***Invited review***

**MASLD: a systemic metabolic disorder with cardiovascular and malignant complications**

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**Contributorship statement**

All authors contributed equally to the writing of the narrative review and were responsible for drafting individual sections that were then reviewed by the other authors. In particular, G.T. wrote the two sections on the epidemiological data on MASLD and the risk of cardiovascular and malignant complications; C.D.B. wrote the section on the cardiovascular risk assessment, lifestyle modification and specific treatments for MASLD that may benefit CVD risk; H.T. wrote the two sections on the pathophysiology of MASLD and its relationship with cardiovascular and malignant complications.

**Abstract**

Non-alcoholic fatty liver disease (NAFLD) has rapidly become the most common chronic liver disease globally and is currently estimated to affect up to 38% of the global adult population. NAFLD is a multisystem disease where systemic insulin resistance and related metabolic dysfunction play a pathogenic role in the development of NAFLD and its most relevant liver-related morbidities (cirrhosis, liver failure and hepatocellular carcinoma) and extrahepatic complications (such as cardiovascular disease (CVD), type 2 diabetes mellitus, chronic kidney disease, and certain types of extrahepatic cancers). In 2023, three large multinational liver associations proposed that metabolic dysfunction-associated steatotic liver disease (MASLD) should replace the term NAFLD; the name chosen to replace non-alcoholic steatohepatitis (NASH) was metabolic dysfunction-associated steatohepatitis (MASH). Emerging epidemiological evidence suggests an excellent concordance rate between NAFLD and MASLD definitions — i.e., ~99% of individuals with NAFLD meet MASLD criteria. In this narrative review, we provide an overview of the literature on (a) the recent epidemiological data on MASLD and the risk of developing CVD and malignant complications, (b) the underlying mechanisms by which MASLD (and factors strongly linked with MASLD) may increase the risk of these extrahepatic complications, and (c) the diagnosis and assessment of CVD risk and potential treatments to reduce CVD risk in people with MASLD or MASH.

**Introduction**

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease globally and is currently estimated to affect up to 38% of the global adult population [1]. The worldwide prevalence of NAFLD is projected to increase further within the next decade, in parallel with the increasing global epidemics of obesity and type 2 diabetes mellitus (T2DM) [1] [2]. In the last 10-15 years, important conceptual advances have been made in understanding the complex pathophysiological mechanisms of this highly prevalent liver condition. In particular, it has been progressively recognized that NAFLD is a multisystem disease [3], where insulin resistance and related metabolic dysfunction play a pathogenic role in the development of NAFLD and its most relevant liver-related morbidities (cirrhosis, liver failure and hepatocellular carcinoma [HCC]) and extrahepatic complications (such as cardiovascular disease [CVD], T2DM, chronic kidney disease [CKD], and certain types of extrahepatic cancers) [4] [5] [6]. Consequently, in 2020, a panel of international experts proposed a change of terminology and definition for NAFLD in adult individuals — i.e., metabolic dysfunction-associated fatty liver disease (MAFLD) [7]. Subsequently, in 2023, three large multinational liver associations proposed that metabolic dysfunction-associated steatotic liver disease (MASLD) should replace the term NAFLD; the name chosen to replace non-alcoholic steatohepatitis (NASH) was metabolic dysfunction-associated steatohepatitis (MASH) [8]. Emerging epidemiological evidence suggests an excellent concordance rate between NAFLD and MASLD definitions — i.e., ~99% of individuals with NAFLD meet MASLD criteria [9]. However, this nomenclature change better reflects the pathophysiology and cardiometabolic implications of this common and burdensome liver disease.

In this narrative review, we provide an overview of the literature on (a) the recent epidemiological data on MASLD and the risk of cardiovascular disease (CVD) and malignant complications, (b) the underlying mechanisms by which MASLD (and factors strongly linked with MASLD) may increase the risk of developing CVD and malignant complications, and (c) the diagnosis and assessment of CVD risk and potential treatments to reduce CVD risk in MASLD. It is beyond the scope of this narrative review to discuss care pathways for identifying patients at high risk of primary liver cancer and extrahepatic complications.

**Epidemiological data on MASLD and the risk of CVD complications**

MASLD is recognized as a risk factor for major adverse cardiovascular events, which are the leading cause of mortality in adults with MASLD [6] [10]. A recent systematic review and meta-analysis of population-based studies published between 1990 and 2019 provided further evidence that among the MASLD population, the pooled mortality rate was 12.6 per 1000 person-years (95%CI 6.7-23.7) for all-cause mortality; 4.2 per 1000 person-years (95%CI 1.3-7.0) for cardiac-specific mortality; 2.8 per 1000 person-years (95%CI 0.8-4.9) for extrahepatic cancer-specific mortality; and 0.92 per 1000 person-years (95%CI 0.0-2.2) for liver-specific mortality, respectively [11].

Substantial epidemiological evidence from large cohort studies indicates that MASLD is an independent risk factor for CVD morbidity and mortality [12] [13]. In a nationwide cohort study of 10,422 Swedish middle-aged individuals with histologically confirmed MASLD and ~50,000 population controls matched by age, sex, calendar year and county, Simon et al. [14] showed that MASLD was associated with an increased risk of developing cardiovascular outcomes (defined as nonfatal coronary heart disease, stroke, heart failure, or cardiovascular death) over a median of 13.6 years. This risk was independent of common cardiometabolic risk factors and increased progressively with worsening severity of MASLD histology, with the highest incidence rates observed with noncirrhotic fibrosis (adjusted HR 1.67, 95%CI 1.47-1.89) and cirrhosis (adjusted HR 2.15, 95%CI 1.77-2.61) [14].

Many of the published cohort studies were included in an updated meta-analysis that incorporated 36 studies (published until July 2021) with ~5.8 million middle-aged individuals from different countries and captured nearly 100,000 fatal and nonfatal CVD events over a median of 6.9-year follow-up. This meta-analysis concluded that MASLD (diagnosed by liver imaging, International Classification of Diseases codes, or histology) conferred a pooled hazard ratio of 1.45 (95%CI 1.31-1.61) for fatal and nonfatal CVD events, a risk that appeared to increase further with more advanced liver disease, especially MASH with higher fibrosis stages (random-effects HR 2.50, 95%CI 1.68-3.72) and remained statistically significant in those studies where analysis was adjusted for common cardiometabolic risk factors [15].

After the publication of this comprehensive meta-analysis, these findings have been further supported by other cohort studies. For instance, using a nationwide health screening database of ~8.8 million South Korean adults followed up for a median of 12.3 years, Lee et al. reported that MASLD (assessed by fatty liver index ≥30) was independently associated with an increased risk of developing CVD events defined as a composite of myocardial infarction, ischemic stroke, heart failure or cardiovascular death (adjusted HR 1.39, 95%CI 1.38-1.40) [16]. In the UK Biobank cohort study involving 330,751 individuals without baseline CVD, Chen et al. confirmed that MASLD was significantly associated with an increased risk of incident CVD events over a median of 11.8 years [17]. Subsequently, in the UK Biobank imaging sub-study (33,616 participants) where liver disease activity (measured by iron-corrected T1 mapping) and liver fat (by proton density fat fraction [PDFF]) were assessed by magnetic resonance imaging using LiverMultiScan®, Roca-Fernandez et al. found that liver disease activity was associated with a higher risk of major CVD events, cardiac hospitalizations and all-cause mortality, independent of pre-existing metabolic syndrome features and liver fat [18]. Data from the Rancho Bernardo study (including 1,523 elderly participants from the USA followed up for a mean of 15.2 years) confirmed that MASLD was independently associated with a ~35% higher risk of CVD mortality [19].

