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REVIEW

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Metabolic dysfunction-associated steatotic liver disease and the heart

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Abstract

The prevalence and severity of metabolic dysfunction–associated steatotic liver disease (MASLD) are increasing. Physicians who treat patients with MASLD may acknowledge the strong coincidence with cardiometabolic disease, including atherosclerotic cardiovascular disease (asCVD). This raises questions on co-occurrence, causality, and the need for screening and multidisciplinary care for MASLD in patients with asCVD, and vice versa. Here, we review the interrelations of MASLD and heart disease and formulate answers to these matters. Epidemiological studies scoring proxies for atherosclerosis and actual cardiovascular events indicate increased atherosclerosis in patients with MASLD, yet no increased risk of asCVD mortality. MASLD and asCVD share common drivers: obesity, insulin resistance and type 2 diabetes mellitus (T2DM), smoking, hypertension, and sleep apnea syndrome. In addition, Mendelian randomization studies support that MASLD may cause atherosclerosis through mixed hyperlipidemia, while such evidence is lacking for liver-derived procoagulant factors. In the more advanced fibrotic stages, MASLD may contribute to heart failure with preserved ejection fraction by reduced filling of the right ventricle, which may induce fatigue upon exertion, often mentioned by patients with MASLD. Some evidence points to an association between MASLD and cardiac arrhythmias. Regarding treatment and given the strong co-occurrence of MASLD and asCVD, pharmacotherapy in development for advanced stages of MASLD would ideally also reduce cardiovascular events, as has been demonstrated for T2DM treatments. Given the common drivers, potential causal factors and especially given the increased rate of cardiovascular

Abbreviations: α, alpha; AF, atrial fibrillation; AGE, advanced glycation end-product; ANG-II, angiotensin-II; asCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcification; cIMT, carotid artery intima-media thickness; CVD, cardiovascular disease; FFA, free fatty acid; FLI, fatty liver index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HIF, hypoxia-inducible factor; IR, insulin resistance; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; NO, nitric oxide; OSAS, obstructive sleep apnea syndrome; PNPLA3, Patatin-like phospholipase domain-containing protein 3; PPAR, peroxisome proliferator-activated receptor; RAAS, renin-angiotensin-aldosterone system; T2DM, type 2 diabetes mellitus; US, ultrasound.

events, comprehensive cardiometabolic risk management is warranted in patients with MASLD, preferably in a multidisciplinary approach.

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) shares its root cause of insulin resistance (IR)[1] with increasing cardiometabolic health problems of obesity,[2] metabolic syndrome,[3] type 2 diabetes mellitus (T2DM),[4] hypertension,[5] and dyslipidemia.[6] These cardiometabolic dysfunctions are highly prevalent and steadily increasing,[7] and the increase in MASLD goes hand in hand with these, including its severe stages.[8] MASLD comprises a spectrum of liver disease stages, ranging from isolated steatosis, characterized by hepatocellular accumulation of lipid droplets, to metabolic dysfunction–associated steatohepatitis (MASH), with additional hepatic inflammation and hepatocyte damage, including ballooning, which can progress into fibrotic stages.[1] Fibrotic MASH, in turn, relates to liver-related mortality and all-cause mortality, and it may lead to cirrhosis and HCC.[1,9] The burgeoning problem of MASLD is a major health issue for the forthcoming decades, driving the incidence of HCC[10] and becoming a major indication for liver transplantation.[11] The average prevalence of MASLD is estimated at 31% of the adult population, mostly in the early stage of isolated steatosis, and with the highest prevalence in the Middle East (43%) and Latin America (35%) and the lowest in central-Africa and South Africa (13%).[12,13]

The link to cardiometabolic dysfunctions is reflected in the new nomenclature and diagnostic criteria: MASLD instead of NAFLD, changing the reliance on exclusionary terms to positive diagnostic cardiometabolic criteria.[14] A very high overlap is expected between those classified as NAFLD in the studies reviewed in this paper, and we therefore deem it justified to use MASLD in reviewing the evidence in this manuscript. Even the great majority of those previously termed to have lean NAFLD (hepatic steatosis yet body mass index < 25 kg/m^2) have cardiometabolic criteria, mostly in the form of insulin resistance, thus also fitting the label MASLD. The new nomenclature classifies patients with steatotic liver disease (SLD) without any cardiometabolic criteria or excessive alcohol use as cryptogenic SLD. These may have been classified as NAFLD with the old nomenclature, but these cases are so rare that they will not affect our interpretation of the reviewed evidence.

Given the link between MASLD and cardiometabolic disease, position statement papers,[15] think tanks,[16] and awareness campaigns[17,18] are being setup to improve multidisciplinary care for the involved patients. This new interaction raises questions on co-occurrence of MASLD and atherosclerotic cardiovascular disease (asCVD), causality and the need for screening and multidisciplinary care for MASLD in patients with asCVD, and vice versa. MASLD constitutes a significant health care assignment, requiring the collaboration of hepatologists with general practitioners, diabetologists, and also cardiologists, who see patients at risk for both asCVD and advanced stages of MASLD. International guidelines increasingly advocate multidisciplinary approaches for patients with MASLD involving all these medical disciplines.[15,19] As part of the AwareNASH campaign,[18] we here review the interrelations of MASLD and heart disease and formulate answers to these matters and the implications for multidisciplinary care development.

Co-occurrence of MASLD and atherosclerotic cardiovascular disease

The clinical observation of co-occurrence of MASLD and asCVD by cardiologists and hepatologists actually finds support in epidemiological studies, both with markers of subclinical asCVD as well as asCVD events. Carotid artery intima-media thickness (cIMT) and coronary artery calcification (CAC) are both well-defined markers and commonly used in epidemiological studies, although only CAC has made it to clinical practice. A large systematic review and meta-analysis by Wong et al evaluated the association between MASLD and cIMT and CAC.[20] MASLD was assessed by ultrasound (US), liver biopsy, CT, magnetic resonance spectroscopy, or Fatty Liver Index (FLI). Forty-four studies containing 41,189 subjects showed that MASLD was associated with increased cIMT (OR 2.00, 95% CI: 1.56, 2.56, see Table 1). Twenty-two studies encompassing 136,294 subjects reported an association between MASLD and the presence of any coronary calcification, CAC score > 0 (OR 1.21, 95% CI: 1.12, 1.32) and significant coronary calcification, CAC score > 100 (OR: 1.28, 95% CI: 1.01, 1.63), and in a smaller sample of 4552 subjects, the development or progression of CAC (OR 1.26, 95% CI: 1.04, 1.52, Table 1). There were no significant differences between Western and Asian subjects.[20] Another meta-analysis including 10,060 subjects stated that MASLD, determined by either US or CT, is associated with significant odds of progression of CAC (OR 1.50, 95% CI: 1.34, 1.68, $p < 0.001$, Table 1).[21] Taken together, the above-mentioned data suggest a clear association between MASLD and subclinical asCVD.

