations observed in Paper I between advanced fibrosis and cardiac arrhythmias, mainly atrial fibrillation, ischaemic heart disease, and malignancy have also been reported in previous studies (95, 301, 302). In accordance with the 2016 European Association for the Study of the Liver (EASL) guidelines, a combined HSI and FIB-4 algorithm was examined as a screening strategy for MASLD in T2D (135). Of the assessable participants, approximately 15% required further assessment in specialist care for advanced fibrosis, which is consistent with previous studies in which age-adjusted thresholds for FIB-4 have been used (298).

Paper II

In Paper II, 49% of participants had at least one microvascular diabetes complication. The prevalence of individual complications was approximately 20%, except for diabetic foot ulcers, which were present in only 4% of participants. No association was observed between MASLD and these complications, which is consistent with some previous studies (303-305). However, previous studies are heterogeneous, and conflicting results have been reported (120, 306, 307). In Paper II, however, ^{1}H-MRS-PDFF was used to define MASLD. ^{1}H-MRS-PDFF can detect very small amounts of fat, and participants classified as having MASLD may therefore have very mild disease (308). Such a sensitive diagnostic method has not been used in most previous studies, which could explain the discrepancy. However these findings are consistent with those of a previous study that used a similar method to examine the association between MASLD and CKD (305). The observed association between fibrosis stage at biopsy and microvascular complications supports this interpretation.

In Paper II, no difference was observed in the prevalence of complications between participants without MASLD, those with simple steatosis, and those with advanced fibrosis.

Associations between advanced fibrosis and complications have been observed in previous studies (118, 122, 307, 309). However, the prevalences of individual complications and advanced fibrosis were considerably higher in those studies than in Paper II, and one possible explanation for this discrepancy is that our population may have had milder disease.

Paper III

In Paper III, plasma activin A levels were elevated in patients with MASLD and biopsy-confirmed advanced fibrosis compared with those without advanced fibrosis. This is consistent with previous findings (154). However, data are conflicting from studies that excluded patients with cirrhosis, which may have weakened the association (153). Other studies have reported elevated activin A levels in MASH with cirrhosis but have not demonstrated an association in non-cirrhotic MASH (151). Because only 5 of 41 participants in Paper III had cirrhosis, the observed association may have been driven by participants with cirrhosis, which could be investigated in larger studies. The homozygous *PNPLA3* I148M G/G genotype is associated with an increased risk of steatosis and cirrhosis, and in Paper III, significantly higher plasma activin A levels were observed in participants with this genotype than in those with the wild-type or heterozygous genotype, a finding that has not, to our knowledge, been reported previously. Activin A showed promising diagnostic performance, with an AUROC for advanced fibrosis comparable to that of FIB-4.

Paper IV

In Paper IV, 308 primary care participants with T2D were examined, and the prevalence of MASLD was 59%. Participants with MASLD had more cardiometabolic risk factors, with an increased prevalence of obesity and signs of increased insulin resistance. Seven percent of the cohort, or 11% of those with MASLD, had findings suggestive of advanced fibrosis. Only five participants had LSM values suggestive of cirrhosis, and only four participants in total had clinical or histological evidence of cirrhosis or HCC.

The prevalences of MASLD and advanced fibrosis are in line with those reported in previous studies of patients with T2D in primary care (198, 310). However, higher prevalences have been reported in some studies, although less sensitive diagnostic methods were used and participants with MetALD were also included (186, 311). The results also differ substantially from previous biopsy studies from specialist care with respect to the prevalence of advanced fibrosis in MASLD with concomitant T2D, suggesting that findings from specialist-care biopsy cohorts may not be directly applicable to primary care populations (312-314).

Paper IV highlights the importance of obesity as a risk factor for advanced fibrosis, with an eightfold higher risk of advanced fibrosis among participants with obesity. Similar results have been reported in previous studies (107, 310, 311). Further evidence supporting the association between MASLD and obesity was the significantly higher volumes of ASAT and VAT in participants with MASLD compared with participants without MASLD. Although differences in MFI were observed, no significant differences were observed in FFMV or AMC. AMC was

present in 13% of the cohort and in 31% of those with suspected advanced fibrosis, but between-group differences were not statistically significant. The prevalence of AMC in MASLD in this primary care population is consistent with previous general population studies (100).

In Paper IV, participants with MASLD had lower left ventricular end-diastolic volume, higher left ventricular concentricity, and lower left ventricular stroke volume. However, ejection fraction was not significantly lower, and these findings are consistent with previous studies that have shown associations between liver fat and diastolic dysfunction and between MASLD and HFpEF (315, 316).

Paper V

In the study, a screening and management algorithm for patients with T2D in primary care, based on FIB-4 followed by VCTE and possible treatment, was compared with SOC. This resulted in an overall ICER of EUR 128,072/QALY, which does not currently meet conventional Swedish thresholds for cost-effectiveness.

However, there was considerable heterogeneity in the results when the different SLD subtypes were examined separately. The ICER ranged from EUR 157,490/QALY for MASLD to EUR 71,975/QALY for MetALD and EUR 5,168/QALY for ALD. The low cost per QALY for screening and treatment in ALD is interesting not only because it could potentially be cost-effective, but also because few patients with ALD currently receive treatment for AUD (317, 318). However, these findings should be interpreted in light of the fact that the evaluated screening strategy targeted SLD as a whole. The reported subtype-specific ICER for ALD was calculated only among individuals with true ALD and therefore does not capture false-positive findings or other screening-related consequences in the overall screened population.

When compared with previously published studies on screening and treatment of MASLD, there were clear differences in cohort composition and expected treatment effects, which probably explain the discrepancy between our results and previous findings. Younossi et al. studied screening for “high-risk MASLD” and treatment with resmetirom (200). One possible explanation for their lower ICER of USD 26,913/QALY is the higher prevalence of significant fibrosis in their cohort, as well as the assumption that resmetirom would have an effect in all treated individuals, which is not currently supported by studies (31). A similar ICER, USD 14,494/QALY, for screening and treatment of MASLD was reported by Park et al. (202). The treatment in their study was an intensive lifestyle programme with an expected cost of USD 92–183 per year. This appears unreasonably inexpensive compared with other studies, and Park et al. also noted that the programme would be 15 times more expensive in the USA (202, 319). Lazarus et al. evaluated a screening and treatment strategy similar to that assessed in our study and reported an ICER three to four times higher than ours (203).

For ALD, our findings are consistent with previous studies. In particular, Aspahug et al. found that a similar screening and treatment algorithm for ALD in patients with harmful alcohol use was cost-effective, with an ICER of USD 5,387–8,430/QALY (204).

Strengths and limitations

Paper I

A strength of the study is that all participating primary care centres had used the same electronic medical record system for many years, and that medical records, laboratory test results and diagnostic imaging from other clinics within Region Östergötland were also accessible. The medical record review was conducted by several reviewers, which is a limitation, but all reviewers used the same standardised case report form to minimise differences in data collection. Few participants had undergone diagnostic imaging or assessment of LSM, and the estimated prevalence of MASLD and advanced fibrosis is therefore largely based on several algorithms. Combining results from different algorithms may overestimate prevalence. This may also be problematic given the low specificity of algorithms for advanced fibrosis, as these algorithms are intended to be followed by a confirmatory test (140, 241). The appropriateness of using steatosis algorithms in clinical practice has also been questioned, and current European guidelines focus on advanced fibrosis, while steatosis algorithms are not mentioned in the screening context (8).

Participants with sufficient blood test data to calculate the algorithms and available diagnostic imaging were probably sicker than those without such data, introducing potential selection bias. Because liver steatosis was not the primary clinical question in most diagnostic imaging examinations, it may not have been reported by the radiologist even when present.

The study is from 2019 and is based on older medical record notes, in some cases dating back as far as 2008. It is therefore uncertain whether these results reflect current awareness in Swedish primary care in 2026. The limited capacity to manage MASLD in primary care has been recognised globally, and in recent years recommendations adapted to primary care have been published (209, 229, 230). Over time, the number of patients with a recorded MASLD diagnosis has increased in Sweden, which may partly reflect increased awareness of the condition within health care (220). Overall, the clinical landscape for MASLD has changed in recent years, as pharmacological treatment has become available and a potential paradigm shift has been discussed, which is also likely to affect primary care in the long term (219).

A recurring statistical issue in Papers I, II and IV is that multiple tests were performed. Despite this, a significance level of <0.05 was used throughout. This probably contributed to the occurrence of type I errors in the studies. One way to address this would have been to lower the significance level to <0.01 or to use Bonferroni correction.

Paper II

All participants were recruited in Sweden, which may affect generalisability to other health care systems and ethnic groups. In the study, the presence of diabetes complications was based on a retrospective medical record review, which may be associated with limitations related to data quality and missing data. However, most participants had undergone routine retinal photography as part of T2D care in Sweden. The presence of CKD was based on routine assessment of blood and urine samples, which was available for almost all participants because of regular T2D follow-up at their primary care centres. Neuropathy was largely based on clinical signs, and few participants had undergone nerve function testing. Therefore, the

prevalence of neuropathy may have been either overestimated or underestimated. The presence of diabetic foot ulcers was based on medical record notes and diagnosis codes, which may have led to underestimation of prevalence. However, the fact that most participants had undergone regular follow-up by podiatrists and assessment of foot risk within T2D care strengthens the credibility of the data regarding both neuropathy and diabetic foot ulcers.

Few participants had advanced fibrosis in the study, and possible associations between advanced fibrosis and diabetes complications may therefore have been missed because of type II errors. Because this study was an add-on to the main EPSOMIP study, the power calculation in the original study design was based on outcome measures other than diabetes complications (238).

Paper III

In this study, plasma activin A levels were analysed in participants who had undergone liver biopsy to establish the diagnosis of MASLD. We examined how activin A levels varied according to different histopathological findings. Liver biopsy has long been considered the gold standard in MASLD but has lost some of its status in recent years (8). Today, VCTE is considered to provide prognostic information comparable to that obtained from liver biopsy (168). Liver biopsy is an invasive method associated with a risk of complications, is performed in specialist care, and the threshold for performing a biopsy is high (320). In view of this selection, the generalisability of the study may be questioned, as the cohort consisted of participants with chronically elevated liver tests who had undergone liver biopsy.

The study was small, and individual histopathological findings were infrequent. Only one participant had MASH. This entails a risk of type II errors.

Paper IV

A strength of the study is the highly detailed examination that participants underwent, including the ability to detect very small amounts of liver fat. When other modalities, such as US, are used, many individuals with mild steatosis may be missed. Because most previous studies of MASLD in T2D have been conducted in specialist care, the study population, consisting of participants with well-treated T2D, is an important asset, particularly since most patients with T2D are managed in primary care (217). It is uncertain whether previous results are generalisable to the typical patient with T2D in primary care.