To date, convincing epidemiological evidence indicates that MASLD promotes not only accelerated coronary atherosclerosis but also affects all other anatomical structures of the heart, conferring an increased risk of left ventricular diastolic dysfunction and hypertrophy, cardiac valvular calcification and arrhythmias (mainly permanent atrial fibrillation) [20] [21] [22] [23, 24]. Furthermore, a recent meta-analysis of eleven longitudinal cohort studies with aggregate data on more than 11 million middle-aged individuals reported that MASLD was associated with a 1.5-fold higher long-term risk of new-onset heart failure (pooled random-effects HR 1.50, 95%CI 1.34-1.67), regardless of the presence of hypertension, T2DM and other common cardiometabolic risk factors [25]. These findings have been confirmed in two cohorts of ~175,000 outpatients with and without MASLD who were propensity score matched for sex, age, index year and known risk factors for heart failure [26]. In this cohort study, the authors found that MASLD was significantly associated with a 10-year higher cumulative incidence of heart failure (HR 1.34, 95%CI 1.28-1.39), in both men and women and across different age strata [26].

Meta-analyses of the excess of fatal and nonfatal CVD events and other cardiac and arrhythmic complications in people with MASLD are summarized in **Table 1**. Collectively, these findings highlight that efforts must continue to raise awareness about MASLD and develop care pathways for identifying and treating patients at increased CVD risk, together with public health efforts to reduce the healthcare burden of MASLD and MASLD-associated cardiovascular morbidity and mortality.

**Epidemiological data on MASLD and the risk of malignant complications**

The global epidemiology of HCC is shifting away from a disease predominated by chronic viral hepatitis and alcohol abuse, with an increasing share of new cases now attributable to MASLD [1].

Substantial epidemiological evidence shows that MASLD is a risk factor for HCC. As recently summarized in an elegant systematic review [27], patients with MASLD-related HCC are more likely to be older and have obesity and other metabolic comorbidities compared to patients with HCC due to other causes. In addition, MASLD-related HCC is associated with a higher proportion of patients without cirrhosis and lower surveillance rates than HCC due to other reasons. Overall survival does not differ between patients with MASLD-related HCC and those with HCC due to other causes, but disease-free survival is longer for patients with MASLD-related HCC. These data suggest that HCC surveillance strategies should be developed not only for those with MASLD who have progressed to cirrhosis but also for MASLD patients without cirrhosis who are at high risk of developing HCC [1] [27]. However, there is currently no consensus regarding HCC surveillance in non-cirrhotic MASLD patients. Future studies are needed to perform MASLD-specific cost-effectiveness analyses for HCC surveillance, principally in those with non-cirrhotic MASH [28].

In a meta-analysis of 64 observational cohort studies (published until August 2020) with 1,903 incident cases of HCC (50 eligible studies, n=625,984 participants) and 2,288 incident cases of any extrahepatic cancer (18 studies, n=41,027 participants), Thomas et al. [29] showed that the HCC incidence rate was 1.25 per 1000 person-years. The HCC incidence rate was remarkably higher in patients with MASLD with advanced fibrosis or cirrhosis (14.5 per 1000 person-years) than in their counterparts without advanced fibrosis/cirrhosis. In this meta-analysis, the authors reported that the pooled extrahepatic cancer incidence rate was 10.6 per 1000 person-years. The most frequently occurring extrahepatic cancers were uterine cancer (4.27 per 1000 person-years), breast cancer (4.02 per 1000 person-years), prostate cancer (1.44 per 1000 person-years), colorectal cancer (1.43 per 1000 person-years), and lung cancer (1.35 per 1000 person-years). Extrahepatic cancer incidence rates did not appear to be significantly higher in patients with MASLD with advanced fibrosis or cirrhosis [29]. Interestingly, this meta-analysis also showed that extrahepatic cancers were over 8-fold more frequent than HCC in people with MASLD. As the global prevalence of MASLD is around 38% and is projected to increase further within the next decade [1], these findings may support the need for early detection of extrahepatic cancers in adults with MASLD, regardless of the coexistence of advanced fibrosis or cirrhosis.

We also recently performed a meta-analysis of observational cohort studies (published until December 2020) to quantify the magnitude of the association between MASLD and the risk of extrahepatic cancers [30]. This meta-analysis included 10 cohort studies with 182,202 middle-aged individuals and ~8,500 incident cases of extrahepatic cancers at different sites over a median of 5.8 years. We found that MASLD was significantly associated with a ~2.5-fold increased risk of thyroid cancer and a ~1.5-fold to twofold increased risk of developing gastrointestinal cancers (esophagus, stomach, pancreas, or colorectal cancers). Furthermore, MASLD was significantly associated with a ~1.2-fold to 1.5-fold increased risk of developing lung, breast, gynecological or urinary system cancers. All risks were independent of age, sex, smoking history, obesity, T2DM, or other potential confounding factors (**Table 1**). The overall heterogeneity for most of the primary pooled analyses was low. However, not enough data were available to examine whether extrahepatic cancer incidence rates increased with the severity of liver disease [30]. Moreover, these findings have recently been confirmed in a retrospective cohort study from Germany [31]. In this study, the investigators identified 86,777 patients with MASLD (defined by International Classification of Diseases codes) and a matched cohort of equal size without MASLD from the Disease Analyzer database (IQVIA), compiling diagnoses and demographic data from general practitioners. During a 10-year follow-up, the investigators reported significantly higher incidence rates of skin cancer, digestive organ cancer, prostate cancer, breast cancer, and female genital organ cancer among MASLD patients than among those without MASLD [31].

The prognostic importance of extrahepatic cancers in MASLD has also been further supported by mortality data reported by Simon et al. in a nationwide cohort of over 10,000 Sweden adult individuals with biopsy-confirmed MASLD and ~50,000 matched controls followed for a median of 14.2 years [32]. In this cohort study, the authors found that all MASLD histological stages were associated with significantly increased overall mortality and that the excess mortality related to MASLD was primarily from extrahepatic cancers, followed by cirrhosis, CVD and HCC [32]. In a subsequent analysis, the same authors examined the incidence rates of both extrahepatic cancers and HCC in a subset of 8,892 individuals with biopsy-proven MASLD followed for a median of 13.8 years [33]. They found that compared with the control population, patients with MASLD had increased overall cancer incidence rates (13.8 vs. 10.9 per 1000 person-years; adjusted HR 1.27, 95%CI 1.18-1.36), driven primarily by HCC. Furthermore, MASLD was associated with significantly increased pancreatic, kidney/bladder, and melanoma rates [33].

After the publication of the two meta-analyses mentioned above [29, 30] other large cohort studies reported that MASLD might be a modifiable risk factor for extrahepatic cancer development (mainly gastrointestinal cancers). For instance, in a nationwide cohort study that included ~5.2 million individuals aged 20-39 years who underwent national health screening under the Korean National Health Insurance Service between 2009 and 2012, Park et al. [34] reported that MASLD (assessed by fatty liver index ≥30) was associated with an increased risk of overall gastrointestinal cancers (adjusted HR 1.16; 95%CI 1.10-1.22), with adjusted HRs ranging from 1.14 to 1.53 for stomach, colorectal, pancreatic, biliary tract, or gallbladder cancers, respectively. These associations remained significant after adjustment for age, sex, smoking, obesity, and alcohol consumption [34]. In a cohort of 151,391 Chinese adults followed for a median of 12.6 years, the authors reported that MAFLD (assessed by ultrasonography) was associated with an increased risk of prostate (HR 1.49, 95%CI 1.07-2.08), thyroid (HR 1.47, 95%CI 1.01-2.12), kidney (HR 1.54, 95% CI 1.18-2.00), colorectal (HR 1.15, 95%CI 0.98-1.34) and breast cancers (HR 1.31, 95%CI 1.04-1.66), even after controlling for age, sex, education level, smoking, alcohol consumption, physical activity, and family history of cancers [35]. Using the Swedish National Patient Registry, Björkström et al. [36] found that patients with MASLD had an increased risk of developing incident cancer over a median follow-up of 6 years compared to control subjects (9.7 vs. 8.6 cases per 1000 person-years; HR 1.22, 95%CI 1.12-1.33). The risk for HCC was particularly high (adjusted HR 12.2, 95%CI 7.1-20.8). The risk for other extrahepatic cancer subtypes was also significantly increased (colorectal [adjusted HR 1.38], kidney [adjusted HR 2.12], bladder [adjusted HR 2.51], and uterine cancers [adjusted HR 1.78]) [36].