TABLE 1 Epidemiological evidence addressing the association between MASLD and incident or prevalent asCVD[20, 21, 22, 23, 24, 25, 26]

References	Year	Study population	Design	Outcomes	Main results
Subclinical					
Wong et al[20]	2021	cIMT: 41,189 subjects CAC: 136,294 subjects CAC progression: 4552 subjects	Systematic review and meta-analysis	cIMT CAC CAC progression	Increased cIMT, CAC, and CAC progression associated with MASLD, associations did not differ between Western and Asian populations, 39 studies with ≥ 8 NOS stars, 25 studies with 5–7 NOS stars
Koulaouzidis et al[21]	2021	10,060 subjects	Systematic review and meta-analysis	CAC progression	Increased baseline CAC and CAC progression associated with MASLD, MASLD severity, and CAC progression was not significantly associated, and the median NOS score was 7 (6–8)
Clinical					
Wu et al[22]	2016	Prevalence: 44,279 subjects Incidence: 120,215 subjects CVD death: 23,839 subjects	Systematic review and meta-analysis	Prevalent CVD Incident CVD CVD mortality	MASLD associated with increased risk of prevalent and incident CVD, not associated with CVD mortality, median NOS score was 4 (3–5) for cross-sectional studies and 8 (5–9) for prospective studies
Hagström et al[23]	2017	646 well-defined biopsied patients with MASLD	Retrospective cohort study	Disease-specific mortality	asCVD is the most common cause of death in patients with MASLD. MASLD activity score was not able to predict overall mortality. Fibrosis stage predicted both overall and disease-specific mortality, median follow-up 20 y
Stepanova et al[24]	2012	11,613 participants	Prospective cohort study	Incident CVD CVD mortality	CVD is the most common cause of death in patients with MASLD (34%). MASLD is independently associated with CVD. MASLD was also associated with CVD mortality, but not when adjusted for confounders.
Liu et al[25]	2019	471,849 participants	Systematic review and meta-analysis	All-cause mortality CVD mortality Cancer mortality Liver mortality	MASLD associated with all-cause mortality and liver mortality, not with CVD mortality, not with cancer mortality, adjusted for body mass index, diabetes, smoking, hypertension, or hyperlipidaemia/hypercholesterolemia, follow-up ranged from 1.9 to 26.4 y, average NOS score 6.5 (5–8)
Targher et al[26]	2016	34,043 subjects	Systematic review and meta-analysis	Incident CVD, CVD mortality Both in severe and overall MASLD group	MASLD was associated with a higher risk of fatal and/or nonfatal CVD events, more severe MASLD was associated with fatal and nonfatal CVD events, median follow-up 6.9 y (range 3–26.4), median NOS score 8 (5–9)

MASLD was diagnosed on the basis of US, CT, MRI, or biopsy findings in all the studies except Wong et al, which included 1 study with the FLI.
Abbreviations: CAC, coronary artery calcification; cIMT, carotid artery intima-media thickness; CVD, cardiovascular disease; FLI, fatty liver index; MASLD, metabolic dysfunction–associated steatotic liver disease; NOS, Newcastle-Ottawa scale; US, ultrasound.

The next question is whether the evidence for more subclinical asCVD in patients with MASLD translates into more clinically manifest asCVD events. A systematic review by Wu et al from 2016 evaluated the risk of prevalent (n = 44,279) and incident (n = 120,215) asCVD in patients with MASLD. MASLD was established by either US, CT, or biopsy. MASLD was associated with an increased risk of prevalent (OR 1.81, 95% CI: 1.23, 2.66) and incident (HR 1.37, 95% CI: 1.10, 1.72) asCVD.[22] When evaluating MASLD and asCVD mortality, several studies are of interest. Hagström et al carried out a 20-year follow-up in a well-characterized liver biopsy cohort of 646 patients with MASLD and found that asCVD was the most common cause of death in patients with MASLD (37%).[23] In a large American cohort study, including 11,613 patients from the general population with a mean follow-up of 14 years, cardiovascular death was the most common cause of death in patients with MASLD although MASLD was not independently associated with cardiovascular mortality after adjustment for age, male sex, ethnicity, obesity, diabetes, smoking, and family history of myocardial infarction.[24]

The systematic review from Wu et al addressed whether MASLD increased the risk of asCVD mortality in a subset of 23,839 subjects. No significant association between MASLD and the risk of asCVD mortality was found (HR 1.10 95% CI: 0.86, 1.41).[22] The relationship between MASLD and CVD mortality was explored to a greater extent in a systematic review by Liu et al in 2019. MASLD was defined as steatosis on either imaging techniques (US or CT) or biopsy. From a total of 7 studies, a pooled estimate from 471,849 subjects showed no significant association between MASLD and CVD mortality (HR 1.13; 95% CI: 0.92, 1.38). Overall mortality was increased in subjects with MASLD (HR 1.34; 95% CI: 1.17, 1.54).[25] Although the study by Liu et al was much larger than the meta-analysis by Wu et al, the average score on the Newcastle-Ottawa scale (assessment of the quality of nonrandomized studies in meta-analyses) of the included studies was generally lower.

Taken together, strong evidence exists that MASLD gives an increased risk of asCVD events and asCVD is the main cause of death in patients with MASLD, not liver-related causes. Yet this does not translate into MASLD conveying an increased risk of asCVD death. MASLD is a spectrum of liver disease, generally of a slowly progressive nature and characterized by a range of histological stages. Stratifying for the different disease stages can further clarify the interrelations between MASLD and asCVD.

In a meta-analysis from 2016 with a sample size of 34,043, Targher et al found that the more advanced stages of MASLD, defined by elevated γ-GT levels, high MASLD fibrosis score, high hepatic activity on PET-CT, or histological fibrosis, were associated with both fatal and combined fatal and nonfatal cardiovascular events.[26] In contrast, a prospective cohort study with 1773 biopsy-delineated patients with MASLD, with a mean follow-up of 4 years, did not show different rates of cardiac events or mortality when comparing different stages of fibrosis.[27] In this study, the presence of MASH was not associated with a higher incidence of asCVD events, although a trend was apparent.

Although current evidence does not support an association between MASLD and cardiovascular mortality risk, evidence for the association with asCVD events is quite robust. Next, in deciphering the relation of MASLD and asCVD, firstly, it is important to investigate the evidence for common drivers of these two diseases.

Common drivers of MASLD and asCVD

MASLD and asCVD are both multifactorial diseases. The epidemiological relations between MASLD and asCVD are in part explained by common pathophysiological drivers, predominantly occurring in the setting of obesity (Figure 1).