In the study, participants were asked to participate either in connection with a routine T2D check-up in primary care or by invitation letter. Given this mode of inclusion, there is a risk of healthy volunteer bias, which may have led to underestimation of disease severity in the primary care population. In VCTE, no repeat examination was performed in participants with elevated values. However, studies have shown that repeated VCTE in the presence of elevated values leads to normalisation in 45% of cases (163). Obesity is also a source of error in VCTE, and the findings in Paper IV regarding an increased prevalence of advanced fibrosis in obesity should therefore be interpreted with caution (174).

Paper V

A strength of Paper V is the use of a complex model that captures most of the SLD spectrum. Previous models have often focused on a single SLD subtype, whereas clinical reality is more complex and patients may transition between subtypes over time (48). However, a complex model requires many parameters to represent this complexity. It may be difficult to identify parameters that reflect the context being studied, and model errors may also be more difficult to detect because of this complexity.

In Paper V, repeated screening for significant fibrosis in SLD was examined. This is consistent with current guidelines, but most previous studies have examined only a single screening episode (8, 200, 202, 203). Repeated screening is important to study because screening strategies are likely to involve recurrent testing rather than a single assessment. At the same time, repeated screening may increase the risk of false-positive results and associated follow-up costs, and it also raises specific challenges in populations that have previously undergone screening.

The main cost driver in Paper V was semaglutide treatment. These costs were based on current Swedish drug prices, which are likely to change over time. The current price of semaglutide does not reflect the actual manufacturing cost, and after patent expiry in Sweden in 2031, substantial price reductions may be expected (321). However, the model does not account for this, and the effect of price reductions on the ICER should be explored in a sensitivity analysis.

In Paper V, FIB-4 was used as the first step in the screening algorithm. However, the diagnostic performance of FIB-4 varies across the SLD spectrum and in the presence of T2D, and false-positive results may occur (78, 209, 274, 293, 294). To examine this further, a sensitivity analysis was performed in which VCTE was used as the first-line screening test instead of FIB-4. However, this did not substantially affect the results.

Earlier data on the natural history of MASLD have recently been called into question, as alcohol consumption is difficult to estimate accurately and objective biomarkers such as PEth have indicated possible misclassification (44, 322). Historically, and still today, SLD subtypes have been defined based on self-reported alcohol consumption (10). The data used to model natural history in Paper V may therefore be questionable. To examine this, a sensitivity analysis was performed in which progression rates were varied by subtype. However, this did not substantially change the results.

Implications for primary care and future research

Paper I

Few cases in which steatosis was noted on diagnostic imaging were documented in the medical record, and even fewer led to any further action. This was interpreted as reflecting low awareness of MASLD or SLD in primary care. The study may have clinical relevance by encouraging general practitioners to pay closer attention to steatosis in radiology reports and, when steatosis is present, to assess possible aetiology and the risk of advanced fibrosis. The

results may also be relevant for health care governance, as they indicate a need for educational initiatives in primary care. In the 2021 article, steatosis algorithms were described as tools that could potentially be used clinically in primary care. However, in recent years the focus in guidelines has shifted towards the presence of advanced fibrosis, and simple steatosis is now regarded as a benign, non-progressive condition in most cases (8, 27). In view of this, these algorithms appear unsuitable for routine clinical use in Swedish primary care but may still be useful in research settings.

Considering that the medical record review covered the period 2008–2019, it would be valuable to repeat this study and examine how steatosis has been managed in primary care in recent years. Given the introduction of pharmacological treatment and the increased focus on MASLD and SLD, a repeated study might provide a different picture. To further explore awareness of MASLD and SLD in primary care, questionnaire studies or qualitative studies among both health care professionals and patients would also be valuable.

Paper II

In Paper II, no associations were observed between MASLD and microvascular diabetes complications. These findings do not support closer monitoring of microvascular complications or different HbA1c targets in patients with T2D and concomitant MASLD. An association was observed between histological fibrosis stage and the presence of complications, but this finding was based on a very small sample. In clinical practice, liver biopsy is used less frequently than before, as NITs often fulfil similar functions. It is therefore unlikely that patients with T2D would undergo liver biopsy to guide follow-up of their T2D.

The number of participants with advanced fibrosis according to VCTE was small, and possible associations should therefore be investigated in larger samples, as type II error cannot be excluded. Diabetic foot ulcers were uncommon in the cohort, and few previous studies have examined their association with MASLD or advanced fibrosis. Further research in populations with a higher prevalence of foot ulcers, such as patients attending primary care wound clinics, could help clarify this potential association (122, 123, 323).

Paper III

In Paper III, increased activin A levels were observed in participants with histologically confirmed advanced fibrosis and in those with the homozygous *PNPLA3* I148M G/G genotype. The study cohort consisted of participants with chronically elevated liver tests who had undergone liver biopsy in specialist care. The appealing aspects of activin A are the potentially low cost of the analysis and the simplicity of the test, characteristics that could make it suitable for use in primary care. It would therefore be valuable to investigate its diagnostic performance in an unselected primary care cohort and to examine how it performs compared with elastography rather than histological findings.

In Paper III, it also remains unclear whether activin A is primarily a marker of advanced fibrosis or cirrhosis. Identifying patients before they develop cirrhosis has prognostic advantages and offers greater opportunities for treatment(209). In view of this, further studies in larger samples with a higher prevalence of advanced disease and of the *PNPLA3* I148M G/G genotype would be valuable. Given the association between activin A and fibrosis development, further experimental mechanistic studies would also be of interest.

Paper IV

Paper IV found that 59% of participants in a primary care cohort with T2D had MASLD, 7% had suspected advanced fibrosis, and cirrhosis was uncommon. This prevalence of advanced disease is considerably lower than that reported in previous studies of the association between MASLD, advanced fibrosis, and T2D. Data from biopsy studies indicating a 40–60% prevalence of advanced fibrosis in MASLD with concomitant T2D do not appear to be applicable to a primary care population (312-314). From a primary care perspective, these findings indicate that advanced fibrosis in MASLD remains relatively uncommon among patients with T2D, although patients with both T2D and obesity warrant particular attention. In resource-limited primary care settings, screening resources may therefore be best focused on this group.

Despite assessment of harmful alcohol use using both questionnaires and a clinical interview, 5% of participants had elevated PEth levels. This may also be important for clinicians, as the combination of T2D, obesity, and harmful alcohol use is likely to substantially increase the risk of progressive liver disease. The results also highlight the importance of conducting research in primary care. For MASLD, and probably also for many other conditions, findings from specialist care studies may not be directly applicable to primary care. The relatively healthy study population is an advantage when illustrating differences between primary and specialist care, but the small number of participants with advanced disease limits the ability to draw firm conclusions about specific associations. In view of this, larger studies are needed to include more patients with advanced disease.

Paper V

In Paper V, the screening and treatment algorithm did not appear to be cost-effective based on current conventional Swedish threshold values. Considering this, further evidence should probably be awaited before systematic screening for significant fibrosis in T2D is introduced in Sweden. If the incremental cost of screening were applied to the entire Swedish T2D population aged 35–75 years, this would entail a lifetime screening cost of EUR 2.3 billion. The algorithm would require approximately 60,000 specialist-care assessments, in addition to the VCTE examinations performed within the screening programme. This raises concerns about whether specialist care would have sufficient capacity to manage the resulting workload (324). One aspect not accounted for in the model is the possibility that patients receiving stable treatment for significant fibrosis, and possibly cirrhosis, could be referred back to primary care (209). This could potentially reduce both resource use and costs. However regardless of where patients are followed up, screening would impose a substantial burden on Swedish health care budgets and resources.

There was a large discrepancy in the ICER depending on SLD subtype. The low ICER in ALD highlights the importance for clinicians of exploring patients' alcohol consumption, providing tailored lifestyle advice, and offering treatment for AUD. However, because the screening strategy in Paper V focused on SLD as a whole, the ICERs for individual subtypes should be interpreted with caution, as noted previously.

Paper V is a late draft but probably not the version that will be submitted to a journal. Examples of likely adjustments before the final version include that 22.1% of individuals in the model will

be treated with semaglutide for the indication T2D, reflecting current Swedish registry data (272). The proportion with cirrhosis among individuals with MASLD appears high compared with data from EPSOMIP and will be adjusted (250). HCC surveillance will be adjusted according to Swedish guidelines (252). Incidental detection of cirrhosis in primary care will be introduced (10). Based on clinical experience, the proportion becoming long-term abstinent after baclofen and brief intervention treatment will be reduced from 70% to 50% (52). New one-way sensitivity analyses will also be performed, including cost adjustment for semaglutide from 2031 onwards (321, 325) and an analysis of the effect of excluding QALY discounting, as this has long been debated (326).

Semaglutide was the main cost driver in the model. However, GLP-1 receptor agonists have effects that extend beyond MASLD. Semaglutide was originally developed for the treatment of T2D but has also shown benefits in obesity and cardiovascular disease and may reduce alcohol consumption (327-329). Future health economic analyses could therefore benefit from a broader perspective that captures effects across SLD, cardiometabolic disease, and alcohol-related outcomes. Such an approach would, however, substantially increase model complexity.

Conclusion

Steatotic liver disease includes the most common chronic liver diseases and affects almost 40% of the global population. This thesis concludes that the subtype MASLD is common in primary care among patients with T2D, but advanced disease is rare (250, 330). Awareness of MASLD has historically been low in Swedish primary care but screening and subsequent treatment for SLD among patients with T2D in primary care are most likely not cost-effective today (331). New biomarkers for advanced disease are under development and focus in the moment from a hepatic standpoint should be on patients with T2D with concomitant obesity and harmful alcohol use (250, 297).