Finally, a meta-analysis of eight observational studies (including 56,745 MASLD individuals and 704 incident cases of gastrointestinal cancers) found that patients with lean MASLD had a greater risk of HCC (random-effects HR 1.77, 95%CI 1.15-2.73), pancreatic (random-effects HR 1.97, 95%CI 1.01-3.86) and colorectal cancers (random-effects HR 1.53, 95%CI 1.12-2.09) than non-lean MASLD patients. No significant differences were observed for esophagus, biliary tract and small intestine cancers [37]. These findings emphasize a possible carcinogenic role for MASLD that is independent of obesity, and further highlight the need to explore tailored cancer prevention strategies for this patient population.

**Pathophysiology of MASLD and its relationship with CVD complications**

**Figure 1** schematically summarizes the main pathophysiological aspects contributing to CVD and malignant complications in people with MASLD.

MASH is present in approximately 20% of individuals with MASLD and is characterized by chronic liver inflammation and low-grade systemic inflammation in most affected individuals [38]. The etiology of chronic liver inflammation and low-grade systemic inflammation is complex and multifactorial, and the concept behind this was discussed in 2010 and referred to as a “multiple parallel hits” hypothesis [39]. These “multiple hits” can activate proinflammatory cascades, including various inflammatory cytokines and inflammasomes, such as the NLR family pyrin domain containing 3 (NLRP3) [40, 41]. Chronic liver inflammation is a major driver of liver fibrosis and further complications of MASLD, both inside and outside of the liver [42]. It is also well established that low-grade systemic inflammation, such as that observed in MASLD and many other associated diseases, may promote CVD outcomes [43] and tumorigenesis [44]. It has recently been demonstrated in a preclinical model of MASLD that small extracellular vesicles drive foam cell formation and thereby support atherogenesis and this effect was mediated by an interaction of miR-30a-3p with ABC transporter A1 (ABCA-1)[45].

Low-grade chronic inflammation is crucial for mediating hepatic and most extrahepatic complications of MASLD. Key pathophysiological components of MASLD include metabolic dysfunction and atherogenic dyslipidemia [46]. These two components may be considered “starting points” for this disease as hepatic insulin resistance characterizes most patients with MASLD and is commonly associated with an increased influx of free fatty acids into the liver, which is also aggravated by systemic insulin resistance. In addition, in MASLD there is increased hepatic de novo lipogenesis and a decrease in fatty acid oxidation and VLDL export [47]. In this context, lipotoxicity reflects an important aspect of MASLD pathogenesis as specific lipids may exert proinflammatory effects and promote the release of several proinflammatory mediators and the accumulation of inflammatory leukocytes within the liver. Diverse lipid species, such as sphingolipids, ceramides, *trans* fatty acids or free cholesterol, can also induce liver inflammation, including up-regulation of multiple proinflammatory cytokines and nuclear factor kappa B (NF-*k*B) [48, 49]. Additionally, other not yet well-characterized lipids might contribute to lipotoxicity-related inflammation. Inflammatory signals cause insulin resistance or may further exacerbate existing insulin resistance [50], and nuclear factor-kappa B has been crucially linked to the generation of hepatic insulin resistance [51, 52]. Inflammation-driven insulin resistance also involves other important pathways in MASLD, such as endoplasmic reticulum stress (ER stress) [53, 54]. Notably, obesity, present in about 80-90% of MASLD patients, is also associated (independently of MASLD) with low-grade systemic inflammation (“metaflammation”), ER stress dysregulation or lipotoxicity [55]. A very high rate of MASLD is observed in obese individuals, further strengthening the pathophysiological link between obesity and MASLD [5]. Genetic factors might also contribute to CVD outcomes as studies have observed a link between certain *PNPLA3* genotypes and CVD, including carotid atherosclerosis or coronary heart disease [56, 57, 58].

Another important component driving chronic inflammation in MASLD is the alteration of gut microbiota. MASLD and especially advanced stages of the disease process are commonly accompanied by substantial gut dysbiosis and the evolution of certain pathobionts [59]. A profound gut dysbiosis in MASLD was demonstrated in patients with advanced liver fibrosis and dysbiosis was accompanied by the appearance of Proteobacteria and pathobionts such as *Escherichia coli [60]*. Interestingly, the gut microbiome assessment has the potential to predict later development of MASLD [61]. The instability of gut microbiota predicts the evolution of metabolic liver disease, as shown in a large prospective German study [62]. Whether targeting the gut microbiome is a promising treatment option for MASLD remains unclear. Several mouse MASH models have shown protective and anti-inflammatory effects using probiotics such as *Faecalibacterium prausnitzii* [63, 64]. An altered gut virome has also been associated with the severity of MASLD, as gut virome diversity decreased in severely diseased patients [65]. A gut dysbiosis might increase hepatic and systemic lipopolysaccharide (LPS) concentrations in patients with MASLD [66, 67]. Dysbiosis, evolution of various pathobionts and gut/bacteria-derived metabolites might contribute to hepatic and systemic low-grade inflammation in MASLD. Besides LPS, increased circulating levels of various proinflammatory metabolites, such as gut microbiome-derived lactate, ethanol or trimethylamine oxide (TMAO), characterize MASLD. Furthermore, MASLD is accompanied by decreased total bile acid pool size, especially secondary bile acids or short-chain fatty acids [68].

What is frequently ignored but equally important is the relevance of diets, especially proinflammatory diets, in MASLD. This concept is important as it has been shown that dietary factors reflect key confounding factors affecting the gut microbiota composition [69, 70]. Research in the past decade has revealed that specific dietary components may induce and promote low-grade inflammation in various organs, including the intestine and the liver. In addition, a proinflammatory state might be promoted when anti-inflammatory diets lack or are not consumed sufficiently [71, 72]. High-fat diets may typically impair the epithelial intestinal barrier and increase systemic LPS [73]. Milk-derived fats may promote the expansion of certain pathobionts, such as *Bacteroides wadsworthia,* and a consequent decrease of beneficial secondary bile acids, and both milk-derived fat and excessive salt consumption drive Th-1 and Th-17-driven inflammation [74]. Other dietary proinflammatory triggers might constitute consumption of palmitic acid or *trans* fatty acids, and dietary components such as phosphatidylcholine may result in higher circulating levels of TMAO, which have been linked to atherosclerosis and low-grade systemic inflammation [75].

The importance of low-grade inflammation in CVD has been highlighted in a recent study by Ridker et al., demonstrating by analyzing three large multinational trials of patients receiving statin therapy that low-grade inflammation as measured by plasma high-sensitivity C-reactive protein (hsCRP) concentrations predicts more strongly the risk of CVD mortality and morbidity than when only assessing plasma low-density lipoprotein cholesterol (LDL-C) concentrations [76]. This finding is important as it suggests that targeting low-grade systemic inflammation would be of major interest in the future in such patients [77]. Patients with MASH show evidence of low-grade systemic inflammation as the circulating levels of hsCRP and IL-1 receptor antagonist (IL-1RA), another sensitive marker of systemic inflammation, are increased [78, 79]. Interestingly, plasma hsCRP concentrations correlate with all-cause mortality in MASLD patients, as well as malignancy-related and CVD mortality [78]. With respect to hepatic and extrahepatic inflammation and their driving forces, it remains unclear which “hits” come first and take the lead. It seems most likely, as originally proposed in our “multiple parallel hits” hypothesis that various pathophysiological factors can adversely act in parallel, such as lipotoxicity, insulin resistance, obesity, proinflammatory diets or intestinal dysbiosis, thereby causing hepatic and extrahepatic chronic inflammation in a concerted manner [39]. Chronic inflammation is crucially involved in MASLD progression, including liver-related complications such as HCC, but may also promote adverse CVD outcomes and extrahepatic cancers. Anti-inflammatory therapies might, therefore, play an important role in the future management of MASLD/MASH [80]. It remains, however, unclear which components in MASLD finally cause accelerated atherosclerosis and CVD, but it can be speculated that similarly as in the liver, “multiple parallel hits” may adversely affect the cardiovascular system and vasculature.