Insulin resistance

Systemic IR is one of the major drivers of MASLD. White adipose tissue IR induces lipolysis, rendering a flux of free fatty acids (FFA) to the liver, inducing hepatic steatosis and lipotoxicity.[1] Particular lipid species, most notably diacylglycerol, in turn induce reduced hepatic expression of the insulin receptor and thereby induce hepatic IR: the unresponsiveness of hepatic gluconeogenesis to insulin. Hepatic steatosis is further compounded in this setting due to increased de novo lipogenesis, driven by overnutrition and fructose consumption, and uninhibited by insulin due to the hepatic IR.[28] Furthermore, it has been demonstrated that IR at the level of the sinusoidal endothelium is linked to MASLD in multiple rat models.[29] Hepatic microcirculatory dysfunction preceded the stages of hepatic inflammation and fibrosis.[30]

In turn, IR also drives asCVD. Systemic IR and hepatic IR induce hyperglycemia, which decreases nitric oxide (NO) release, promoting the activation of platelets and adhesion to arterial endothelium.[31] Direct effects of insulin on endothelial NO synthase and activation of vascular smooth muscle cells have been observed as well.[32,33] Hyperglycemia also induces advanced glycation end products (AGEs), stimulating nuclear factor κ-light-chain-enhancer of activated B cells, and increases the expression of vascular cell adhesion molecule-1.[34] Atheroma collagen glycation stimulates LDL deposition in the arterial wall, leading to the progression of atherosclerotic lesions, and LDL can

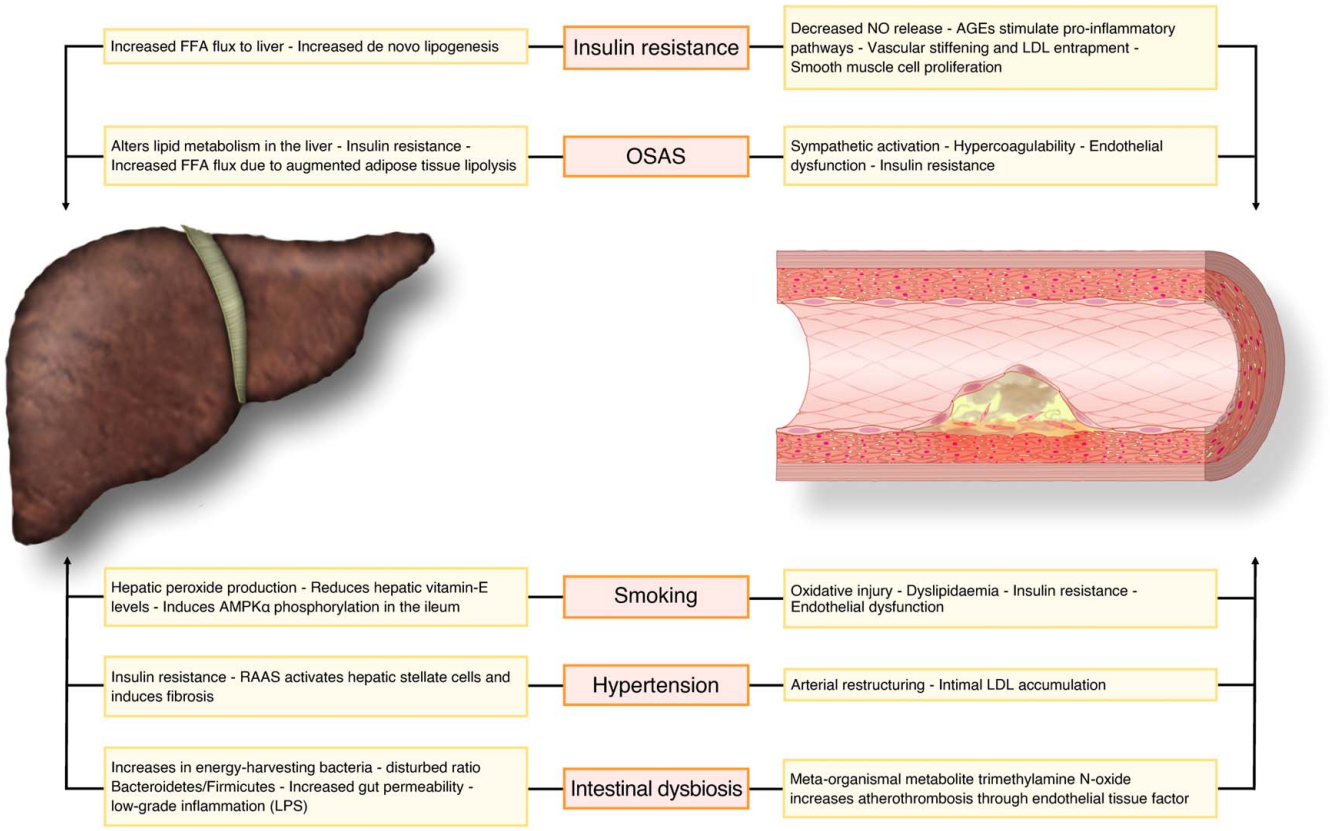

FIGURE 1 MASLD and asCVD are both multifactorial diseases. The epidemiological relations between MASLD and asCVD are in part explained by common pathophysiological drivers occurring predominantly in the setting of obesity. Abbreviations: AGE, advanced glycation end products; AMPKα, 5' adenosine monophosphate-activated protein kinase α; asCVD, atherosclerotic cardiovascular disease; FFA, free fatty acid; NO, nitric oxide; LPS, lipopolysaccharide; MASLD, metabolic dysfunction–associated steatotic liver disease; OSAS, obstructive sleep apnea syndrome; RAAS, renin-angiotensin-aldosterone system.

also undergo glycation and subsequent oxidation.[35,36] AGEs can induce crosslinking of collagen, leading to vascular stiffening and further entrapment of LDL particles.[31] Together, this promotes LDL accumulation and foam cell formation in the process of atherogenesis.