In conclusion:

- The proportion of undiagnosed MASLD cases among patients with T2D has historically been high in primary care
- Awareness of MASLD has historically been low in primary care
- The prevalence of microvascular diabetes complications is probably not higher among patients with T2D and concomitant MASLD compared to patients without MASLD in primary care
- Activin A is a potential biomarker for advanced fibrosis in MASLD
- MASLD is common among patients with T2D in Swedish primary care
- The proportion with severe liver disease among patients with MASLD and concomitant T2D in primary care is low and differs significantly from that among patients in specialist care
- Patients in primary care with T2D and concomitant obesity have an increased prevalence of MASLD, with and without advanced fibrosis, compared to patients without obesity
- A screening and management algorithm for SLD in T2D is probably not cost-effective in Swedish primary care
- Identifying and treating harmful use of alcohol in SLD among patients with T2D may be cost saving in Swedish primary care

References

1. Pearce JM. Thomas Addison (1793-1860). J R Soc Med. 2004;97(6):297–300.
2. Ayonrinde OT. Historical narrative from fatty liver in the nineteenth century to contemporary NAFLD - Reconciling the present with the past. JHEP Rep. 2021;3(3):100261.
3. Geier A, Tiniakos D, Denk H, Trauner M. From the origin of NASH to the future of metabolic fatty liver disease. Gut. 2021;70(8):1570–9.
4. Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006;44(4):865–73.
5. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology. 2005;129(1):113–21.
6. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology. 2005;42(1):44–52.
7. Dai JJ, Zhang YF, Zhang ZH. Global trends and hotspots of treatment for nonalcoholic fatty liver disease: A bibliometric and visualization analysis (2010-2023). World J Gastroenterol. 2023;29(37):5339–60.
8. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024;81(3):492–542.
9. Ho GJK, Tan FXN, Sasikumar NA, Tham EKJ, Ko D, Kim DH, et al. High Global Prevalence of Steatotic Liver Disease and Associated Subtypes: A Meta-analysis. Clin Gastroenterol Hepatol. 2025;23(13):2423–32.e1.
10. Israelsen M, Francque S, Tsochatzis EA, Krag A. Steatotic liver disease. Lancet. 2024;404(10464):1761–78.
11. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023;79(6):1542–56.
12. Younossi ZM, Alqahtani SA, Alswat K, Yilmaz Y, Keklikkiran C, Funuyet-Salas J, et al. Global survey of stigma among physicians and patients with nonalcoholic fatty liver disease. J Hepatol. 2024;80(3):419–30.
13. 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(2):e76–e7.
14. Hagström H, Shang Y, Hegmar H, Nasr P. Natural history and progression of metabolic dysfunction-associated steatotic liver disease. Lancet Gastroenterol Hepatol. 2024;9(10):944–56.
15. Torp N, Israelsen M, Krag A. The steatotic liver disease burden paradox: unravelling the key role of alcohol. Nat Rev Gastroenterol Hepatol. 2025;22(4):281–92.
16. Krag A, Tacke F, Israelsen M, Younossi ZM. Is liver steatosis a disease or the emperor's new clothes? J Hepatol. 2026.
17. 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(4):1335–47.
18. Global burden of metabolic dysfunction-associated steatotic liver disease, 1990-2023, and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2023. Lancet Gastroenterol Hepatol. 2026.
19. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell. 2021;184(10):2537–64.
20. Souza M, Al-Sharif L, Diaz I, Mantovani A, Villela-Nogueira CA. Global Epidemiology and Implications of PNPLA3 I148M Variant in Metabolic Dysfunction-

Associated Steatotic Liver Disease: A Systematic Review and Meta-analysis. J Clin Exp Hepatol. 2025;15(3):102495.
21. Le P, Payne JY, Zhang L, Deshpande A, Rothberg MB, Alkhouri N, et al. Disease State Transition Probabilities Across the Spectrum of NAFLD: A Systematic Review and Meta-Analysis of Paired Biopsy or Imaging Studies. Clin Gastroenterol Hepatol. 2023;21(5):1154–68.
22. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015;13(4):643–54.e1–9; quiz e39–40.
23. Tilg H, Petta S, Stefan N, Targher G. Metabolic Dysfunction-Associated Steatotic Liver Disease in Adults: A Review. Jama. 2026;335(2):163–74.
24. 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(6):1265–73.
25. Pennisi G, Enea M, Romero-Gomez M, Viganò M, Bugianesi E, Wong VW, et al. Liver-related and extrahepatic events in patients with non-alcoholic fatty liver disease: a retrospective competing risks analysis. Aliment Pharmacol Ther. 2022;55(5):604–15.
26. Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology. 2020;158(6):1611–25.e12.
27. Younossi ZM, Krag A, Zelber-Sagi S, Kalligeros M, Arrese M, Diaz LA, et al. Binge drinking, metabolic dysfunction, and the spectrum of steatotic liver disease in the USA: a cross-sectional and longitudinal analysis. Lancet Gastroenterol Hepatol. 2026.
28. Issa G, Shang Y, Strandberg R, Hagström H, Wester A. Cause-specific mortality in 13,099 patients with metabolic dysfunction-associated steatotic liver disease in Sweden. J Hepatol. 2025;83(3):643–51.
29. 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(11):903–13.
30. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015;149(2):367–78.e5; quiz e14–5.
31. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024;390(6):497–509.
32. Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025;392(21):2089–99.
33. Li W, Alazawi W, Loomba R. Current and emerging therapeutic landscape for metabolic dysfunction-associated steatohepatitis. Lancet Gastroenterol Hepatol. 2026;11(2):150–62.
34. Papavramidou N, Fee E, Christopoulou-Aletra H. Jaundice in the Hippocratic Corpus. J Gastrointest Surg. 2007;11(12):1728–31.
35. Robinson K, Shah VH. Alcohol-Related Liver Disease. Clin Liver Dis (Hoboken). 2021;18(Suppl 1):93–106.
36. Seitz HK, Neuman MG. The History of Alcoholic Liver Disease: From an Unrecognized Disease to One of the Most Frequent Diseases in Hepatology. J Clin Med. 2021;10(4).
37. Amonker S, Houshmand A, Hinkson A, Rowe I, Parker R. Prevalence of alcohol-associated liver disease: a systematic review and meta-analysis. Hepatol Commun. 2023;7(5).
38. Mandrekar P, Mandal A. Pathogenesis of Alcohol-Associated Liver Disease. Clin Liver Dis. 2024;28(4):647–61.

39. Galvanin C, Buch S, Nahon P, Trépo E. PNPLA3 in Alcohol-Related Liver Disease. Liver Int. 2025;45(1):e16211.
40. Singal AK, Mehta H, Clemente-Sanchez A, Arab JP, Dunn W, Bataller R. Chapter 28 - Alcohol-associated liver disease⊛. In: Satapathy SK, Mamun Al M, Singh SP, editors. Hepatology: Academic Press; 2025. p. 761–803.
41. Lee BP, Dodge JL, Terrault NA. National prevalence estimates for steatotic liver disease and subclassifications using consensus nomenclature. Hepatology. 2024;79(3):666–73.
42. 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(6):1330–2.e4.
43. Tampaki M, Tsochatzis E, Lekakis V, Cholongitas E. Prevalence, characteristics and outcomes of patients with metabolic and alcohol related/associated liver disease (MetALD): a systematic review and meta-analysis. Metabolism. 2025;163:156101.
44. Krag A, Torp N, Younossi ZM, Israelsen M. Reporting discrepancy of alcohol intake affecting estimated prevalence of MetALD and ALD. Lancet Gastroenterol Hepatol. 2025;10(4):282–4.
45. Lackner C, Spindelboeck W, Haybaeck J, Douschan P, Rainer F, Terracciano L, et al. Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. J Hepatol. 2017;66(3):610–8.
46. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol. 2018;69(1):154–81.
47. Deleuran T, Grønbaek H, Vilstrup H, Jepsen P. Cirrhosis and mortality risks of biopsy-verified alcoholic pure steatosis and steatohepatitis: a nationwide registry-based study. Aliment Pharmacol Ther. 2012;35(11):1336–42.
48. Hansen ED, Torp N, Johansen S, Hansen JK, Bergmann ML, Hansen CD, et al. Quantification of alcohol intake in patients with steatotic liver disease and excessive alcohol intake. JHEP Rep. 2025;7(1):101200.
49. Celsa C, Pennisi G, Tulone A, Ciancimino G, Vaccaro M, Pecorella F, et al. Risk of hepatic and extrahepatic outcomes associated with metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction and alcohol-associated steatotic liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2025;10(11):998–1012.
50. Ochoa-Allemant P, Hubbard RA, Kaplan DE, Serper M. Adverse Liver Outcomes, Cardiovascular Events, and Mortality in Steatotic Liver Disease. JAMA Intern Med. 2025;185(8):986–95.
51. Zhang W, Hwang SY, Luther J. Pharmacotherapy to Prevent Alcohol Relapse in Alcohol-Associated Liver Disease. Curr Gastroenterol Rep. 2025;27(1):74.
52. Lim WH, Tay P, Ng CH, Tan DJH, Ong C, Koh JH, et al. Meta-analysis: Prevalence and impact of alcohol abstinence in alcohol-associated cirrhosis. Aliment Pharmacol Ther. 2024;59(6):730–41.
53. Rogal S, Youk A, Zhang H, Gellad WF, Fine MJ, Good CB, et al. Impact of Alcohol Use Disorder Treatment on Clinical Outcomes Among Patients With Cirrhosis. Hepatology. 2020;71(6):2080–92.
54. Gratacós-Ginès J, Ariño S, Sancho-Bru P, Bataller R, Pose E. MetALD: Clinical aspects, pathophysiology and treatment. JHEP Rep. 2025;7(2):101250.
55. Wagner AC, Jung J, Pacher P, Lohoff FW. Treatment approaches for alcohol use disorder with metabolic dysfunction. Pharmacol Ther. 2026;277:108957.
56. Israelsen M, Torp N, Johansen S, Thiele M, Krag A. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. Lancet Gastroenterol Hepatol. 2023;8(10):866–8.
57. Ayares G, Diaz LA, Idalsoaga F, Alkhouri N, Noureddin M, Bataller R, et al. MetALD: New Perspectives on an Old Overlooked Disease. Liver Int. 2025;45(5):e70017.