**Pathophysiology of MASLD and potential associations with hepatic and extrahepatic malignancies**

***Hepatocellular carcinoma***

HCC is a typical complication of MASLD-related cirrhosis but also appears at earlier non-cirrhotic stages of the disease. MASLD-related HCC might evolve in the next years as the most prevalent cause of HCC in humans [81]. The pathophysiology of HCC is still not completely understood as it reflects a feature of many different liver diseases accompanied by chronic liver injury and inflammation. Both innate and adaptive immunity may contribute to the development of MASLD-related HCC. Preclinical studies strongly support a role for innate immunity and proinflammatory cytokines. Obesity-driven HCC development is dependent on the proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor (TNF), as demonstrated in dietary and genetic models of fatty liver disease in mouse models [82]. This effect was driven by the transcription factor signal transducer and activator of transcription 3 (STAT3) and NF-*k*B [83]. Interestingly, specific liver cancer progenitor cells in the liver may progress towards a malignant phenotype in an IL-6-dependent manner [84]. Other proinflammatory cytokines, such as IL-1 alpha, may promote liver tumorigenesis [85]. Various additional pathways drive inflammation-related HCC, such as ER stress [86], a pathway that is also activated in human MASLD. Many other proinflammatory “hits” have the potential to drive hepatic carcinogenesis, including mammalian target of rapamycin complex 1 (mTORC1) and oxidative stress as demonstrated in nicotinamide adenine dinucleotide phosphate oxidase (NOX) knockout mice [87, 88]. Whereas several previous studies have highlighted that innate immunity and its key proinflammatory players constitute major drivers of HCC development, more recent studies reported that adaptive immunity is also involved in HCC development [89]. A landmark study from Dudek and colleagues revealed a crucial role for T cells in liver immunopathology and MASH [90]. These authors observed hepatic accumulation of CD8+ T cells with phenotypes that combined tissue residency with effector and exhaustion characteristics, such as programmed cell death protein (PD1) expression. IL-15 induced the forkhead box O1 (FOXO1) downregulation and C-X-C chemokine receptor 6 (CXCR6) upregulation, which together rendered liver-resident CXCR6+CD8+T cells susceptible to metabolic stimuli and triggered auto-aggression. Such auto-aggressive CD8+ PD1+ T cells accumulate especially in MASH patients, and this cell type has been linked to a lack of immune surveillance in mice and human studies [90, 91]. Such a micro-milieu might favor liver carcinogenesis, explaining why HCC evolves even in a non-cirrhotic liver. It remains unclear how metabolic signals interfere with this type of immunity. Specific T cells such as CD8+ PD1+ CXCR6+ T cells respond to metabolic stimuli even in an antigen-independent manner and thereby can kill hepatocytes, causing a highly proinflammatory *milieu*. The role of immunity in MASLD-related HCC has been recently reviewed [89]. Besides chronic inflammation and immunity, some genetic polymorphisms related to a greater susceptibility to MASLD and MASH, such as the *PNPLA3, TM6SF2, MBOAT7* and *HSD17B13* genetic variants, have also been linked to HCC development [92]. In support of this, a recent study reported familial clustering of liver-related complications, including HCC, in biopsy-proven MASLD patients [93].

***Extrahepatic cancers***

MASLD is associated with an increase in extrahepatic malignancies, as discussed in the first section of this review [30, 94]. An increased rate of malignancies is also seen in obesity, and it is assumed that common mechanisms can contribute to extrahepatic malignancies in obesity +/- MASLD. A common feature of both disorders is chronic inflammation, as chronic inflammation, including NF-B activation, is a crucial driver of cancer development [44]. The importance of obesity as a significant cancer driver is also supported by bariatric surgery studies where death rates from cancer were decreased with weight loss [95]. In addition, rates of gastrointestinal cancers such as esophageal adenocarcinoma decreased after bariatric surgery-induced weight loss [96]. Other pathways may contribute to an increased risk of extrahepatic cancers that involve adipokine signaling. Adipokines are key products secreted by adipose tissue, either released in excess or impaired production, as in severe metabolic disturbances. Prototypic adipokines, such as adiponectin or leptin, have opposing effects as leptin favors a proinflammatory *milieu*, whereas adiponectin has substantial anti-inflammatory and insulin-sensitizing effects [97]. A common cancer associated with MASLD is colorectal carcinoma (CRC) [98] and cancers such as CRC, esophageal cancer, prostate cancer or breast cancer are associated with lower plasma adiponectin concentrations [99]. Visceral adiposity, common in MASLD and associated with lower adiponectin levels, is also a risk factor for CRC [100]. Preclinical studies highlighted the importance of adiponectin in CRC carcinogenesis as this adipokine may inhibit CRC cell growth dependent on the activation of adenosine monophosphate-activated protein kinase (AMPK) and mTOR [101]. Besides adipokine disturbances observed in MASLD [102], several other mechanisms might promote carcinogenesis either directly or indirectly, such as increased production of reactive oxygen species, insulin-like growth factor 1 (IGF-1) or insulin resistance mainly via activation of other inflammatory pathways, such as mitogen-activated protein kinase (MAPK) p38 signaling pathways.

**CVD risk assessment, lifestyle modification and specific treatments for MASLD that may benefit CVD risk**

In this section, we consider the CVD risk assessment and recommendations for lifestyle changes and pharmacological treatments targeting CVD risk in people with MASLD. Although, as mentioned above, MASLD is an independent risk factor for CVD, and the severity of liver disease further amplifies that risk of CVD events, existing algorithms and risk calculators do not, to date, consider MASLD as a CVD risk factor in the estimation of an individual’s level of CVD risk using available risk calculators. Since liver fibrosis markedly increases the risk of adverse CVD outcomes, it might be expected that liver fibrosis would further improve CVD risk prediction in people with MASLD. However, to date, this issue remains unresolved, and CVD risk calculators do not consider any of the individual measures of liver disease in MASLD. Nevertheless, CVD risk assessment in all patients with MASLD is clinically mandatory to inform appropriate management and treatment decisions focused on attenuating CVD risk [103]. Patients with MASLD represent a heterogeneous group of individuals concerning their CVD risk, and with the considerable treatment options now available, clinicians need to make personalized treatment decisions since not all patients with MASLD have the same cluster of CVD risk factors nor the same absolute risk of CVD events.

***CVD risk assessment in MASLD***

The first consideration is how CVD risk should be assessed in patients with MASLD? Most patients with MASLD are likely to be middle-aged, and although there are exceptions, women with MASLD are most likely to be peri- or post-menopausal. Because of the age demographic of patients with MASLD, this patient group should be considered for a CVD health check as most patients will be >40 years old. It is also important to consider ethnicity and the region of the globe in which the person’s risk of CVD is being assessed.

Beyond the presence of MASLD, various factors increase a person’s risk of developing CVD. These risk factors can be divided into non-modifiable and modifiable risk factors. Briefly, CVD risk factors are: (a) non-modifiable, e.g., older age, male sex, having a strong family history of premature CVD, and being of a certain ethnicity (such as South Asian ethnicity) or having early menopause (<40 years); and (b) modifiable, e.g., smoking, having an increased plasma LDL-C concentration, being sedentary, eating an unhealthy diet and having factors linked with obesity and specifically abdominal obesity, such as hypertension, insulin resistance, atherogenic dyslipidemia (see below), and T2DM as key features of metabolic syndrome [104].

With many of these modifiable CVD risk factors (e.g., T2DM, hypertension and obesity), there is a further amplification of CVD risk when associated comorbidities such as CKD also occur. For example, T2DM is a strong risk factor for CKD stage ≥3 (defined by eGFR <60 mL/min/1.73 m2 with/without coexisting abnormal albuminuria or overt proteinuria), and each of these associated renal factors, as well as chronic dialysis or renal transplantation, are strong independent risk factors for CVD.

Although increased plasma LDL-C concentration is a common risk factor in middle-aged subjects (and occurs independently of MASLD), an increased plasma LDL-C concentration will further increase the risk of CVD in people with MASLD [15]. A more common dyslipidemia frequently occurring with MASLD is the atherogenic lipoprotein phenotype, comprising increased small-dense LDL particles, low HDL-cholesterol and high triglyceride concentrations. Although subjects with MASLD with atherogenic dyslipidemia may have normal plasma LDL-C concentrations, it is in this situation that treatment with a statin will decrease CVD risk (see below).