Hypertension

MASLD may be aggravated in the state of hypertension. Alterations in renin-angiotensin-aldosterone system (RAAS), either renin, angiotensin-converting enzyme (ACE), or angiotensin-II (ANG-II), induce both hepatic steatosis and fibrosis in rat and mouse models.[37–39] Steatosis may be induced by increased adipose tissue IR through ANG-II, leading to an increased hepatic FFA flux.[40–42] ANG-II also contributes to functional alterations through vascular hyperreactivity to vasoconstrictors, contributing to liver damage.[43] ANG-II also induces reactive oxygen species, which can lead to the activation of HSC, the main hepatic cell type responsible for the induction of fibrotic scarring.[44]

Epidemiologically, hypertension is closely linked to asCVD; multiple mechanisms have been proposed. Both the high pressure and accompanying endocrine dysregulation may drive vascular wall restructuring and intimal LDL accumulation.[45,46]

Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is a relatively common condition in obese individuals with both MASLD and asCVD. A meta-analysis with 2183 participants corroborated an independent relation of OSAS with MASLD, with ORs for various comparisons ranging between 2.01 and 2.99.[47] Periodic hypoxia in OSAS has even been suggested as a driver of MASLD. The intermittent hypoxia caused by OSAS might directly induce MASLD by altering the lipid metabolism in the liver. Intermittent hypoxia induces a downregulation of prolyl hydrolase domain, leading to the stabilization and activation of multiple variants of hypoxia-inducible factor (HIF)-α (alpha), and subsequently HIF-beta.[48] Absence of HIF2-α protects against lipid accumulation, and HIF2-α induces CD36 expression, which is the major driver of FFA uptake.[49] Activation of CD36 through HIF2-α instigates lipid accumulation in hepatocytes both *in vitro* and *in vivo*.[50]

Epidemiologically, OSAS is independently associated with an increased incidence of coronary heart disease,[51] heart failure,[52] stroke,[53] and atrial fibrillation.[54] Periodic hypoxia induces sympathetic activation, low-grade inflammation, hypercoagulability, and arterial endothelial dysfunction.[55] Hypoxia might also contribute to both MASLD and asCVD by inducing IR. A mouse model showed that periodic hypoxia leads to periodic IR, disturbing diurnal blood glucose variation and promoting compensatory pancreatic beta-cell replication.[56] A randomized trial in 35 individuals with OSAS confirmed this phenomenon of IR during hypoxemia and additionally showed that participants had increased levels of circulating FFAs.[57]

Smoking

The causal relation between smoking and asCVD has been well established, most notably through prothrombotic actions and endothelial dysfunction.[58] Several studies suggest a relation with MASLD. Two large prospective cohort studies found that smoking was significantly associated with the onset of MASLD, with adjusted HRs ranging from 1.25 to 1.98.[59,60] A rat model showed that smokeless tobacco initiated inflammation of the liver.[61] A mouse model showed an increased hepatic lipid peroxide production and reduced hepatic vitamin E levels when mice were exposed to smoke.[62] A recently published study suggested an interesting role for gut microbiota in protection against MASLD aggravated by intestinal nicotine.[63] Several bacteria inhibited nicotine-induced AMP-activated protein kinase α phosphorylation in the ileum, which in turn reduced the progression of hepatic steatosis, inflammation, and fibrosis in a mouse model.

Gut dysbiosis

Small intestine bacterial overgrowth is frequently observed in patients with MASLD.[64,65] Through increased gut permeability and alterations in tight junctions, microbial products enter the portal circulation and trigger hepatic inflammation.[66] Also, coronary artery disease is linked to alterations in the gut microbiome; small intestine bacterial overgrowth is independently associated with poor outcomes in heart failure.[67,68] Multiple bacterial components and metabolites may mediate atherogenesis, from which trimethylamine N-oxide has the most compelling evidence.[67,69]

Systemic inflammation

The link between pro-inflammatory cytokines and atherogenesis is well-known. Patients with carotid artery disease have a distinct cytokine profile compared to healthy controls, suggesting that certain cytokines may have a pivotal role in the development of asCVD.[70] Multiple trials showed that treatment with anti-inflammatory agents can improve cardiovascular end points.[71,72] Some of these cytokines might derive from the liver in the state of MASH.[73] Several knockout models suggested a role for cytokines in the development of MASLD.[74–76] Cytokines as a mediator of MASLD development and progression could also explain the observed association between MASLD and pro-inflammatory diseases such as psoriasis.[77] It should be noted that systemic inflammation always results from an underlying pathophysiological mechanism and should not be viewed as a common driver per se.

Altogether there is extensive pathophysiological evidence explaining the strong co-occurrence between MASLD and asCVD. Moreover, the prevalence of several aforementioned risk factors (obesity, arterial hypertension, and T2DM) increases concomitantly with increasing MASLD fibrosis stages.[78] Determining whether MASLD actually contributes to asCVD is the next step.

Does MASLD causally contribute to asCVD?

Amid the common drivers, evidence for causal links between MASLD and asCVD is emerging. Factors directly deriving from the liver are the most plausible mediators along this liver-heart axis, that is, particular lipoproteins and procoagulant factors. Mendelian randomization can help distinguish causality from epiphenomenon or common driver. Variation in particular genes predisposes to the development of MASLD, among others, *PNPLA3* and *TM6SF2*. *PNPLA3* affects the remodeling of lipid droplets in hepatocytes, and it has been associated with impaired very VLDL secretion, suggesting a possible effect on plasma lipids and asCVD risk.[79] *TM6SF2* affects hepatic VLDL secretion and therefore also plasma lipids and asCVD risk.[80,81]

Brouwers et al tested 12 well-defined MASLD predisposition genes for their association with coronary artery disease and lipids in the Coronary Artery Disease Genome-Wide Replication and Meta-Analysis and the Coronary Artery Disease Genetics Consortium data set.[82] The entire cluster of MASLD genes was not associated with coronary artery disease, but when excluding the genes relating to MASLD through impaired VLDL secretion (*PNPLA3*, *TM6SF2*, *MTTP,* and *PEMT*), a significant (but weak) association was found (OR 1.01, 95% CI: 1.00, 1.02). Clustering the four excluded genes showed a negative association (OR 0.97, 95% CI: 0.96, 0.99). Of note, the effect of

PNPLA3 on VLDL secretion has been debated.[79,81] The heterogeneity in results in different genes is best explained by pleiotropic effects. Several single nucleotide polymorphisms and their pleiotropic effects are delineated in Figure 2.

MASLD may also causally contribute to asCVD by the release of procoagulant factors.[83] Small studies in patients with MASLD have both higher prothrombotic (eg, fibrinogen, Plasminogen activator inhibitor-1 (PAI-1), soluble intercellular adhesion molecule-1, CC-chemokine ligand-2, monocyte chemoattractant protein-1) and pro-inflammatory (eg, C-reactive protein, IL-6, IL-8, TNF-α) parameters than healthy individuals and these parameters were higher in patients with MASH than in those with isolated steatosis. A larger more recent study, which prospectively recruited and biopsied patients at risk for MASLD, found MASLD and its advanced stages only to be independently associated with PAI-1.[84] All other associations were due to dysmetabolic context, most notably obesity. More prospective studies are warranted to firmly determine the potential causal role of procoagulant factors in driving asCVD in patients with MASLD.

Several hepatokines (proteins exclusively/predominantly produced by liver tissue) are associated with both MASLD and asCVD. Fetuin-A inhibits the hepatic insulin receptor tyrosine kinase, possibly causing IR. MASLD, and to a greater extend MASH, is related to higher fetuin-A levels.[85,86] In turn, fetuin-A is related to myocardial infarction and stroke.[87]

Patients with MASLD have increased serum levels and hepatic expression of FGF21.[88] Although FGF21 has beneficial effects on insulin sensitivity and cholesterol levels, increased levels are associated with asCVD.[89] Selenoprotein p is increased in patients with MASLD and is positively correlated with IR, HSC-reactive protein, arterial stiffness, and cIMT.[90,91]

Taken together, some evidence exists for a causal relationship between MASLD and asCVD, although a firm conclusion cannot be drawn yet.