58. Arab JP, Díaz LA, Rehm J, Im G, Arrese M, Kamath PS, et al. Metabolic dysfunction and alcohol-related liver disease (MetALD): Position statement by an expert panel on alcohol-related liver disease. J Hepatol. 2024.
59. Anderson P, Wojnar M, Jakubczyk A, Gual A, Reynolds J, Segura L, et al. Managing alcohol problems in general practice in Europe: results from the European ODHIN survey of general practitioners. Alcohol Alcohol. 2014;49(5):531–9.
60. Scholten K, Twohig P, Samson K, Brittan K, Fiedler A, Warner J, et al. You can't handle the truth! Comparing serum phosphatidylethanol to self-reported alcohol intake in chronic liver disease patients. Dig Liver Dis. 2024;56(7):1215–9.
61. Staufer K, Huber-Schönauer U, Strebinger G, Pimingstorfer P, Suesse S, Scherzer TM, et al. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. J Hepatol. 2022;77(4):918–30.
62. Nasr P, Wester A, Ekstedt M, Strandberg R, Kechagias S, Shang Y, et al. Misclassified Alcohol-related Liver Disease is Common in Presumed Metabolic Dysfunction-associated Steatotic Liver Disease and Highly Increases Risk for Future Cirrhosis. Clin Gastroenterol Hepatol. 2024;22(5):1048–57.e2.
63. Israelsen M, Torp N, Johansen S, Hansen CD, Hansen ED, Thorhauge K, et al. Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: an analysis of data from a prospective cohort study. Lancet Gastroenterol Hepatol. 2024;9(3):218–28.
64. Männistö V, Salomaa V, Jula A, Lundqvist A, Männistö S, Perola M, et al. ALT levels, alcohol use, and metabolic risk factors have prognostic relevance for liver-related outcomes in the general population. JHEP Rep. 2024;6(10):101172.
65. Tavaglione F, Amangurbanova M, Yang AH, Tincopa MA, Ajmera V, Richards L, et al. Head-to-Head Comparison Between Phosphatidylethanol Versus Indirect Alcohol Biomarkers for Diagnosis of MetALD Versus MASLD: A Prospective Study. Aliment Pharmacol Ther. 2025.
66. Torp N, Israelsen M, Thiele M, Rinella ME, Krag A. Phosphatidylethanol in steatotic liver disease. J Hepatol. 2025.
67. Feng Q, Manousou P, Izzi-Engbeaya CN, Loomba R, Thursz M, Woodward M. Unveiling the Burden of Steatotic Liver Disease: Mortality Risks by Subtype and Fibrosis Stage in a Nationwide Cohort. Liver Int. 2026;46(2):e70485.
68. Tavaglione F, Díaz LA, Ajmera V, Madamba E, Singh S, Bettencourt R, et al. Clinical utility of phosphatidylethanol to detect underreported alcohol use and enhance steatotic liver disease subclassification. J Hepatol. 2025.
69. Vaz J, Nasr P, Helander A, Shang Y, Wester A, Strandberg R, et al. Phosphatidylethanol levels distinguish steatotic liver disease subgroups and are associated with risk of major liver outcomes. J Hepatol. 2025.
70. Lian LY, Liu WY, Li W, Arab JP, Díaz LA, Loomba R, et al. The challenge of defining metabolic dysfunction and alcohol-associated liver disease. Lancet Gastroenterol Hepatol. 2026.
71. Sedki M, Yang Z, Singal AK, Pessoa MG, Krag A, Schattenberg JM, et al. Longitudinal risk of cirrhosis by steatotic liver disease subtype among 1.5 million individuals in the US. JHEP Rep. 2026;8(3):101680.
72. Johansen S, Åberg F, Tsochatzis EA, Krag A. Screening for advanced steatotic liver disease. Lancet Gastroenterol Hepatol. 2025;10(9):842–54.
73. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005;115(2):209–18.
74. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313–21.
75. Targher G, Valenti L, Byrne CD. Metabolic Dysfunction-Associated Steatotic Liver Disease. N Engl J Med. 2025;393(7):683–98.
76. Kim GA, Jang H, Kim MY, Park JH, Park JG, Cho EY, et al. Multicenter Prospective Cohort Study on Clinical Outcomes and Fibrosis Patterns in Biopsy-Proven Steatotic Liver Disease Subtypes. Gastroenterology. 2026.

77. Rasmussen DN, Thiele M, Johansen S, Kjærgaard M, Lindvig KP, Israelsen M, et al. Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease. J Hepatol. 2021;75(5):1017–25.
78. Torp N, Israelsen M, Johansen S, Semmler G, Dalby Hansen C, Bech KT, et al. MetALD: Diagnosis and Prognosis With Non-Invasive Tests. Aliment Pharmacol Ther. 2025.
79. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. The Lancet. 2021;398(10308):1359–76.
80. Reiberger T. The Value of Liver and Spleen Stiffness for Evaluation of Portal Hypertension in Compensated Cirrhosis. Hepatol Commun. 2022;6(5):950–64.
81. Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology. 2016;150(4):835–53.
82. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76(3):681–93.
83. Chait A, den Hartigh LJ. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. Front Cardiovasc Med. 2020;7:22.
84. Mellergaard M, Askeland A, Rasmussen RW, Cliff KL, Nielsen MH, Eschen RB, et al. Circulating Liver-Derived and CD36(+) Extracellular Vesicles Correlate With Ectopic Liver Fat and Markers of Fibrosis in Metabolic Dysfunction-Associated Steatotic Liver Disease and Decrease During Weight Loss Intervention. J Extracell Vesicles. 2026;15(3):e70257.
85. Bosy-Westphal A, Braun W, Albrecht V, Müller MJ. Determinants of ectopic liver fat in metabolic disease. Eur J Clin Nutr. 2019;73(2):209–14.
86. Khawaja T, Nied M, Wilgor A, Neeland IJ. Impact of Visceral and Hepatic Fat on Cardiometabolic Health. Curr Cardiol Rep. 2024;26(11):1297–307.
87. Liu Y, Zhong G-C, Tan H-Y, Hao F-B, Hu J-J. Nonalcoholic fatty liver disease and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis. Scientific Reports. 2019;9(1):11124.
88. Fu CE, Ng CH, Yong JN, Chan KE, Xiao J, Nah B, et al. A Meta-analysis on Associated Risk of Mortality in Nonalcoholic Fatty Liver Disease. Endocr Pract. 2023;29(1):33–9.
89. Tejani S, McCoy C, Ayers CR, Powell-Wiley TM, Després JP, Linge J, et al. Cardiometabolic Health Outcomes Associated With Discordant Visceral and Liver Fat Phenotypes: Insights From the Dallas Heart Study and UK Biobank. Mayo Clin Proc. 2022;97(2):225–37.
90. Khawaja T, Linge J, Leinhard OD, Al-Kindi SG, Rajagopalan S, Khera A, et al. Coronary artery calcium, hepatic steatosis, and atherosclerotic cardiovascular disease risk in patients with type 2 diabetes mellitus: Results from the Dallas heart study. Prog Cardiovasc Dis. 2023;78:67–73.
91. Henin G, Loumaye A, Leclercq IA, Lanthier N. Myosteatosis: Diagnosis, pathophysiology and consequences in metabolic dysfunction-associated steatotic liver disease. JHEP Rep. 2024;6(2):100963.
92. Xue H, Liu Y, Liu Y, Li H, Liang Q, Ma L, et al. Myosteatosis and the clinical outcomes of patients with liver cirrhosis: A meta-analysis. PLoS One. 2024;19(9):e0310017.
93. Kamiliou A, Lekakis V, Xynos G, Cholongitas E. Prevalence of and Impact on the Outcome of Myosteatosis in Patients with Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Cancers (Basel). 2024;16(5).
94. Capone F, Häseli SP, Liu L, Strocchi S, Langenberg C, Lusis AJ, et al. HFpEF and MASLD: converging mechanisms and clinical implications. Nat Rev Cardiol. 2026.
95. Stahl EP, Dhindsa DS, Lee SK, Sandesara PB, Chalasani NP, Sperling LS. Nonalcoholic Fatty Liver Disease and the Heart: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(8):948–63.

96. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.
97. Tantai X, Liu Y, Yeo YH, Praktiknjo M, Mauro E, Hamaguchi Y, et al. Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. J Hepatol. 2022;76(3):588–99.
98. Kuchay MS, Martínez-Montoro JI, Kaur P, Fernández-García JC, Ramos-Molina B. Non-alcoholic fatty liver disease-related fibrosis and sarcopenia: An altered liver-muscle crosstalk leading to increased mortality risk. Ageing Res Rev. 2022;80:101696.
99. Cespiati A, Meroni M, Lombardi R, Oberti G, Dongiovanni P, Fracanzani AL. Impact of Sarcopenia and Myosteatosis in Non-Cirrhotic Stages of Liver Diseases: Similarities and Differences across Aetiologies and Possible Therapeutic Strategies. Biomedicines. 2022;10(1).
100. Linge J, Nasr P, Sanyal AJ, Dahlqvist Leinhard O, Ekstedt M. Adverse muscle composition is a significant risk factor for all-cause mortality in NAFLD. JHEP Rep. 2023;5(3):100663.
101. for the EpatoSarco working g, Di Cola S, D'Amico G, Caraceni P, Schepis F, Loredana S, et al. Myosteatosis is closely associated with sarcopenia and significantly worse outcomes in patients with cirrhosis. Journal of Hepatology. 2024;81(4):641–50.
102. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. Nat Rev Gastroenterol Hepatol. 2017;14(1):32–42.
103. Ward B, Theodoreson M, Aithal G, Allison M, Brahmania M, Forrest E, et al. Diabetes mellitus in alcohol-associated liver disease: Prevalence and outcomes. Hepatol Commun. 2025;9(8).
104. Steiner JL, Lang CH. Alcohol, Adipose Tissue and Lipid Dysregulation. Biomolecules. 2017;7(1).
105. Björkström K, Franzén S, Eliasson B, Miftaraj M, Gudbjörnsdottir S, Trolle-Lagerros Y, et al. Risk Factors for Severe Liver Disease in Patients With Type 2 Diabetes. Clin Gastroenterol Hepatol. 2019;17(13):2769–75.e4.
106. Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. Hepatology. 2018;67(6):2141–9.
107. Younossi ZM, Golabi P, Price JK, Owrangi S, Gundu-Rao N, Satchi R, et al. The Global Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among Patients With Type 2 Diabetes. Clin Gastroenterol Hepatol. 2024;22(10):1999–2010.e8.
108. Kaya E, Vilar-Gomez E, Vuppalanchi R, Yilmaz Y. Body mass index and diabetes predict severity of liver fibrosis across the spectrum of steatotic liver disease. Ann Hepatol. 2025;30(1):101907.
109. Molzen L, Winther-Jensen M, Madsen LG, Osler M, Jepsen P, Askgaard G. Risk of alcohol-related liver disease and cause-specific mortality in individuals seeking treatment for alcohol use disorder. J Hepatol. 2026;84(2):266–74.
110. Blaney H, Zhang W, Bandhari P, Elfeki M, Xie C, Dunn W, et al. Impact of diabetes and obesity on patient outcomes in alcohol-associated liver disease: Analysis of 3 databases. Dig Liver Dis. 2025;57(12):2390–8.
111. Huang DQ, Wilson LA, Behling C, Kleiner DE, Kowdley KV, Dasarathy S, et al. Fibrosis Progression Rate in Biopsy-Proven Nonalcoholic Fatty Liver Disease Among People With Diabetes Versus People Without Diabetes: A Multicenter Study. Gastroenterology. 2023;165(2):463–72.e5.
112. Israelsen M, Juel HB, Detlefsen S, Madsen BS, Rasmussen DN, Larsen TR, et al. Metabolic and Genetic Risk Factors Are the Strongest Predictors of Severity of Alcohol-Related Liver Fibrosis. Clin Gastroenterol Hepatol. 2022;20(8):1784–94.e9.
113. Whitfield JB, Schwantes-An TH, Darlay R, Aithal GP, Atkinson SR, Bataller R, et al. A genetic risk score and diabetes predict development of alcohol-related cirrhosis in drinkers. J Hepatol. 2022;76(2):275–82.