While these modifiable and non-modifiable risk factors and associated comorbidities must be considered in assessing CVD risk, it is also important to recognize that some people with MASLD may have other unrelated but relatively common comorbid conditions (unrelated to MASLD) that may also increase the CVD risk. These comorbid conditions that need to be considered and recognized as important additional CVD risk factors include rheumatoid arthritis, severe mental ill-health and associated treatments, and periodontal disease.

For assessing global CVD risk, some countries/regions/organizations now recommend vascular health checks or risk assessments targeted at individuals of a certain age and who do not have pre-existing CVD, T2DM or CKD as recognized easily identifiable risk factors for CVD. For example, the ACC/AHA (American College of Cardiology/American Heart Association) guidelines and in England and Wales, the NICE (National Institute for Health and Care Excellence) guidelines recommend that everyone between the ages of 40 and 75 years should be invited for a health check [105] [106]. This health check includes a CVD risk assessment, evaluation of alcohol consumption, physical activity levels, plasma LDL-C level, body mass index, and screening for T2DM and CKD with an assessment of hemoglobin A1c and eGFR. Additionally, it is important to assess psychological stressors and health literacy and provide appropriate support where necessary [103]. The CVD risk assessment tools should be specific to the region/country of interest, and in England and Wales, it is recommended that the QRISK CVD risk calculator is used, as this has been validated in the UK. In the USA, pooled cohort equations are recommended for CVD risk assessment [103]. The European Society of Cardiology (ESC) recommends using sex-specific SCORE-2 calculators in European populations. For example, the ESC recommends the use of the SCORE-2 risk calculator up to the age of 70 years; for older persons (OP) above this age, the SCORE-2 OP calculator, and for people with diabetes, the SCORE-2 Diabetes calculator [107, 108, 109]. The SCORE-2 Diabetes calculator was validated in people with T2DM without pre-existing CVD. Sex-specific competing risk-adjusted models were used, including both traditional CVD risk factors (age, smoking, systolic blood pressure, total cholesterol and HDL-cholesterol levels) and diabetes-related variables (age at diabetes diagnosis, hemoglobin A1c and eGFR). These models were recalibrated to CVD incidence in four European risk regions [108].

It is recommended that global CVD risk is assessed every ~5 years [103, 106], and it is important to bear in mind that aging is the major unmodifiable risk factor that powerfully influences the estimate of the risk of a CVD event over the next 10 years. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the primary prevention of CVD [103] contains appropriate guidance that should be used for people with MASLD, bearing in mind all of the other CVD risk factors linked (and not linked) to MASLD considered above. In the ACC/AHA guideline, it is recommended that adults who are 40 to 75 years of age and are being evaluated for cardiovascular disease prevention should undergo a 10-year CVD risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin, or aspirin (aspirin should be used infrequently in the routine primary prevention of CVD because of lack of net benefit) [103]. For younger individuals, e.g., 20-39 years of age, it is reasonable to assess common CVD risk factors every ~5 years [103].

Statin therapy is the first-line treatment for primary prevention of CVD in people considered to be at increased risk. There is still uncertainty about the level of risk at which healthcare practitioners should advocate intervention with statin treatment. In the USA, it is considered good practice to recommend statin treatment in individuals at ‘intermediate risk’ (i.e., ≥7.5% 10-year estimated CVD risk) [103], whereas in the UK a ≥10% threshold for intervention is advocated [106]. With the lower threshold of CVD risk, it is important to realize that virtually every 60-year-old man would be treated with a statin based on their age alone, regardless of CVD risk factors. In certain individuals with other risk-enhancing factors or in persons at intermediate CVD risk who are not keen to start statin treatment, high-resolution computed tomography (CT) scanning of the coronary arteries to detect coronary artery calcium has a place in helping refine decision-making regarding reassurance, advice that treatment is recommended, or advice that referral to Cardiology specialists is needed for consideration of further diagnostic cardiac tests [105]. In such subjects, assessment of coronary artery calcium with high-resolution CT of the coronary arteries to assess the presence, quantity and location of coronary artery calcium is a valuable investigation to assist in refining risk prediction either upwards or downwards, as part of the process of helping shared decisions between patients and health care professionals. For example, if the coronary artery calcium score is ≥100 Agatston Units (or ≥75th age/sex/race percentile), a subject might be moved upward, and if the coronary artery calcium score is zero, a subject can be reassured [103]. For younger adults, an estimation of lifetime CVD risk in the 20 to 59-year age group may also be considered. Additionally, non-pharmacological interventions are recommended for all adults with elevated blood pressure or hypertension, and for those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mmHg [103].

***Lifestyle changes and drug treatments for CVD prevention in MASLD***

Healthcare professionals should advocate the cessation of smoking and the consumption of a healthy diet that encourages vegetables, fruits, nuts and minimally processed whole grains. Vegetables, lean animal or fish proteins will reduce the consumption of *trans* fats and red meats, processed meats, refined carbohydrates, sucrose, fructose and sweetened drinks should be limited [105]. For most individuals with MASLD who are overweight or obese, the benefits of calorie restriction to decrease body fat, reduce liver fat and inflammation, and improve the associated metabolic syndrome features should be emphasized. There remains debate about whether small amounts of daily alcohol consumption are harmful or beneficial. That said, mild-moderate alcohol intake and metabolic syndrome are highly prevalent in the population and can frequently coexist. The few available prospective studies have indicated that mild-moderate alcohol intake is associated with an increased risk of liver-related outcomes [110]. Systems biology analyses have suggested that alcohol intake and metabolic syndrome may potentiate the effects of each other, affecting common pathways in fatty liver disease to worsen liver-related outcomes [110]. Consequently, regardless of any impact of modest alcohol intake on the risk of CVD in MASLD, for benefitting liver health, it would seem prudent to advocate alcohol abstinence for patients with MASLD. Patients should also be encouraged to undertake ≥150 minutes of moderately intense or 75 minutes of vigorous physical activity per week [105]. When considering the effects of lifestyle advice to specifically treat obesity and reduce CVD risk in patients with MASLD, it is important to consider that weight loss is best achieved with calorie restriction. For example, it has been shown that marked calorie restriction induces T2DM remission in overweight or obese people recently diagnosed with T2DM [111]. In this open-label, cluster-randomized, controlled trial (DiRECT trial), participants randomly assigned to an integrated structured, intense, weight-management programme (intervention) reached a significantly greater weight reduction ≥15 kg and remission of T2DM at 2 years compared to those assigned to the best-practice care in accordance with guidelines (control) [111]. Thus, a structured calorie restriction programme focussed on weight loss induces T2DM remission over 2 years, although in this trial, it was uncertain how many patients also had MASLD. Losing body fat is very important for decreasing plasma glucose levels, ameliorating MASH, and improving metabolic syndrome features but, to date, in MASLD it is uncertain whether these benefits can be sustained, not least if people relapse and re-gain body fat. It is also uncertain whether the improvement in cardiometabolic risk factors caused by calorie restriction and weight loss, translates into longer-term benefits on CVD events.

When considering potential drug treatments that may benefit MASLD and CVD, it is important to consider drug actions that are beneficial for treating cardiometabolic risk factors and that are at least neutral or may benefit liver disease in MASLD. Ideally, a treatment for improving CVD risk factors in MASLD would also attenuate hepatic steatosis, inflammation and fibrosis. Many of the risk factors for CVD (that also characterize a diagnosis of MASLD), such as the features of metabolic syndrome, are also strong risk factors for comorbidities such as T2DM, hypertension and CKD associated with MASLD as a multisystem disease. These cardiometabolic risk factors include increased blood pressure, atherogenic dyslipidemia, dysglycemia and abdominal obesity.