MASLD and heart failure

The bidirectional relationship between liver diseases and heart failure is well established. Heart failure can lead to congestive hepatopathy, and advanced liver disease can cause cirrhotic cardiomyopathy. Increasing evidence, however, points towards an association between heart failure and early-stage liver disease, for example, noncirrhotic MASLD. Evidence is also emerging that MASLD might be associated with heart failure with preserved ejection fraction.[92]

A large meta-analysis of 11,242,231 subjects found that MASLD was associated with a significantly higher risk for new-onset heart failure, yielding an HR of 1.50

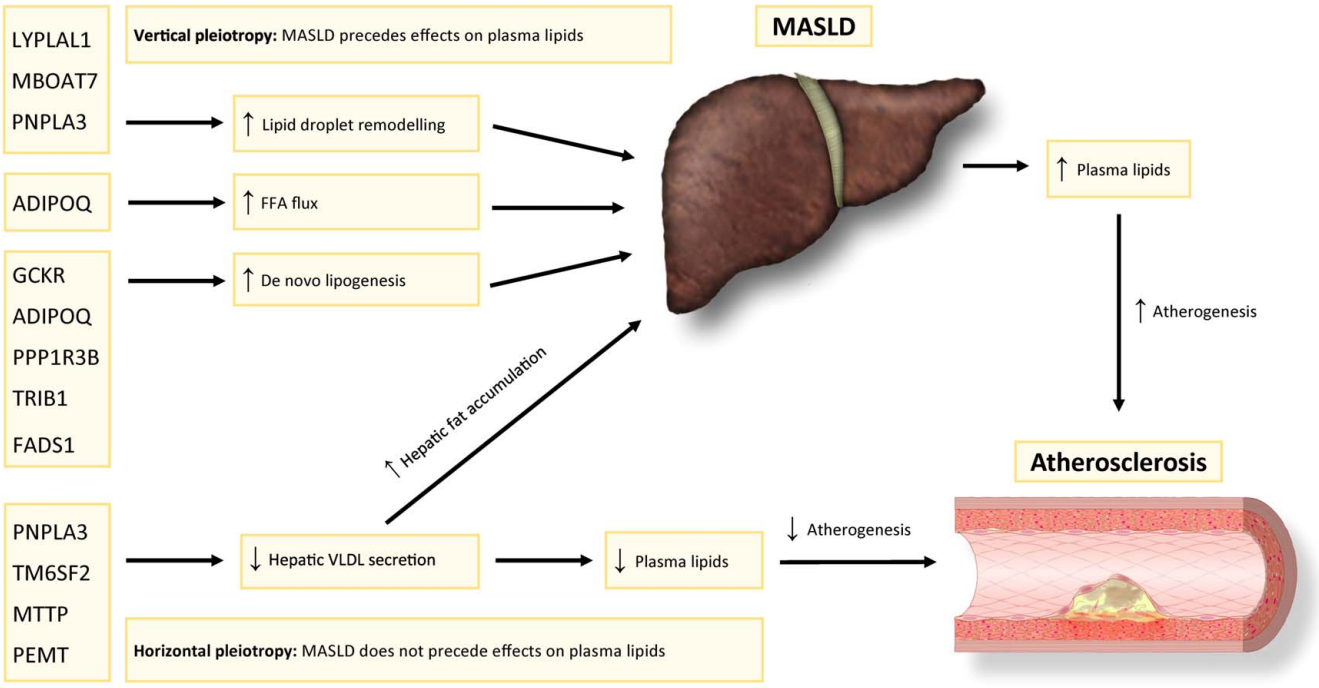

FIGURE 2 MASLD susceptibility genes can have different effects on coronary artery disease, depending on the different types of pleiotropy that can occur. When gene variants affect two or more phenotypic traits, pleiotropy occurs. Vertical pleiotropy happens when traits are further downstream in a physiological pathway and do not invalidate Mendelian randomization assumptions. SNPs that predispose to MASLD through VLDL impairment, simultaneously might lower plasma lipids and create horizontal pleiotropy, therefore invalidating Mendelian randomization assumptions. Abbreviations: FFA, free fatty acid; MASLD, metabolic dysfunction–associated steatotic liver disease; SNP, single nucleotide polymorphism.

(95% CI: 1.34, 1.67).[93] MASLD was most often defined by the FLI, which is less accurate and specific than imaging or histological assessment. The observed association possibly exists because of the metabolic factors included in the FLI and not the hepatic steatosis *per se*. The single study from this meta-analysis that based the diagnosis of MASLD on imaging did not find a significant association between MASLD and HF.[94] By contrast, Simon et al used the gold standard of liver biopsy and matched 10,422 biopsy-proven patients with MASLD with 46,517 controls without MASLD.[95] This study did find MASLD to be significantly associated with heart failure with an HR of 1.75 (95% CI: 1.63, 1.87). This risk was independent of typical cardiometabolic risk factors and increased progressively with liver disease severity. Although the use of liver biopsy in a fairly large cohort seems robust, the matched cohort study design still poses a risk for unaddressed confounding.

Underlying cardiac remodeling has recently been described in association with MASLD and can constitute structural changes contributing to the development of heart failure (Figure 3). In a cross-sectional study, liver fat was positively associated with left ventricular mass, left ventricular wall thickness, mass volume ratio, mitral peak velocity, and left ventricular filling pressure and inversely associated with global systolic longitudinal strain and diastolic annular velocity.[96,97]

The mechanisms explaining the relation of MASLD and cardiac remodeling are partly overlapping with those described in asCVD, but the data is less exhaustive. Both metabolic and mechanical factors have been implicated.