114. Hagström H, Thiele M, Roelstraete B, Söderling J, Ludvigsson JF. Mortality in biopsy-proven alcohol-related liver disease: a population-based nationwide cohort study of 3453 patients. Gut. 2021;70(1):170–9.
115. Mantovani A, Dalbeni A, Beatrice G, Cappelli D, Gomez-Peralta F. Non-Alcoholic Fatty Liver Disease and Risk of Macro- and Microvascular Complications in Patients with Type 2 Diabetes. J Clin Med. 2022;11(4).
116. Mantovani A, Zaza G, Byrne CD, Lonardo A, Zoppini G, Bonora E, et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: A systematic review and meta-analysis. Metabolism. 2018;79:64–76.
117. Lv WS, Sun RX, Gao YY, Wen JP, Pan RF, Li L, et al. Nonalcoholic fatty liver disease and microvascular complications in type 2 diabetes. World J Gastroenterol. 2013;19(20):3134–42.
118. Mikolasevic I, Rahelic D, Turk-Wensween T, Ruzic A, Domislovic V, Hauser G, et al. Significant liver fibrosis, as assessed by fibroscan, is independently associated with chronic vascular complications of type 2 diabetes: A multicenter study. Diabetes Res Clin Pract. 2021;177:108884.
119. Lombardi R, Airaghi L, Targher G, Serviddio G, Maffi G, Mantovani A, et al. Liver fibrosis by FibroScan(®) independently of established cardiovascular risk parameters associates with macrovascular and microvascular complications in patients with type 2 diabetes. Liver Int. 2020;40(2):347–54.
120. Song D, Li C, Wang Z, Zhao Y, Shen B, Zhao W. Association of non-alcoholic fatty liver disease with diabetic retinopathy in type 2 diabetic patients: A meta-analysis of observational studies. J Diabetes Investig. 2021;12(8):1471–9.
121. Huang J, Li R, Liu N, Yi N, Zheng H, Zhang Q, et al. Liver fibrosis is independently associated with diabetic peripheral neuropathy in type 2 diabetes mellitus. J Diabetes Investig. 2021;12(11):2019–27.
122. de Lédinghen V, Vergniol J, Gonzalez C, Foucher J, Maury E, Chemineau L, et al. Screening for liver fibrosis by using FibroScan(®) and FibroTest in patients with diabetes. Dig Liver Dis. 2012;44(5):413–8.
123. Zhang L, Lin Y, Huang X, Zhai Z, Wei R, Mo J, et al. Metabolic dysfunction-associated fatty liver disease in the elderly with diabetic foot ulcers: A longitudinal cohort study. Int Wound J. 2024;21(4):e14586.
124. Tian G, Kong D, Jiang T, Li L. Complications After Percutaneous Ultrasound-Guided Liver Biopsy: A Systematic Review and Meta-analysis of a Population of More Than 12,000 Patients From 51 Cohort Studies. J Ultrasound Med. 2020.
125. Israelsen M, Rungratanawanich W, Thiele M, Liangpunsakul S. Non-invasive tests for alcohol-associated liver disease. Hepatology. 2024;80(6):1390–407.
126. Loomba R, Lim JK, Patton H, El-Serag HB. AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review. Gastroenterology. 2020;158(6):1822–30.
127. Dyson JK, McPherson S, Anstee QM. Non-alcoholic fatty liver disease: non-invasive investigation and risk stratification. J Clin Pathol. 2013;66(12):1033–45.
128. Feng G, Wong VW, Targher G, Byrne CD, Zheng MH. Non-invasive tests of fibrosis in the management of MASLD: revolutionising diagnosis, progression and regression monitoring. Gut. 2025;74(10):1741–50.
129. Wang L, Wang Y. Non-Invasive Tests for the Detection of MASLD: Biomarkers and Imaging for Staging Steatosis, MASH, and Fibrosis. Int J Gen Med. 2026;19:593387.
130. 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.
131. Kotronen A, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, Johansson LM, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology. 2009;137(3):865–72.
132. Yip TC, Ma AJ, Wong VW, Tse YK, Chan HL, Yuen PC, et al. Laboratory parameter-based machine learning model for excluding non-alcoholic fatty liver disease (NAFLD) in the general population. Aliment Pharmacol Ther. 2017;46(4):447–56.

133. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis. 2010;42(7):503–8.
134. Fedchuk L, Nascimbeni F, Pais R, Charlotte F, Housset C, Ratziu V. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2014;40(10):1209–22.
135. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
136. Chen JL, Duan SJ, Xie S, Yao SK. Diagnostic accuracy of noninvasive steatosis biomarkers with magnetic resonance imaging proton density fat fraction as gold standard. World J Radiol. 2025;17(5):104272.
137. 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(5):1797–835.
138. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25.
139. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010;59(9):1265–9.
140. McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gomez M, Allison M, et al. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. Am J Gastroenterol. 2017;112(5):740–51.
141. Hamelius L, Nordin G, Bjellerup P, Larsson A. Age- and sex-specific reference values for FIB-4 derived from the Nordic Reference Interval Project (NORIP). Scand J Clin Lab Invest. 2025:1–6.
142. Hagström H, Talbäck M, Andreasson A, Walldius G, Hammar N. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. J Hepatol. 2020;73(5):1023–9.
143. van Kleef LA, Pustjens J, Schattenberg JM, Holleboom AG, Castro Cabezas M, Tushuizen ME, et al. Comparison of diagnostic accuracy and utility of non-invasive tests for clinically significant liver disease in a general population with metabolic dysfunction. Hepatology. 2026;83(3):591–602.
144. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75(3):659–89.
145. Kjaergaard M, Lindvig KP, Thorhauge KH, Andersen P, Hansen JK, Kastrup N, et al. Using the ELF test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. J Hepatol. 2023;79(2):277–86.
146. Grady JT, Cyrus JW, Sterling RK. Novel Noninvasive Tests for Liver Fibrosis: Moving Beyond Simple Tests in Metabolic Dysfunction-associated Steatotic Liver Disease. Clin Gastroenterol Hepatol. 2026;24(2):342–54.e2.
147. Rama K, Jahagirdar V, Idalsoaga F, Blaney H, Rhoads SF, Díaz LA, et al. Novel biomarkers for alcohol-associated liver disease and their implications across clinical settings. Clin Mol Hepatol. 2026;32(2):443–63.
148. Kreidl E, Oztürk D, Metzner T, Berger W, Grusch M. Activins and follistatins: Emerging roles in liver physiology and cancer. World J Hepatol. 2009;1(1):17–27.
149. Polyzos SA, Perakakis N, Boutari C, Kountouras J, Ghaly W, Anastasilakis AD, et al. Targeted Analysis of Three Hormonal Systems Identifies Molecules Associated with the Presence and Severity of NAFLD. J Clin Endocrinol Metab. 2020;105(3):e390–400.
150. Cui X, Liu H, Liu Y, Yu Z, Wang D, Wei W, et al. The role and mechanisms of myokines in sarcopenia: new intervention strategies for the challenges of aging. Front Med (Lausanne). 2025;12:1665708.
151. Kiagiadaki F, Kampa M, Voumvouraki A, Castanas E, Kouroumalis E, Notas G. Activin-A causes Hepatic stellate cell activation via the induction of TNFα and TGFβ in Kupffer cells. Biochim Biophys Acta Mol Basis Dis. 2018;1864(3):891–9.

152. Valenzuela-Vallejo L, Chrysafi P, Kouvari M, Guatibonza-Garcia V, Mylonakis SC, Katsarou A, et al. Circulating hormones in biopsy-proven steatotic liver disease and steatohepatitis: A Multicenter Observational Study. Metabolism. 2023;148:155694.
153. Polyzos SA, Kountouras J, Anastasilakis AD, Triantafyllou G, Mantzoros CS. Activin A and follistatin in patients with nonalcoholic fatty liver disease. Metabolism. 2016;65(10):1550–8.
154. Yndestad A, Haukeland JW, Dahl TB, Bjøro K, Gladhaug IP, Berge C, et al. A complex role of activin A in non-alcoholic fatty liver disease. Am J Gastroenterol. 2009;104(9):2196–205.
155. Bakir ASM, Abohalima AS, Ghait RS, Atalla SYB. Role of Activin A as a Novel Marker for Diagnosis and Evaluation of Nonalchoholic Fatty Liver Disease. QJM: An International Journal of Medicine. 2023;116(Supplement_1).
156. Mekala S, Rai R, Reed SL, Bowen B, Michalopoulos GK, Locker J, et al. Antagonizing Activin A/p15(INK4b) Signaling as Therapeutic Strategy for Liver Disease. Cells. 2024;13(7).
157. Liu H, Yerevanian A, Westerhoff M, Hastings MH, Guerra JRB, Zhao M, et al. Roles of Activin A and Gpnmb in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Diabetes. 2024;73(2):260–79.
158. de Lédinghen V, Vergniol J. Transient elastography (FibroScan). Gastroenterol Clin Biol. 2008;32(6 Suppl 1):58–67.
159. Nguyen-Khac E, Chatelain D, Tramier B, Decrombecque C, Robert B, Joly JP, et al. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests. Aliment Pharmacol Ther. 2008;28(10):1188–98.
160. Díaz LA, Tavaglione F, Mittal N, Bettencourt R, Amangurbanova M, Johnson A, et al. Noninvasive pathway for stratifying fibrosis in suspected metabolic dysfunction and alcohol-associated liver disease (MetALD). Hepatol Commun. 2025;9(6).
161. Benedito J, Carcel J, Clemente G, Mulet A. Cheese Maturity Assessment Using Ultrasonics. Journal of Dairy Science. 2000;83(2):248–54.
162. Sirli R, Sporea I, Bota S, Jurchiş A. Factors influencing reliability of liver stiffness measurements using transient elastography (M-probe)-monocentric experience. Eur J Radiol. 2013;82(8):e313–6.
163. Lindfors A, Strandberg R, Hagström H. Screening for advanced liver fibrosis due to metabolic dysfunction-associated steatotic liver disease alongside retina scanning in people with type 2 diabetes: a cross-sectional study. Lancet Gastroenterol Hepatol. 2025;10(2):125–37.
164. Mózes FE, Lee JA, Vali Y, Alzoubi O, Staufer K, Trauner M, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(8):704–13.
165. Bansal MB, Patton H, Morgan TR, Carr RM, Dranoff JA, Allen AM. Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance. Hepatology. 2025.
166. Nguyen-Khac E, Thiele M, Voican C, Nahon P, Moreno C, Boursier J, et al. Non-invasive diagnosis of liver fibrosis in patients with alcohol-related liver disease by transient elastography: an individual patient data meta-analysis. Lancet Gastroenterol Hepatol. 2018;3(9):614–25.
167. Thorhauge KH, Semmler G, Johansen S, Lindvig KP, Kjærgaard M, Hansen JK, et al. Using liver stiffness to predict and monitor the risk of decompensation and mortality in patients with alcohol-related liver disease. J Hepatol. 2024;81(1):23–32.
168. Hagström H. Utredning och handläggning av metabolt associerad steatotisk leversjukdom (MASLD, tidigare NAFLD). Svensk Gastroenterologisk Förening; 2023.
169. Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World J Gastroenterol. 2018;24(30):3361–73.