The presence of T2DM further increases the risk of both macrovascular disease and microvascular disease, both of which may increase the risk of CKD, and when CKD or microalbuminuria/proteinuria occurs, these renal abnormalities will further increase the risk of CVD. Since chronic hyperglycemia that happens with T2DM is also a significant risk factor for microvascular disease, it is therefore essential to treat hyperglycemia with glucose-lowering agents to attenuate the risk of microvascular disease to reduce the risk of end-organ disease in the kidneys that will further affect the risk of CVD. Although it should be noted that there is no randomized placebo-controlled trial evidence specifically testing the effect of drugs on CVD outcomes in people with MASLD, we have considered the available evidence from cardiovascular endpoint trials and then extrapolated that evidence to people with MASLD. In doing this, we have considered the benefits, harms, and licensed indications of drugs and whether these drugs may have a place in attenuating CVD risk in MASLD. In **Supplementary Table 1 (supplementary file)**, we summarize the drug classes, principal modes and sites of action, indications for use, benefits and side effects of drugs that may potentially reduce CVD risk in MASLD. For people with obesity, it should be noted that incretin receptor agonists can induce ~10-15% decreases in body weight. In **Figure 2** we have summarized in a flow diagram a pragmatic approach to the assessment and management of CVD risk in adults with MASLD. **Figure 3** summarizes the randomized controlled trial evidence of current therapeutic approaches for MASLD or MASH that also have beneficial or neutral effects on the CVD risk profile.

**Conclusion**

Epidemiological evidence suggests an excellent concordance rate between NAFLD and MASLD definitions — i.e., ~99% of individuals with NAFLD meet MASLD criteria. MASLD is a multisystem disease where insulin resistance and related metabolic dysfunction play a pathogenic role in the development of MASLD and its most relevant liver-related morbidities and extrahepatic complications (such as CVD, T2DM, CKD, and certain extrahepatic cancers). Since MASLD is an independent risk factor for CVD and most patients die from the consequences of CVD rather than from liver-related complications, it is important to try and attenuate that risk of CVD. Patients with MASLD have a heterogeneous cluster of CVD risk factors, and the absolute risk of CVD events varies considerably according to age, sex, ethnicity, region, and individual risk factors. Consequently, it is essential to assess CVD risk in subjects with MASLD using region-specific CVD risk calculators. Statins are usually safe in people with MASLD and should be advocated where the 10-year estimated CVD risk of a vascular event is ≥10% (or ≥7.5% as recommended in the USA). Beyond supporting lifestyle improvements, many licensed treatments for T2DM, e.g., GLP-1 receptor agonists, SGLT2 inhibitors or pioglitazone, have now been shown to reduce the risk of adverse CVD outcomes and improve coexisting risk factors. These and other well-established drug treatments that have also been shown to be beneficial for attenuating CVD risk (e.g., RAS inhibitors) should be considered in individual patients with MASLD as part of a holistic approach to reducing CVD risk in this patient population.

**Table 1.** Meta-analytic quantification of the excess risk of developing fatal and nonfatal CVD events, permanent atrial fibrillation, new-onset heart failure, or extrahepatic cancers in middle-aged individuals with MASLD.

|  |  |  |  |
| --- | --- | --- | --- |
| **Author(s), Year, [Ref]** | **Study** **Characteristics** | **Study** **outcomes** | **Random-effects hazard ratios (95% confidence intervals)**  |
| ***Fatal and nonfatal CVD events***  |
| Mantovani A et al., 2021 [15] | 36 longitudinal cohort studies involving a total of about 5.8 million individuals; median follow-up of 6.5 years | Any fatal or nonfatal CVD events, n=36 studies | 1.45 (1.31-1.61) |
| Fatal CVD events (only), n=12 studies | 1.30 (1.08-1.56) |
| Nonfatal CVD events (only), n=13 studies  | 1.40 (1.20-1.64)  |
| Fatal and nonfatal CVD events (combined endpoint), n=11 studies | 1.81 (1.39-2.36) |
| Subgroup analyses in patients with “more severe” MASLD (MASLD with increasing severity of fibrosis assessed by histology or fibrosis scores) | Fatal CVD events (only), n=4 studies | 2.03 (1.17-3.54) |
| Nonfatal CVD events (only), n=2 studies | 2.30 (1.20-4.42) |
| Fatal and nonfatal CVD events (combined endpoint), n=6 studies | 2.54 (1.73-3.73) |
| ***Permanent atrial fibrillation*** |
| Cai X et al., 2020 [24] | 6 longitudinal cohort studies involving a total of 614,673 individuals; median follow-up of 10 years | Incident atrial fibrillation,n=6 studies | 1.19 (1.04-1.31) |
| Subgroup analyses in patients with “more severe” MASLD  | Not enough data available for analysis | Not available  |
| ***Heart failure*** |
| Mantovani A et al., 2022 [25] | 11 longitudinal cohort studies involving a total of about 12.2 million individuals; median follow-up of 10 years | Incident heart failure, n=11 studies | 1.50 (1.34-1.67) |
| Subgroup analyses in patients with “more severe” MASLD (MASLD with increasing severity of fibrosis assessed by histology or fibrosis scores) | Incident heart failure, n=2 studies  | 1.76 (0.75-4.36) |
| ***Extrahepatic cancers*** |
| Mantovani A et al., 2022 [30] | 10 longitudinal cohort studies involving a total of 182,202 individuals; median follow-up of 5.8 years | Incident esophagus cancer, n=5 studies  | 1.93 (1.19-3.12) |
| Incident stomach cancer n=6 studies | 1.81 (1.19-2.75) |
| Incident pancreas cancer, n=3 studies  | 1.84 (1.23-2.74)  |
| Incident colorectal cancer, n=8 studies | 1.64 (1.24-2.19) |
| Incident thyroid cancer, n=2 studies | 2.63 (1.27-5.45) |
| Incident lung cancer, n=5 studies | 1.30 (1.14-1.48) |
| Incident urinary system cancer, n=4 studies | 1.33 (1.04-1.70) |
| Incident breast cancer, n=4 studies | 1.39 (1.13-1.71) |
| Incident female genital organ cancer, n=4 studies | 1.62 (1.13-2.32) |
| Incident prostate cancer, n=5 studies | 1.16 (0.82-1.64) |
| Incident hematological cancers, n=2 studies | 1.47 (0.69-3.12) |
| Subgroup analyses in patients with “more severe” MASLD  | Not enough data available for analysis | Not available  |

**Figure Legends**

**Figure 1. Pathophysiological aspects contributing to cardiovascular and malignant complications in people with MASLD.**

Multiple “parallel hits”, such as lipotoxicity, insulin resistance, proinflammatory diets and intestinal dysbiosis, can contribute to the development of liver inflammation and systemic low-grade inflammation in MASLD or MASH. Chronic liver inflammation promotes liver fibrogenesis and further progression of liver disease towards cirrhosis and HCC. Liver-driven systemic low-grade inflammation contributes to development of cardiovascular inflammation/atherosclerosis, chronic kidney disease, as well as support cancer development in various organs, such as the colon, stomach, pancreas and others. Both innate and adaptive immunity can participate in the development of chronic liver inflammation in MASLD.

*Abbreviations*: CXCR6, C-X-C chemokine receptor 6; ER stress, endoplasmic reticulum stress; HCC, hepatocellular carcinoma; JNK, c-Jun N-terminal kinase; MASH, metabolic dysfunction-associated steatohepatitis; NLRP3, NLR family pyrin domain containing 3; NF-kB, nuclear factor kappa B; PD1, programmed cell death 1; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3.

**Figure 2. Flow diagram describing a pragmatic approach to the assessment and management of CVD risk in people with MASLD.**

This flow diagram emphasizes the need to assess individual cardiovascular disease (CVD) risk factors and estimate CVD risk in patients with MASLD. The flow diagram also illustrates specific treatments to attenuate CVD risk in patients at high risk of CVD, where those treatments have been shown to have proven efficacy in reducing incident CVD events.