A putative mechanism in which MASLD *per se* might cause heart failure with preserved ejection fraction is through reducing the preload reserve. Almost 25% of the circulatory blood volume passes through the splanchnic compartment, correspondingly playing a substantial role in venous return.[98] An increased intrahepatic resistance (leading to an increased pressure in the hepatic sinusoids) can therefore lead to decreased preload reserve. Although portal hypertension is most well recognized in patients with cirrhosis, transhepatic blood flow changes have been shown to start in the earliest stages of MASLD.[99] Signs of portal hypertension were examined in a cohort of biopsy-delineated patients with MASLD through ultrasound Doppler and splenic elastography. Even steatosis grade is independently associated with an increased HVPG in a biopsy-proven cohort of patients with MASLD.[100] Both early-stage functional alterations (endothelial dysfunction and hyperreactivity to vasoconstrictors such as endothelin-1, ANG-II, and thromboxane A_2)[43,101] and structural changes, including both early-stage fibrosis and hepatocellular enlargement due to lipid accumulation, are thought to cause a mechanical impediment to the sinusoidal flow, although other possible mechanisms are still to be determined.[102]

AGEs resulting from IR lead to the activation of cardiac fibrosis-inducing factors, like several different mitogen-activated protein kinases.[103] Moreover, IR contributes to the formation of reactive oxygen species, both through autoxidation of glucose resulting in NAD(P)H oxidase and through the effects of AGEs.[104,105]

RAAS activation promotes several cardiac changes, both using intracrine, paracrine, and endocrine influences. Although ANG-II is mainly known as a vasoactive peptide, it regulates many aspects of cellular function unrelated to vasoconstriction in different tissues. Binding to angiotensin-1 receptor initiates a cascade that results in cardiomyocyte hypertrophy and proliferation of cardiac fibroblasts.[106]

Upregulation of the sympathetic nervous system has also been linked to both MASLD and cardiac remodeling. A rat model utilizing sympathectomy showed that the sympathetic nervous system is involved in the development of cardiac remodeling through both α and β-adrenergic receptors (α-receptors by inducing cardiac fibrosis and β-receptors by inducing hypertrophy).[107] The sympathetic nervous system crosstalk with RAAS leads to cardiac fibrosis as well.[108]

MASLD and arrhythmias

Cardiac structural and functional alterations are well-established risk factors for cardiac arrhythmias.[109–111] A few recent meta-analyses reported an association between MASLD and atrial fibrillation (AF) with varying strength (RR 1.65 (95% CI: 1.23, 2.20) in 614,673 patients, OR 1.27 (95% CI: 1.18, 1.37) in 8,115,545).[112,113] Both meta-analyses based their results largely on studies that used the FLI instead of imaging. Another recent meta-analysis selected only studies with imaging-based MASLD diagnoses and did not find an association between MASLD and AF in a pooled estimate of 9243 participants.[114] Interestingly, one of the studies from this meta-analysis did not find an association between hepatic steatosis and AF but did find an association between liver stiffness as defined by transient elastography, a relatively well-validated proxy for hepatic fibrosis, with AF. Of note, transient elastography results are altered during congestion, so this might be explanatory too. Overall, the evidence concerning this topic is currently too limited and conflicting to firmly establish a possible association. More longitudinal studies will have to be conducted, preferably with well-defined cohorts with an accurate steatosis assessment.

Studies that evaluated a possible association between MASLD and other cardiac arrhythmias are even more limited. A meta-analysis with 3651 subjects demonstrated that MASLD is associated with

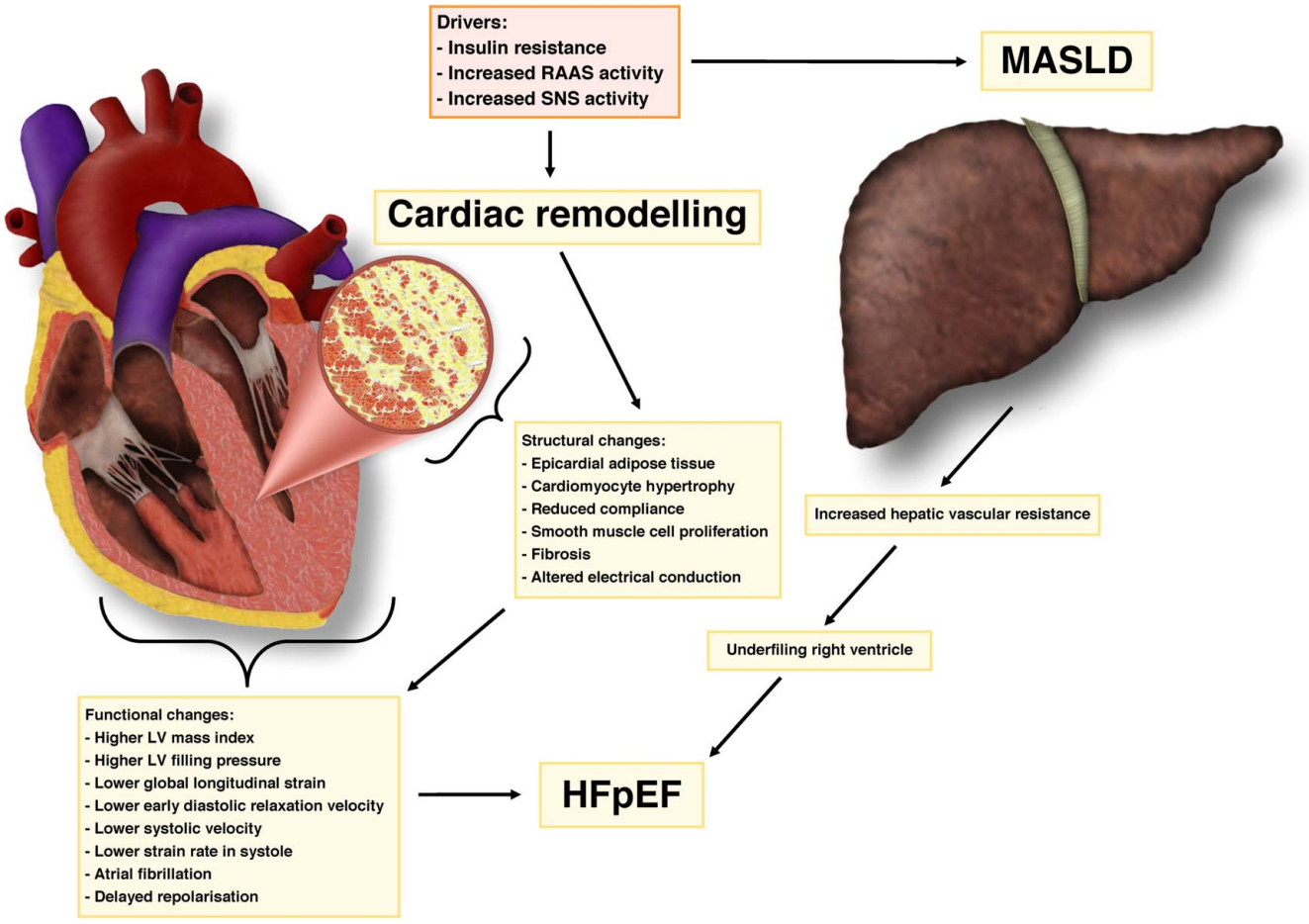

FIGURE 3 Cardiac remodelling and MASLD have several common pathophysiological drivers and can both lead to HFpEF. Cardiac remodelling occurs through structural changes, which lead to functional alterations and, subsequently, HFpEF. MASLD leads to hepatic flow obstruction due to increased vascular resistance, resulting in preload reserve failure. Abbreviations: HFpEF, heart failurewith preserved ejection fraction; LV, left ventricle; MASLD, metabolic dysfunction–associated steatotic liver disease; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

cardiac conduction defects based on three cross-sectional studies which addressed right bundle branch blocks, atrioventricular blocks, and fascicular blocks, with an OR of 5.17 (95% CI: 1.34, 20.01, I^2 96%).[115] MASLD was defined as having steatosis on US or CT scan.