170. Machado MV, Cortez-Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal. J Hepatol. 2013;58(5):1007–19.
171. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J Hepatol. 2009;51(3):433–45.
172. Zhang S, Mak LY, Yuen MF, Seto WK. Screening strategy for non-alcoholic fatty liver disease. Clin Mol Hepatol. 2023;29(Suppl):S103–s22.
173. Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019;156(5):1264–81.e4.
174. Kechagias S, Ekstedt M, Simonsson C, Nasr P. Non-invasive diagnosis and staging of non-alcoholic fatty liver disease. Hormones (Athens). 2022;21(3):349–68.
175. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol. 2017;66(5):1022–30.
176. Lee YH, Cho Y, Lee BW, Park CY, Lee DH, Cha BS, et al. Nonalcoholic Fatty Liver Disease in Diabetes. Part I: Epidemiology and Diagnosis. Diabetes Metab J. 2019;43(1):31–45.
177. Minhas AS, Oliver R. Magnetic Resonance Imaging Basics. Adv Exp Med Biol. 2022;1380:47–82.
178. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative Assessment of Liver Fat with Magnetic Resonance Imaging and Spectroscopy. J Magn Reson Imaging. 2011;34(4):729–49.
179. Ridgway JP. Cardiovascular magnetic resonance physics for clinicians: part I. J Cardiovasc Magn Reson. 2010;12(1):71.
180. Rashid I, Cruz G, Seiberlich N, Hamilton JI. Cardiac MR Fingerprinting: Overview, Technical Developments, and Applications. J Magn Reson Imaging. 2024;60(5):1753–73.
181. Heiberg E, Sjögren J, Ugander M, Carlsson M, Engblom H, Arheden H. Design and validation of Segment--freely available software for cardiovascular image analysis. BMC Med Imaging. 2010;10:1.
182. Linge J, Borga M, West J, Tuthill T, Miller MR, Dumitriu A, et al. Body Composition Profiling in the UK Biobank Imaging Study. Obesity (Silver Spring). 2018;26(11):1785–95.
183. Wilson JMGJ, G. Principles and practice of screening for disease. World Health Organization; 1968.
184. Dobrow MJ, Hagens V, Chafe R, Sullivan T, Rabeneck L. Consolidated principles for screening based on a systematic review and consensus process. Cmaj. 2018;190(14):E422–e9.
185. van Eekhout KMA, Broekman LD, de Jong VD, Michel M, Grobbee R, Maya-Miles D, et al. Care Pathways for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-of-The-Art Review. Liver Int. 2026;46(4):e70603.
186. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65(8):1359–68.
187. Roulot D, Roudot-Thoraval F, G NK, Kouacou N, Costes JL, Elourimi G, et al. Concomitant screening for liver fibrosis and steatosis in French type 2 diabetic patients using Fibroscan. Liver Int. 2017;37(12):1897–906.
188. Doycheva I, Cui J, Nguyen P, Costa EA, Hooker J, Hofflich H, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment Pharmacol Ther. 2016;43(1):83–95.
189. Mansour D, Grapes A, Herscovitz M, Cassidy P, Vernazza J, Broad A, et al. Embedding assessment of liver fibrosis into routine diabetic review in primary care. JHEP Rep. 2021;3(4):100293.

190. Kjaergaard M, Lindvig KP, Thorhauge KH, Johansen S, Hansen JK, Andersen P, et al. Screening for Fibrosis Promotes Lifestyle Changes: A Prospective Cohort Study in 4796 Individuals. Clin Gastroenterol Hepatol. 2024;22(5):1037–47.e9.
191. Graupera I, Thiele M, Castera L, Pera G, Piano S, Sòria A, et al. Prevalence of liver fibrosis in the general population (the LiverScreen project): a multinational European cohort study. Lancet. 2026;407(10537):1448–58.
192. Ginès P, Juanola A, Mellinger J, Thiele M, Pose E. Population screening for cirrhosis. Hepatology Communications. 2024;8(9).
193. de Jong VD, Alings M, Bruha R, Cortez-Pinto H, Dedoussis GV, Doukas M, et al. Global research initiative for patient screening on MASH (GRIPonMASH) protocol: rationale and design of a prospective multicentre study. BMJ Open. 2025;15(5):e092731.
194. Zhang E, Wartelle-Bladou C, Lepanto L, Lachaine J, Cloutier G, Tang A. Cost-utility analysis of nonalcoholic steatohepatitis screening. Eur Radiol. 2015;25(11):3282–94.
195. Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME. Screening for Nonalcoholic Fatty Liver Disease in Persons with Type 2 Diabetes in the United States Is Cost-effective: A Comprehensive Cost-Utility Analysis. Gastroenterology. 2020.
196. Tanajewski L, Harris R, Harman DJ, Aithal GP, Card TR, Gkountouras G, et al. Economic evaluation of a community-based diagnostic pathway to stratify adults for non-alcoholic fatty liver disease: a Markov model informed by a feasibility study. BMJ Open. 2017;7(6):e015659.
197. Corey KE, Klebanoff MJ, Tramontano AC, Chung RT, Hur C. Screening for Nonalcoholic Steatohepatitis in Individuals with Type 2 Diabetes: A Cost-Effectiveness Analysis. Dig Dis Sci. 2016;61(7):2108–17.
198. Forlano R, Stanic T, Jayawardana S, Mullish BH, Yee M, Mossialos E, et al. A prospective study on the prevalence of MASLD in people with type-2 diabetes in the community. Cost effectiveness of screening strategies. Liver Int. 2024;44(1):61–71.
199. Younossi ZM, Paik JM, Henry L, Pollock RF, Stepanova M, Nader F. Economic evaluation of non-invasive test pathways for high-risk metabolic dysfunction-associated steatotic liver disease (MASLD) in the United Kingdom (UK). Ann Hepatol. 2025:101789.
200. Younossi Z, Paik J, Henry L, Stepanova M, Nader F. Pharmaco-Economic Assessment of Screening Strategies for High-Risk MASLD in Primary Care. Liver International. 2024.
201. Gruneau L, Kechagias S, Sandström P, Ekstedt M, Henriksson M. Cost-effectiveness analysis of noninvasive tests to identify advanced fibrosis in non-alcoholic fatty liver disease. Hepatol Commun. 2023;7(7).
202. Park H, Yoon EL, Kim M, Kwon SH, Kim D, Cheung R, et al. Cost-effectiveness study of FIB-4 followed by transient elastography screening strategy for advanced hepatic fibrosis in a NAFLD at-risk population. Liver Int. 2024;44(4):944–54.
203. Lazarus JV, Agirre-Garrido L, Díaz LA, Danpanichkul P, Kivuyo SL, Kondili LA, et al. Cost-Effectiveness of MASH Diagnosis and Management Approaches Among Those With Type 2 Diabetes. JAMA Netw Open. 2025;8(11):e2542750.
204. Asphaug L, Thiele M, Krag A, Melberg HO. Cost-Effectiveness of Noninvasive Screening for Alcohol-Related Liver Fibrosis. Hepatology. 2020;71(6):2093–104.
205. Vidal-Trécan T, Julla JB, El Khoury T, Venteclef N, Riveline JP, Paradis V, et al. Effectiveness of Six International Guidelines Using Fibrosis-4 and FibroScan for Risk Stratification of Metabolic Dysfunction-associated Steatotic Liver Disease in Type 2 Diabetes. Clin Gastroenterol Hepatol. 2025;23(12):2176–86.e2.
206. Lazarus JV, Agirre-Garrido L, Miralles-Sanchez JE, Manolas MI, Tacke F, Villela-Nogueira CA, et al. Cost of Metabolic Dysfunction-Associated Steatotic Liver Disease Screening Among All People Living With Diabetes in Six Countries. Liver Int. 2025;45(12):e70390.
207. Schattenberg JM, Anstee QM, Caussy C, Bugianesi E, Popovic B. Differences between current clinical guidelines for screening, diagnosis and management of nonalcoholic fatty liver disease and real-world practice: a targeted literature review. Expert Rev Gastroenterol Hepatol. 2021;15(11):1253–66.

208. Lazarus JV, Palayew A, Carrieri P, Ekstedt M, Marchesini G, Novak K, et al. European NAFLD Preparedness Index - Is Europe ready to meet the challenge of fatty liver disease? JHEP Reports. 2021;3(2).
209. Jarvis H, Brennan PN, Casanovas T, Casler K, Desai M, Evans PH, et al. The role of primary care in response to the global liver disease syndemic: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2026;11(9):821–62.
210. Nationella riktlinjer för diabetesvård. Socialstyrelsen; 2018.
211. Typ 2-diabetes - riktlinje för primärvården. Region Skåne; 2026.
212. Diabetes vårdprogram. Region Östergötland; 2025.
213. Diabetes typ 2 hos vuxna – behandling och uppföljning. Region Stockholm; 2026.
214. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S52–s76.
215. Kim SH, Hui G, Pike CW, Jackson ML, Levine M, Kwo P. Screening for Metabolic Dysfunction-Associated Steatotic Liver Disease in Patients With Type 2 Diabetes: Are We Doing Enough? Diabetes Spectr. 2025;38(4):496–501.
216. Socialdepartementet. Hälso- och sjukvårdslag (2017:30). 2026.
217. En Li Cho E, Ang CZ, Quek J, Fu CE, Lim LKE, Heng ZEQ, et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. Gut. 2023;72(11):2138–48.
218. Paik JM, Hobbs K, Gupta A, Alkalbani RJ, Reyes MA, Younossi ZM. Prevalence of MASLD, Met-ALD, and ALD and Associated Fibrosis Among US Adults: Insights From NHANES 2017 to 2023. J Clin Gastroenterol. 2025.
219. Lazarus JV, Brennan PN, Mark HE, Alazawi W, Allen AM, Byrne CD, et al. A call for doubling the diagnostic rate of at-risk metabolic dysfunction-associated steatohepatitis. Lancet Reg Health Eur. 2025;54:101320.
220. Nasr P, von Seth E, Mayerhofer R, Ndegwa N, Ludvigsson JF, Hagström H. Incidence, prevalence and mortality of chronic liver diseases in Sweden between 2005 and 2019. Eur J Epidemiol. 2023;38(9):973–84.
221. Alexander M, Loomis AK, Fairburn-Beech J, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, et al. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. BMC Med. 2018;16(1):130.
222. Allen AM, Kim WR, Carrieri P, Canning R, Ou FS, Benson J, et al. Population perspectives on benefits and harms of screening for metabolic dysfunction-associated steatotic liver disease. Hepatology. 2026;83(2):362–73.
223. Gracen L, Hayward KL, Aikebuse M, Williams S, Russell A, O'Beirne J, et al. An exploration of barriers and facilitators to implementing a nonalcoholic fatty liver disease pathway for people with type 2 diabetes in primary care. Diabet Med. 2022;39(6):e14799.
224. Hallsworth K, Dombrowski SU, McPherson S, Anstee QM, Avery L. Using the theoretical domains framework to identify barriers and enabling factors to implementation of guidance for the diagnosis and management of nonalcoholic fatty liver disease: a qualitative study. Translational Behavioral Medicine. 2020;10(4):1016–30.
225. Castera L, Alazawi W, Bugianesi E, Caussy C, Federici M, Romero-Gómez M, et al. A European Survey to Identify Challenges in the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease. Liver Int. 2025;45(2):e16224.
226. Islam KB, Brandman D, Chu JN, Goldman ML, Fox RK. Primary Care Providers and Nonalcoholic Fatty Liver Disease: A Needs Assessment Survey. Dig Dis Sci. 2023;68(2):434–8.
227. Patel PJ, Banh X, Horsfall LU, Hayward KL, Hossain F, Johnson T, et al. Underappreciation of non-alcoholic fatty liver disease by primary care clinicians: limited awareness of surrogate markers of fibrosis. Intern Med J. 2018;48(2):144–51.
228. van Asten M, Verhaegh P, Koek G, Verbeek J. The increasing burden of NAFLD fibrosis in the general population: Time to bridge the gap between hepatologists and primary care. Hepatology. 2017;65(3):1078.