The flow diagram illustrates the importance of assessing the co-existence of T2DM, CKD, hypertension or previously diagnosed CVD causing a vascular event, such as acute myocardial infarction or ischemic stroke. The presence of these conditions may warrant additional disease-specific treatments. For example, for patients with known CVD, it may prove necessary to focus on high-dose statin treatment with the goal of achieving a plasma LDL-C level <1.8 mmol/L. For patients with T2DM who have microvascular disease affecting the kidneys (abnormal urine ACR), it may be necessary to implement treatment with sodium-glucose co-transporter-2 (SGLT-2*)*inhibitors. The flow diagram also illustrates the importance of estimating the 10-year risk of a first CVD event using a specific CVD risk calculator tool. Such a tool needs to have been validated in the region and population in which it will be used.

For patients with “intermediate” CVD risk or those who are unconvinced by the benefit of taking a statin, consideration of whether further noninvasive investigation of potential CVD is required. Where high-resolution computed tomography (CT) is available, coronary artery calcium scoring (CACS) assessment can offer a quick but relatively expensive investigation for refining CVD risk prediction. Where the CVD score is increased (e.g., ≥90th centile adjusted for age and sex or the score is high, e.g., >300 Agatston Units), referral to Cardiology specialists for further investigation should be considered. Such individuals may require not only treatment with a high-dose statin to achieve plasma LDL-C targets (see above) but also low-dose aspirin and angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers. Although statins are safe in people with MASLD or MASH, some individuals will not be able to tolerate statin treatment. In these individuals, other lipid-lowering drugs, such as ezetimibe, bempedoic acid or proprotein convertase subtilisin/kexin type-9 (PCSK9) monoclonal antibody treatment, may be warranted and further specialist lipid management advice should be sought.

Antihyperglycemic drugs such as GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists have beneficial hepatic effects, mainly through weight loss. GLP-1 receptor agonists have proven efficacy to benefit type 2 diabetes, CVD, and CKD. In particular, GLP-1 receptor agonists are effective in the brain and decrease appetite and induce satiety, thus reducing dietary calorie intake. These effects can facilitate weight loss, which benefits MASLD, type 2 diabetes and CVD risk factors. Angiotensin II receptor blockers or renin-angiotensin system (RAS) inhibitors have beneficial effects on the vasculature and kidneys, reducing blood pressure, while pioglitazone that is licensed for the treatment of T2DM has been shown to have beneficial effects to treat liver disease in MASLD, decrease the risk of acute myocardial infarction and ischemic stroke, and has durable effects to lower plasma glucose concentrations in patients with, or at risk of, type 2 diabetes.

*Abbreviations***:** CACS, coronary artery calcium score; CKD, chronic kidney disease; MASLD, metabolic dysfunction-associated steatotic liver disease. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; RAS, renin-angiotensin system; SGLT2, sodium glucose co-trasporter-2; T2DM, type 2 diabetes mellitus, ACR, albumin-to-creatinine ratio.

**Figure 3. Current therapeutic approaches for MASLD or MASH with beneficial or neutral effects on the cardiovascular risk profile.**

There are currently no licensed treatments for MASLD or MASH. The figure summarizes the evidence mainly derived from phase 2 or phase 3 randomized placebo-controlled trials of current therapeutic approaches showing promise in the treatment of this common and burdensome liver disease, in terms of improvement in liver steatosis, steatohepatitis or fibrosis. Licensed treatments for type 2 diabetes mellitus (for example, GLP-1 receptor agonists, pioglitazone or SGLT2 inhibitors) are among the most promising treatment options for MASLD or MASH and effectively also decrease the future risk of fatal and nonfatal CVD events.

*Abbreviations***:** PPAR, peroxisome proliferator-activated receptors; GLP-1, glucagon-like peptide-1; SGLT2, sodium glucose co-trasporter-2.

**References**

1 Wong VW, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol 2023;**79**:842-52.

2 Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, Bugianesi E*, et al.* The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. Lancet 2021.

3 Byrne CD, Targher G. NAFLD: A multisystem disease. J Hepatol 2015;**62**:S47-S64.

4 Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. The lancet Gastroenterology & hepatology 2021;**6**:578-88.

5 Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. Nat Rev Gastroenterol Hepatol 2021;**18**:599-612.

6 Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;**66**:1138-53.

7 Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M*, et al.* A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;**73**:202-9.

8 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.

9 Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. J Hepatol 2023.

10 Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P*, et al.* Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015;**149**:389-97.e10.

11 Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;**77**:1335-47.

12 Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z*, et al.* Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol 2022;**42**:e168-e85.

13 Zhou XD, Targher G, Byrne CD, Somers V, Kim SU, Chahal CAA*, et al.* An international multidisciplinary consensus statement on MAFLD and the risk of CVD. Hepatology international 2023.

14 Simon TG, Roelstraete B, Hagström H, Sundström J, Ludvigsson JF. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: results from a nationwide histology cohort. Gut 2021.

15 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. The lancet Gastroenterology & hepatology 2021;**6**:903-13.

16 Lee HH, Lee HA, Kim EJ, Kim HY, Kim HC, Ahn SH*, et al.* Metabolic dysfunction-associated steatotic liver disease and risk of cardiovascular disease. Gut 2023.

17 Chen J, Sun Y, Fu T, Lu S, Shi W, Zhao J*, et al.* Risk of incident cardiovascular disease among patients with gastrointestinal disorder: a prospective cohort study of 330,751 individuals. European heart journal Quality of care & clinical outcomes 2023.

18 Roca-Fernandez A, Banerjee R, Thomaides-Brears H, Telford A, Sanyal A, Neubauer S*, et al.* Liver disease is a significant risk factor for cardiovascular outcomes - a UK Biobank study. J Hepatol 2023.

19 de Avila L, Henry L, Paik JM, Ijaz N, Weinstein AA, Younossi ZM. Nonalcoholic Fatty Liver Disease Is Independently Associated With Higher All-Cause and Cause-Specific Mortality. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2023;**21**:2588-96.e3.

20 Anstee QM, Mantovani A, Tilg H, Targher G. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2018;**15**:425-39.

21 Yong JN, Ng CH, Lee CW, Chan YY, Tang ASP, Teng M*, et al.* Non-alcoholic fatty liver disease association with structural heart, systolic and diastolic dysfunction: a meta-analysis. Hepatology international 2022;**16**:269-81.

22 Di Minno MN, Di Minno A, Ambrosino P, Songia P, Tremoli E, Poggio P. Aortic valve sclerosis as a marker of atherosclerosis: Novel insights from hepatic steatosis. Int J Cardiol 2016;**217**:1-6.

23 Mantovani A, Dauriz M, Sandri D, Bonapace S, Zoppini G, Tilg H*, et al.* Association between non-alcoholic fatty liver disease and risk of atrial fibrillation in adult individuals: An updated meta-analysis. Liver Int 2019;**39**:758-69.

24 Cai X, Zheng S, Liu Y, Zhang Y, Lu J, Huang Y. Nonalcoholic fatty liver disease is associated with increased risk of atrial fibrillation. Liver Int 2020;**40**:1594-600.

25 Mantovani A, Petracca G, Csermely A, Beatrice G, Bonapace S, Rossi A*, et al.* Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals. Gut 2022.

26 Roderburg C, Krieg S, Krieg A, Vaghiri S, Mohr R, Konrad M*, et al.* Non-Alcoholic Fatty Liver Disease (NAFLD) and risk of new-onset heart failure: a retrospective analysis of 173,966 patients. Clinical research in cardiology : official journal of the German Cardiac Society 2023;**112**:1446-53.

27 Tan DJH, Ng CH, Lin SY, Pan XH, Tay P, Lim WH*, et al.* Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. The Lancet Oncology 2022;**23**:521-30.

28 Singal AG, El-Serag HB. Rational HCC screening approaches for patients with NAFLD. J Hepatol 2022;**76**:195-201.

29 Thomas JA, Kendall BJ, Dalais C, Macdonald GA, Thrift AP. Hepatocellular and extrahepatic cancers in non-alcoholic fatty liver disease: A systematic review and meta-analysis. European journal of cancer (Oxford, England : 1990) 2022;**173**:250-62.

30 Mantovani A, Petracca G, Beatrice G, Csermely A, Tilg H, Byrne CD*, et al.* Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut 2022;**71**:778-88.