The possible association between MASLD and prolonged QT interval was assessed in two cross-sectional studies. One study comprised a T2DM population of 400 patients and yielded an OR of 2.26 (95% CI: 1.4, 3.7). The other study included 31,116 patients from a health management program and showed ORs varying between 1.11 and 1.87 (95% CI: 1.01, 1.21 and 1.16–2.24), depending on the severity of MASLD and whether the subjects were male or female.[116,117] Both studies based their MASLD diagnosis on US.

Finally, MASLD might be associated with ventricular arrhythmias based on a retrospective cross-sectional study that demonstrated an increased odds of ventricular arrhythmias (OR 3.01, 95% CI: 1.26, 7.17).[118] Furthermore, 1 prospective cohort study, including 1780 men without cardiovascular medical history, showed that serum γ-GT was log-linearly associated with the risk of incident ventricular arrhythmias, with an HR 1.58 (95% CI: 1.06, 2.37).[119] This association remained significant when adjusting for common risk factors and by accounting for the development of impaired renal function and incident coronary heart disease.

Drugs potentially targeting both MASLD and cardiovascular events

Currently, MASLD management is limited to lifestyle modifications, or treatments licensed for other indications for which at least phase II histological efficacy data exist and if within their current approved indications.[19] Multiple agents are currently under evaluation for their effectiveness to treat fibrotic MASLD. Given the strong co-occurrence and shared etiology of MASLD and asCVD, compounds able to target both MASLD and

CVD would be highly valuable, analogous to glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium glucose co-transporter 2-inhibitors showing efficacy for both T2DM and asCVD.[120,121] A liver-specific drug for MASLD, which also reduces asCVD events, would also shed light on the matter of causality in the MASLD-asCVD axis. However, reducing the hepatic steatosis and, subsequently its metabolic effects, will probably alter several factors which can contribute to asCVD as well. Determining if these alterations occur as a result of MASLD resolution (vertical pleiotropy) or concomitant with MASLD resolution (horizontal pleiotropy) will be pivotal in establishing possible causality.

Opportunities might lie in the repurposing of existing agents. Statins have been suggested as potentially beneficial in the treatment of MASLD with the notion that their lipid-lowering effects might affect MASLD through pleiotropic effects. Physicians are reluctant to prescribe statins in patients with pre-existing liver disease or altered liver enzymes, even though their safety has been proven in multiple RCTs.[122,123] A mouse MASLD model showed that simvastatin improved multiple microcirculatory processes, restored oxidative and ALE-RAGE pathway activation, decreased HSC activation, and reduced steatosis, fibrosis, and inflammatory parameters.[124]

A recent meta-analysis encompassing 1,247,503 subjects found a reduced risk of MASLD development in statin users, OR 0.69, 95% CI: 0.57, 0.84, $I^2 = 36\%$. The use of statins led to a reduction of steatosis grade, SMD: −2.59, 95% CI: (−4.61, −0.56), $I^2 = 95\%$, MASLD activity score, weighted mean difference: −1.03, 95% CI: (−1.33, −0.74), $I^2 = 33\%$ and necro-inflammatory score weighted mean difference: −0.19, 95% CI: (−0.26, −0.13), $I^2 = 0\%$. No significant effects on the fibrosis stage were found, however.[125]

Given the possible influence of RAAS on MASLD, antihypertensive treatments might be beneficial for MASLD as well. A rabbit model showed that both ramipril and olmesartan diminished the development of MASLD, MASH, and fibrosis.[126] A nested case-control study did not show an overall association between the use of RAAS inhibitors and less development or progression of MASLD but did suggest a protective effect of RAAS inhibitors in several subgroups, such as obese individuals.[127] Currently, no trials with antihypertensive treatment in human subjects with MASLD have been conducted so far.

Sodium glucose co-transporter 2-inhibitors are registered for T2DM treatment but have beneficial effects on cardiovascular outcomes.[128] Several studies have suggested that sodium glucose co-transporter 2-inhibitors may decrease liver fat content and improve liver function tests, although no large RCTs have been conducted.[129] These effects are most often attributed to weight loss and glucose-regulating effects, although 1 study evaluating the effects of empagliflozin on MASLD in a cohort of patients with T2DM and with excellent glycemic control, also saw a reduction in liver fat, as assessed by MRI.[130]

Another promising subclass are those regulating glucagon-inhibiting incretins. GLP-1 RAs are indicated for diabetes and obesity, but given their ability to improve weight loss and glycemic and lipid metabolism, they are considered for other metabolism-associated diseases as well. A meta-analysis concerning several different GLP-1 RAs found that GLP-1 RAs effectuate a significantly reduced HR (0.86, 95% CI: 0.80, 0.93) for 3-point major adverse cardiovascular events regardless of the structural basis of the agent.[131] The effects of GLP-1 RAs on MASLD have not been studied as thoroughly as CVD, but two promising phase II trials in MASH have been completed.[132,133] Both trials showed a significant reduction in inflammation grade but also a lack of reduction in fibrosis grade, regardless of substantial weight loss in the participants. A phase-III trial with semaglutide is currently underway (ClinicalTrials.gov Identifier: NCT04822181). Interestingly, it has major adverse cardiovascular events as a secondary end point.

Several dual and triple incretin analogues have shown even greater reductions in body weight than GLP-1 RAs[134,135] and have also shown promising results in reducing hepatic steatosis. In a substudy of the phase III SURPASS obesity trial, the glucose-dependent insulinotropic polypeptide and GLP-1 RA tirzepatide showed a significant reduction of liver fat content compared to controls receiving insulin, with an estimated treatment difference of –4.71%, (95% CI: –6.72, –2.70).[136] In a substudy of a phase II obesity trial, the two highest dosages of the glucose-dependent insulinotropic polypeptide/GLP-1/glucagon RA retatrutide showed a normalization of liver fat content in 90% of the participants.[137] The dual GLP-1/glucagon RA efinopegdutide was originally designed for obesity and T2DM, but registration currently focuses on MASH. In a phase IIa trial, efinopegdutide showed a least squares mean relative reduction from baseline in liver fat content of 72.7% (90% CI: 66.8, 78.7).[138] Positive effects of these dual and triple agents on cardiovascular end points are anticipated, considering their significantly beneficial metabolic effects.