229. Lionis C, Papadakis S, Anastasaki M, Aligizakis E, Anastasiou F, Francque S, et al. Practice Recommendations for the Management of MASLD in Primary Care: Consensus Results. Diseases. 2024;12(8).
230. Allen AM, Charlton M, Cusi K, Harrison SA, Kowdley KV, Noureddin M, et al. Guideline-based management of metabolic dysfunction-associated steatotic liver disease in the primary care setting. Postgrad Med. 2024;136(3):229–45.
231. Qadri S, Yki-Järvinen H. Surveillance of the liver in type 2 diabetes: important but unfeasible? Diabetologia. 2024;67(6):961–73.
232. Etiska principer för prioritering. Socialstyrelsen; 2026.
233. Briggs AC, K. Sculoher, M. Decision Modelling for Health Economic Evaluation: Oxford University Press; 2006.
234. Utvärdering av insatser i hälso- och sjukvården och socialtjänsten. Statens beredning för medicinsk och social utvärdering; 2025.
235. Drummond ME, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes: Oxford University Press; 2005 31 Oct 2023.
236. Praktiska förutsättningar för stärkt tillgång till läkemedel vid sällsynta hälsotillstånd.: Tandvårds- och Läkemedelsförmånsverket; 2024.
237. Rutter CM, Zaslavsky AM, Feuer EJ. Dynamic microsimulation models for health outcomes: a review. Med Decis Making. 2011;31(1):10–8.
238. Nasr P, Iredahl F, Dahlström N, Rådholm K, Henriksson P, Cedersund G, et al. Evaluating the prevalence and severity of NAFLD in primary care: the EPSONIP study protocol. BMC Gastroenterol. 2021;21(1):180.
239. Bergman H, Källmén H. Alcohol use among Swedes and a psychometric evaluation of the alcohol use disorders identification test. Alcohol Alcohol. 2002;37(3):245–51.
240. Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res. 2007;31(7):1208–17.
241. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846–54.
242. McPherson S, Jarvis H, McGonigle J, Bedlington J, Dean J, Hallsworth K, et al. Stratification Of LIver Disease (SOLID): protocol for a prospective observational cohort study to determine the optimum biomarker strategies for the detection of advanced liver disease at the primary-secondary care interface. BMJ Open Gastroenterol. 2023;10(1).
243. Negoita F, Blomdahl J, Wasserstrom S, Winberg ME, Osmark P, Larsson S, et al. PNPLA3 variant M148 causes resistance to starvation-mediated lipid droplet autophagy in human hepatocytes. Journal of Cellular Biochemistry. 2019;120(1):343–56.
244. Stefan D, Cesare FD, Andrasescu A, Popa E, Lazariev A, Vescovo E, et al. Quantitation of magnetic resonance spectroscopy signals: the jMRUI software package. Measurement Science and Technology. 2009;20(10):104035.
245. Vanhamme L, van den Boogaart A, Van Huffel S. Improved Method for Accurate and Efficient Quantification of MRS Data with Use of Prior Knowledge. Journal of Magnetic Resonance. 1997;129(1):35–43.
246. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317(17):1098.
247. Bedossa P. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology. 2014;60(2):565–75.
248. Alqahtani SA, Schattenberg JM. NAFLD in the Elderly. Clin Interv Aging. 2021;16:1633–49.
249. Caussy C, Vergès B, Leleu D, Duvillard L, Subtil F, Abichou-Klich A, et al. Screening for Metabolic Dysfunction-Associated Steatotic Liver Disease-Related Advanced Fibrosis in Diabetology: A Prospective Multicenter Study. Diabetes Care. 2025.

250. Balkhed W, Bergram M, Iredahl F, Holmberg M, Edin C, Carlhäll CJ, et al. Evaluating the prevalence and severity of metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus in primary care. J Intern Med. 2025.
251. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007;370(9603):1915–22.
252. Stål P. Nationellt vårdprogram för levercirros. Nationellt system för kunskapsstyrning Hälso- och sjukvård; 2022.
253. Engstrand J, Stål P, Gilg S, Jansson A, Strömberg C. Hepatocellular carcinoma in cirrhotic versus non-cirrhotic liver: Treatment and survival differences in a nationwide cohort. Scand J Surg. 2024;113(2):120–30.
254. Levercellscancer - Nationellt vårdprogram version 4.0. Regionala cancercentrum; 2024.
255. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78(6):1922–65.
256. Bzeizi KI, Abdullah M, Vidyasagar K, Alqahthani SA, Broering D. Hepatocellular Carcinoma Recurrence and Mortality Rate Post Liver Transplantation: Meta-Analysis and Systematic Review of Real-World Evidence. Cancers (Basel). 2022;14(20).
257. Toubert C, Guiu B, Al Taweel B, Assenat E, Panaro F, Souche FR, et al. Prolonged Survival after Recurrence in HCC Resected Patients Using Repeated Curative Therapies: Never Give Up! Cancers (Basel). 2022;15(1).
258. Baganate F, Beal EW, Tumin D, Azoulay D, Mumtaz K, Black SM, et al. Early mortality after liver transplantation: Defining the course and the cause. Surgery. 2018;164(4):694–704.
259. Nationellt vårdprogram för Levertransplantation. Svensk Gastroenterologisk Förening,; 2023.
260. Hernández-Évole H, Jiménez-Esquivel N, Pose E, Bataller R. Alcohol-associated liver disease: Epidemiology and management. Ann Hepatol. 2024;29(1):101162.
261. Allmänna riktlinjer för subvention och prissättning av läkemedel.: Tandvård- och Läkemedelsförmånsverket; 2026.
262. Yang AH, Tincopa MA, Tavaglione F, Ajmera VH, Richards LM, Amangurbanova M, et al. Prevalence of steatotic liver disease, advanced fibrosis and cirrhosis among community-dwelling overweight and obese individuals in the USA. Gut. 2024;73(12):2045–53.
263. Hagström H, Hegmar H, Moreno C. Interactions between the metabolic syndrome and alcohol consumption increases the risk of liver disease. United European Gastroenterol J. 2024;12(2):168–76.
264. Parker R, Aithal GP, Becker U, Gleeson D, Masson S, Wyatt JI, et al. Natural history of histologically proven alcohol-related liver disease: A systematic review. J Hepatol. 2019;71(3):586–93.
265. Kositamongkol C, Tantiyavarong P, Ratanatawan A, Sripongpun P, Mahawithitwong P, Kositamongkol P, et al. Cost-effectiveness of transient elastography for liver fibrosis screening in Thai patients with diabetes mellitus. World J Gastroenterol. 2025;31(32):110333.
266. Marti-Aguado D, Calleja JL, Vilar-Gomez E, Iruzubieta P, Rodríguez-Duque JC, Del Barrio M, et al. Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease. J Hepatol. 2024;81(6):930–40.
267. Gal P, Feldmajer G, Augusto M, Gani R, Hook E, Bullement A, et al. De Novo Cost-Effectiveness Model Framework for Nonalcoholic Steatohepatitis-Modeling Approach and Validation. Pharmacoeconomics. 2023;41(12):1629–39.
268. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020;115(10):1642–9.

269. Mehta N, Sarkar M, Dodge JL, Fidelman N, Roberts JP, Yao FY. Intention to treat outcome of T1 hepatocellular carcinoma with the "wait and not ablate" approach until meeting T2 criteria for liver transplant listing. Liver Transpl. 2016;22(2):178–87.
270. Five-Year Life Expectancy Table for the Whole Country by Sex and Age, Year 2020-2024. Statistics Sweden; 2026.
271. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, et al. Excess Mortality among Persons with Type 2 Diabetes. N Engl J Med. 2015;373(18):1720–32.
272. Eeg-Olofsson K, Åkesson K, Thoren A, Nyden A, Hermansson Carter V, Linder E. Nationella Diabetesregistret - ÅRSRAPPORT 2024 ÅRS RESULTAT. Nationella diabetesregistret; 2025.
273. 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(5):1547–54.
274. Wilson MP, Singh R, Mehta S, Murad MH, Fung C, Low G. Comparing FIB-4, VCTE, pSWE, 2D-SWE, and MRE Thresholds and Diagnostic Accuracies for Detecting Hepatic Fibrosis in Patients with MASLD: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2025;15(13).
275. Oh JH, Ahn SB, Cho S, Nah EH, Yoon EL, Jun DW. Diagnostic performance of non-invasive tests in patients with MetALD in a health check-up cohort. J Hepatol. 2024;81(5):772–80.
276. Duarte-Rojo A, Taouli B, Leung DH, Levine D, Nayfeh T, Hasan B, et al. Imaging-based noninvasive liver disease assessment for staging liver fibrosis in chronic liver disease: A systematic review supporting the AASLD Practice Guideline. Hepatology. 2025;81(2):725–48.
277. Papatheodoridi M, Hiriart JB, Lupsor-Platon M, Bronte F, Boursier J, Elshaarawy O, et al. Refining the Baveno VI elastography criteria for the definition of compensated advanced chronic liver disease. J Hepatol. 2021;74(5):1109–16.
278. Singal AG, Haaland B, Parikh ND, Ozbay AB, Kirshner C, Chakankar S, et al. Comparison of a multitarget blood test to ultrasound and alpha-fetoprotein for hepatocellular carcinoma surveillance: Results of a network meta-analysis. Hepatol Commun. 2022;6(10):2925–36.
279. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med. 2021;384(12):1113–24.
280. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016;387(10019):679–90.
281. Roerecke M, Vafaei A, Hasan OSM, Chrystoja BR, Cruz M, Lee R, et al. Alcohol Consumption and Risk of Liver Cirrhosis: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2019;114(10):1574–86.
282. Henriksson M, Björnsson B, Sternby Eilard M, Lindell G, Strömberg C, Hemmingsson O, et al. Treatment patterns and survival in patients with hepatocellular carcinoma in the Swedish national registry SweLiv. BJS Open. 2020;4(1):109–17.
283. Priser och ersättningar för Sydöstra sjukvårdsregionen 2026. Sydöstra sjukvårdsregionen; 2025.
284. Prislista 2025-2026 Röntgen Östergötland. Region Östergötland; 2026.
285. Bild- och Funktionsmedicin - Prislista 2026. Region Skåne; 2026.
286. Pris semaglutid. Apoteket AB,; 2026.
287. FASS. Läkemedelsindustriföreningen; 2026.
288. Upphandlade läkemedel Region Östergötland från 1 mars 2025. Region Östergötland; 2025.
289. Teni FS, Gerdtham UG, Leidl R, Henriksson M, Åström M, Sun S, et al. Inequality and heterogeneity in health-related quality of life: findings based on a large

sample of cross-sectional EQ-5D-5L data from the Swedish general population. Qual Life Res. 2022;31(3):697–712.
290. Thornburg B, Bray JW, Wittenberg E. Health Utility of Drinkers' Family Members: A Secondary Analysis of a US Population Data Set. MDM Policy Pract. 2022;7(2):23814683221128507.
291. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971–84.
292. Reynaud M, Aubin HJ, Trinquet F, Zakine B, Dano C, Dematteis M, et al. A Randomized, Placebo-Controlled Study of High-Dose Baclofen in Alcohol-Dependent Patients-The ALPADIR Study. Alcohol Alcohol. 2017;52(4):439–46.
293. Boursier J, Canivet CM, Costentin C, Lannes A, Delamarre A, Sturm N, et al. Impact of Type 2 Diabetes on the Accuracy of Noninvasive Tests of Liver Fibrosis With Resulting Clinical Implications. Clin Gastroenterol Hepatol. 2023;21(5):1243–51.e12.
294. Han JW, Kim HY, Yu JH, Kim MN, Chon YE, An JH, et al. Diagnostic accuracy of the Fibrosis-4 index for advanced liver fibrosis in nonalcoholic fatty liver disease with type 2 diabetes: A systematic review and meta-analysis. Clin Mol Hepatol. 2024;30(Suppl):S147–s58.
295. Skråstad RB, Aamo TO, Andreassen TN, Havnen H, Hveem K, Krokstad S, et al. Quantifying Alcohol Consumption in the General Population by Analysing Phosphatidylethanol Concentrations in Whole Blood: Results from 24,574 Subjects Included in the HUNT4 Study. Alcohol Alcohol. 2023;58(3):258–65.
296. Agabio R, Saulle R, Rösner S, Minozzi S. Baclofen for alcohol use disorder. Cochrane Database Syst Rev. 2023;1(1):Cd012557.
297. Jönsson C, Bergram M, Kechagias S, Nasr P, Ekstedt M. Activin A levels in metabolic dysfunction-associated steatotic liver disease associates with fibrosis and the PNPLA3 I148M variant. Scand J Gastroenterol. 2024;59(6):737–41.
298. Ciardullo S, Muraca E, Perra S, Bianconi E, Zerbini F, Oltolini A, et al. Screening for non-alcoholic fatty liver disease in type 2 diabetes using non-invasive scores and association with diabetic complications. BMJ Open Diabetes Res Care. 2020;8(1).
299. Nielsen EM, Anderson KP, Marsden J, Zhang J, Schreiner AD. Nonalcoholic Fatty Liver Disease Underdiagnosis in Primary Care: What Are We Missing? J Gen Intern Med. 2022;37(10):2587–90.
300. Armstrong MJ, Houlihan DD, Bentham L, Shaw JC, Cramb R, Olliff S, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. J Hepatol. 2012;56(1):234–40.
301. Käräjämäki AJ, Hukkanen J, Ukkola O. The association of non-alcoholic fatty liver disease and atrial fibrillation: a review. Ann Med. 2018;50(5):371–80.
302. Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism. 2020;111s:154170.
303. Afarideh M, Aryan Z, Ghajar A, Ganji M, Ghaemi F, Saadat M, et al. Association of non-alcoholic fatty liver disease with microvascular complications of type 2 diabetes. Prim Care Diabetes. 2019;13(6):505–14.
304. Yan LH, Mu B, Guan Y, Liu X, Zhao N, Pan D, et al. Assessment of the relationship between non-alcoholic fatty liver disease and diabetic complications. J Diabetes Investig. 2016;7(6):889–94.
305. Adrian T, Hornum M, Knop FK, Almdal T, Rossing P, L ÍL, et al. Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes and Chronic Kidney Disease. Nephron. 2023;147(6):317–28.
306. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Schattenberg JM, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. Gut. 2022;71(1):156–62.
307. Williams KH, Burns K, Constantino M, Shackel NA, Prakoso E, Wong J, et al. An association of large-fibre peripheral nerve dysfunction with non-invasive measures of

liver fibrosis secondary to non-alcoholic fatty liver disease in diabetes. J Diabetes Complications. 2015;29(8):1240–7.
308. Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: Clinical trials to clinical practice. J Hepatol. 2016;65(5):1006–16.
309. Kim K, Oh TJ, Cho HC, Lee YK, Ahn CH, Koo BK, et al. Liver fibrosis indices are related to diabetic peripheral neuropathy in individuals with type 2 diabetes. Sci Rep. 2021;11(1):24372.
310. Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol. 2023;78(3):471–8.
311. Michel M, Doll M, Albert N, Morgenstern M, Behr A, Maxeiner S, et al. Obesity and harmful alcohol consumption are predictors for advanced liver disease in the disease management program for type 2 diabetes. United European Gastroenterol J. 2024;12(1):11–21.
312. Leite NC, Villela-Nogueira CA, Pannain VL, Bottino AC, Rezende GF, Cardoso CR, et al. Histopathological stages of nonalcoholic fatty liver disease in type 2 diabetes: prevalences and correlated factors. Liver Int. 2011;31(5):700–6.
313. Bazick J, Donithan M, Neuschwander-Tetri BA, Kleiner D, Brunt EM, Wilson L, et al. Clinical Model for NASH and Advanced Fibrosis in Adult Patients With Diabetes and NAFLD: Guidelines for Referral in NAFLD. Diabetes Care. 2015;38(7):1347–55.
314. Goh GB, Pagadala MR, Dasarathy J, Unalp-Arida A, Sargent R, Hawkins C, et al. Clinical spectrum of non-alcoholic fatty liver disease in diabetic and non-diabetic patients. BBA Clin. 2015;3:141–5.
315. 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(4):1032–41.
316. Itier R, Guillaume M, Ricci JE, Roubille F, Delarche N, Picard F, et al. Non-alcoholic fatty liver disease and heart failure with preserved ejection fraction: from pathophysiology to practical issues. ESC Heart Fail. 2021;8(2):789–98.
317. Singal AK, Zhang W, Shetty A, Patel A, Mohammed S, Bhandari P, et al. Treatment of alcohol use disorder in alcohol-associated liver disease: A meta-analysis. Hepatol Commun. 2025;9(5).
318. Månsson A, Danielsson AK, Sjöqvist H, Glatz T, Lundin A, Wallhed Finn S. Pharmacotherapy for alcohol use disorder among adults with medical disorders in Sweden. Addict Sci Clin Pract. 2024;19(1):41.
319. Polignano M, Bianco A, Guido D, Trisolini P, Franco I, Bonfiglio C, et al. Economic value and clinical association of a supervised lifestyle-improving program for MASLD. Front Pharmacol. 2025;16:1708451.
320. West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology. 2010;139(4):1230–7.
321. Barber MJ, Gotham D, Bygrave H, Cepuch C. Estimated Sustainable Cost-Based Prices for Diabetes Medicines. JAMA Netw Open. 2024;7(3):e243474.
322. Fredriksson M, Werner M. AUDIT C compared to PEth in middle-aged volunteers. Alcohol Alcohol. 2024;59(5).
323. Huang X, Li Z, Zhai Z, Wang Q, Wei R, Mo J, et al. Association Between Metabolic Dysfunction-Associated Fatty Liver Disease and MACCEs in Patients with Diabetic Foot Ulcers: An Ambispective Longitudinal Cohort Study. Diabetes Metab Syndr Obes. 2024;17:1119–30.
324. Thiele M, Kamath PS, Graupera I, Castells A, de Koning HJ, Serra-Burriel M, et al. Screening for liver fibrosis: lessons from colorectal and lung cancer screening. Nat Rev Gastroenterol Hepatol. 2024;21(7):517–27.
325. Levi J, Wang J, Venter F, Hill A. Estimated minimum prices and lowest available national prices for antiobesity medications: Improving affordability and access to treatment. Obesity (Silver Spring). 2023;31(5):1270–9.

326. Claxton K, Paulden M, Gravelle H, Brouwer W, Culyer AJ. Discounting and decision making in the economic evaluation of health-care technologies. Health Economics. 2011;20(1):2–15.
327. Eshraghi R, Ghadimi DJ, Montazerinamin S, Bahrami A, Kachela Y, Rezasoltani M, et al. Effects of glucagon-like peptide-1 receptor agonists on alcohol consumption: a systematic review and meta-analysis. EClinicalMedicine. 2025;90:103645.
328. McGuire DK, Marx N, Mulvagh SL, Deanfield JE, Inzucchi SE, Pop-Busui R, et al. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. N Engl J Med. 2025;392(20):2001–12.
329. Patel S, Niazi SK. Emerging Frontiers in GLP-1 Therapeutics: A Comprehensive Evidence Base (2025). Pharmaceutics. 2025;17(8).
330. Bergram M, Kechagias S, Iredahl F, Balkhed W, Holmberg M, Dahlström N, et al. Microvascular complications of type 2 diabetes with or without MASLD: the EPSOMIP study, a primary care cohort study. BMC Prim Care. 2025;26(1):354.
331. Bergram M, Nasr P, Iredahl F, Kechagias S, Rådholm K, Ekstedt M. Low awareness of non-alcoholic fatty liver disease in patients with type 2 diabetes in Swedish Primary Health Care. Scand J Gastroenterol. 2022;57(1):60–9.

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