Resmetirom is a highly selective thyroid hormone receptor-β agonist designed to improve MASH by increasing hepatic fat metabolism and reducing lipotoxicity. Thyroid hormone receptor-β is the predominant thyroid hormone receptor in the liver, and in animal models, it has been shown to influence several metabolic processes, such as the reduction of triglycerides and cholesterol and the improvement of insulin sensitivity.[139] Interim analysis of a phase III trial in patients with MASH recently finished, and resmetirom met both primary histologic end points, and the key

secondary end point (LDL cholesterol lowering) at both doses, being the first agent to achieve this.[140] Cardiovascular end points are of interest in future studies, given the effects on lipid metabolism.

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that function as transcription factors regulating the expression of genes. They have multiple effects on glucose-metabolism and fatty acid metabolism, inflammation, and fibrogenesis.[141] Three PPAR isotypes have been identified, α, γ, and δ, all regulating a different panel of processes, depending also on the organ and organ cell type in which they are expressed. PPARα is the main target of fibrate drugs that are used in hypertriglyceridemia, and PPARγ is the primary target of thiazolidinediones, which are used for treating IR in patients with T2DM. There are currently no registered PPARδ agonist agents, but Seladelpar is currently being tested for primary biliary cholangitis and is studied for MASH as well.[142,143] Despite the predominant role of PPARα in hepatocytes and the inverse link between PPARα and disease severity,[144] mono PPARα agonists have failed to demonstrate an effect in patients with MASH while pioglitazone, a mono PPARγ agonist (albeit with also some PPARα activity), clearly induces MASH resolution and improves the mean fibrosis stage without hitting the end point of 1 stage fibrosis regression in several phase II trials of different duration.[145] It is important to note, however, that no large phase III trial is available demonstrating the efficacy data of pioglitazone. Metabolic side effects of pioglitazone, most notably fluid retention, have tempered the eagerness to use thiazolidinediones, although it has become clear from large and long-term studies that pioglitazone significantly improves cardiovascular outcomes.[146,147] Dual-PPAR or pan-PPAR agonists might improve efficacy and/or overcome the aforementioned adverse effects of drugs with a PPARγ activity. Lanifibranor, a balanced pan-PPAR agonist, was the first drug to show a significant effect on both the resolution of MASH and improvement of fibrosis in a phase IIb trial,[148] and a phase III trial is currently underway (ClinicalTrials.gov Identifier: NCT04849728). Weight gain was apparent in more participants in the treatment group than in the placebo group. However, no episodes of heart failure were registered in the treatment group. Dual-PPAR agonists demonstrated more mixed results with Saroglitazar, a dual α/γ agonist, showing some promising results in phase II trials, while elafibranor failed in a phase III trial.[149,150]

Aramchol is a fatty acid/bile acid conjugate that is a partial inhibitor of hepatic stearoyl-CoA desaturase-1, which is an enzyme in the endoplasmic reticulum that catalyzes the rate-limiting step of biosynthesis of monounsaturated fatty acids. It is a regulator of body adiposity, energy expenditure, hepatic fatty acid β-oxidation, and insulin sensitivity,[151,152] and improved inflammation, oxidative stress, and fibrosis in *in vivo* models.[153,154] Even though stearoyl-CoA desaturase- 1 deficiency reduced IR, obesity, hepatic steatosis, and fibrosis in multiple mouse models, it also stimulates atherogenesis, which was hypothetically attributed to increased ICAM-1 expression, IL-6 production, and altered macrophage toll-like receptor 4 function.[155,156] Despite its mode of action, in mice treated with Aramchol, this atherogenic effect was not replicated.[157] Although it did not hit the current regulatory end points, Aramchol showed positive trends in MASH resolution and fibrosis in phase III.[158,159] A phase III trial is planned to start soon (ClinicalTrials.gov Identifier: NCT04104321). It would be interesting to monitor the effects on CVD end points in these trials.

Organization of care

With the rising prevalence and severity of MASLD and its interconnected cardiometabolic comorbidities, multidisciplinary management between hepatologists, endocrinologist, cardiologists, general physicians, and related practitioners is warranted. This means that those experienced in cardiometabolic prevention should expand their scope to MASLD and that hepatologists should be aware of comorbid T2DM, dyslipidemia, and increased asCVD risk affecting their patients with metabolic liver as severely as their liver risk and adopt preventive strategies rather than strategies focused around end-stage organ damage.[15,19] Do we have evidence that multidisciplinary cardiometabolic management of patients with MASLD is effective? Indeed, a study from the United Kingdom showed that multidisciplinary management of MASLD can improve liver-related and cardio-metabolic–related health parameters while remaining cost-effective.[160] The clinic consisted of hepatologists, diabetologists, and metabolic physicians, but also allied health professionals, including diet and lifestyle experts. Interventions that were offered included lifestyle advice, signposting to weight loss services, and pharmacological treatment of diabetes and cardiovascular risk factors. After a mean follow-up time of 13 months, significant reductions were seen in weight, ALT, HbA1c, total cholesterol, and liver stiffness. Despite its relatively modest sample size, this study offers valuable real-world data that can serve as a blueprint for future clinical practices. Multidisciplinary management also provides opportunities for the incorporation of lifestyle counseling and guidance in everyday practice. Irrespective of potential emerging pharmacological therapies, lifestyle guidance should remain the cornerstone in preventing both MASLD and CVD. Although there has been a gradual increase in the provision of lifestyle counseling over the years, there remains room for enhancement.[161]

The intricate hepato-cardiovascular axis holds implications for treatment and management for either organ system. Potential future therapeutic agents are highly likely to have pleiotropic cardiometabolic effects (or, in the case of GLP1RA, already have established protective cardiometabolic effects). Comprehensive scientific and clinical collaboration is therefore warranted.

CONCLUSIONS

Epidemiological evidence strongly supports an association between MASLD and asCVD. MASLD and asCVD are closely linked through several common driving pathophysiological mechanisms. A causal relation between MASLD and asCVD, independent of common risk factors, exists by mixed hyperlipidemia, but more evidence is needed. The repurposing of established pharmaca and development of agents primarily targeting MASLD and potentially also reducing asCVD events can provide major breakthroughs in the future, both for causal proof between MASLD and asCVD as well as for the development of multidisciplinary liver/cardiometabolic treatments and care.

AUTHOR CONTRIBUTIONS

Maarten E. Tushuizen and Adriaan G. Holleboom: Conceptualization and supervision; Stan Driessen: Writing—original draft; Sven M. Francque, Stefan D. Anker, Manuel Castro Cabezas, Diederick E. Grobbee, Maarten E. Tushuizen, and Adriaan G. Holleboom: Writing—review and editing.

CONFLICTS OF INTEREST

Stephan D. Anker consults, advises, in on the speakers' bureau, received grants, and owns stock in Abbott Vascular, Actimed, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Occlutech, Pfizer, Repairon, Sensible Medical, Servier, Vectorious, Vifor, and V-Wave. The remaining authors have no conflicts to report.

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