31 Roderburg C, Kostev K, Mertens A, Luedde T, Loosen SH. Non-alcoholic fatty liver disease (NAFLD) is associated with an increased incidence of extrahepatic cancer. Gut 2023;**72**:2383-4.

32 Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. Gut 2021;**70**:1375-82.

33 Simon TG, Roelstraete B, Sharma R, Khalili H, Hagström H, Ludvigsson JF. Cancer Risk in Patients With Biopsy-Confirmed Nonalcoholic Fatty Liver Disease: A Population-Based Cohort Study. Hepatology 2021;**74**:2410-23.

34 Park JH, Hong JY, Shen JJ, Han K, Park JO, Park YS*, et al.* Increased Risk of Young-Onset Digestive Tract Cancers Among Young Adults Age 20-39 Years With Nonalcoholic Fatty Liver Disease: A Nationwide Cohort Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2023;**41**:3363-73.

35 Yuan X, Wang X, Wu S, Chen S, Wang Y, Wang J*, et al.* Associations between metabolic dysfunction-associated fatty liver disease and extrahepatic cancers: a cohort in China. Hepatobiliary Surg Nutr 2023;**12**:671-81.

36 Björkström K, Widman L, Hagström H. Risk of hepatic and extrahepatic cancer in NAFLD: A population-based cohort study. Liver Int 2022;**42**:820-8.

37 Souza M, Diaz I, Barchetta I, Mantovani A. Gastrointestinal cancers in lean individuals with non-alcoholic fatty liver disease: A systematic review and meta-analysis. Liver Int 2023.

38 Tilg H, Adolph TE, Dudek M, Knolle P. Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. Nat Metab 2021;**3**:1596-607.

39 Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology 2010;**52**:1836-46.

40 Petrasek J, Bala S, Csak T, Lippai D, Kodys K, Menashy V*, et al.* IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. J Clin Invest 2012;**122**:3476-89.

41 Mridha AR, Wree A, Robertson AAB, Yeh MM, Johnson CD, Van Rooyen DM*, et al.* NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. J Hepatol 2017;**66**:1037-46.

42 Tilg H, Adolph TE, Tacke F. Therapeutic modulation of the liver immune microenvironment. Hepatology 2023;**78**:1581-601.

43 Lawler PR, Bhatt DL, Godoy LC, Luscher TF, Bonow RO, Verma S*, et al.* Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J 2021;**42**:113-31.

44 Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;**454**:436-44.

45 Chen X, Chen S, Pang J, Huang R, You Y, Zhang H*, et al.* Hepatic steatosis aggravates atherosclerosis via small extracellular vesicle-mediated inhibition of cellular cholesterol efflux. J Hepatol 2023.

46 Marchesini G, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ*, et al.* Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med 1999;**107**:450-5.

47 Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;**24**:908-22.

48 Tardelli M, Bruschi FV, Trauner M. The Role of Metabolic Lipases in the Pathogenesis and Management of Liver Disease. Hepatology 2020;**72**:1117-26.

49 Alsamman S, Christenson SA, Yu A, Ayad NME, Mooring MS, Segal JM*, et al.* Targeting acid ceramidase inhibits YAP/TAZ signaling to reduce fibrosis in mice. Sci Transl Med 2020;**12**.

50 Tilg H, Hotamisligil GS. Nonalcoholic fatty liver disease: Cytokine-adipokine interplay and regulation of insulin resistance. Gastroenterology 2006;**131**:934-45.

51 Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J*, et al.* Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nature medicine 2005;**11**:183-90.

52 Kiechl S, Wittmann J, Giaccari A, Knoflach M, Willeit P, Bozec A*, et al.* Blockade of receptor activator of nuclear factor-kappaB (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. Nat Med 2013;**19**:358-63.

53 Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell 2010;**140**:900-17.

54 Sethi JK, Hotamisligil GS. Metabolic Messengers: tumour necrosis factor. Nat Metab 2021;**3**:1302-12.

55 Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature 2017;**542**:177-85.

56 Wu JT, Liu SS, Xie XJ, Liu Q, Xin YN, Xuan SY. Independent and joint correlation of PNPLA3 I148M and TM6SF2 E167K variants with the risk of coronary heart disease in patients with non-alcoholic fatty liver disease. Lipids in health and disease 2020;**19**:29.

57 Akuta N, Kawamura Y, Arase Y, Saitoh S, Fujiyama S, Sezaki H*, et al.* PNPLA3 genotype and fibrosis-4 index predict cardiovascular diseases of Japanese patients with histopathologically-confirmed NAFLD. BMC Gastroenterol 2021;**21**:434.

58 Petta S, Valenti L, Marchesini G, Di M, V, Licata A, Camma C*, et al.* PNPLA3 GG genotype and carotid atherosclerosis in patients with non-alcoholic fatty liver disease. PLoS ONE 2013;**8**:e74089.

59 Sharpton SR, Schnabl B, Knight R, Loomba R. Current Concepts, Opportunities, and Challenges of Gut Microbiome-Based Personalized Medicine in Nonalcoholic Fatty Liver Disease. Cell Metab 2021;**33**:21-32.

60 Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A*, et al.* Gut Microbiome-Based Metagenomic Signature for Non-invasive Detection of Advanced Fibrosis in Human Nonalcoholic Fatty Liver Disease. Cell Metab 2017;**25**:1054-62 e5.

61 Leung H, Long X, Ni Y, Qian L, Nychas E, Siliceo SL*, et al.* Risk assessment with gut microbiome and metabolite markers in NAFLD development. Sci Transl Med 2022;**14**:eabk0855.

62 Frost F, Kacprowski T, Ruhlemann M, Pietzner M, Bang C, Franke A*, et al.* Long-term instability of the intestinal microbiome is associated with metabolic liver disease, low microbiota diversity, diabetes mellitus and impaired exocrine pancreatic function. Gut 2021;**70**:522-30.

63 Aron-Wisnewsky J, Warmbrunn MV, Nieuwdorp M, Clement K. Nonalcoholic Fatty Liver Disease: Modulating Gut Microbiota to Improve Severity? Gastroenterology 2020;**158**:1881-98.

64 Shin JH, Lee Y, Song EJ, Lee D, Jang SY, Byeon HR*, et al.* Faecalibacterium prausnitzii prevents hepatic damage in a mouse model of NASH induced by a high-fructose high-fat diet. Front Microbiol 2023;**14**:1123547.

65 Lang S, Demir M, Martin A, Jiang L, Zhang X, Duan Y*, et al.* Intestinal Virome Signature Associated With Severity of Nonalcoholic Fatty Liver Disease. Gastroenterology 2020;**159**:1839-52.

66 Carpino G, Del Ben M, Pastori D, Carnevale R, Baratta F, Overi D*, et al.* Increased Liver Localization of Lipopolysaccharides in Human and Experimental NAFLD. Hepatology 2020;**72**:470-85.

67 Sookoian S, Salatino A, Castano GO, Landa MS, Fijalkowky C, Garaycoechea M*, et al.* Intrahepatic bacterial metataxonomic signature in non-alcoholic fatty liver disease. Gut 2020;**69**:1483-91.

68 Aron-Wisnewsky J, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J*, et al.* Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol 2020;**17**:279-97.

69 Alexander M, Turnbaugh PJ. Deconstructing Mechanisms of Diet-Microbiome-Immune Interactions. Immunity 2020;**53**:264-76.

70 Tilg H, Moschen AR. Food, immunity, and the microbiome. Gastroenterology 2015;**148**:1107-19.

71 Kiss EA, Vonarbourg C, Kopfmann S, Hobeika E, Finke D, Esser C*, et al.* Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. Science 2011;**334**:1561-5.

72 Li Y, Innocentin S, Withers DR, Roberts NA, Gallagher AR, Grigorieva EF*, et al.* Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. Cell 2011;**147**:629-40.

73 Pendyala S, Walker JM, Holt PR. A high-fat diet is associated with endotoxemia that originates from the gut. Gastroenterology 2012;**142**:1100-1 e2.

74 Devkota S, Wang Y, Musch MW, Leone V, Fehlner-Peach H, Nadimpalli A*, et al.* Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10-/- mice. Nature 2012;**487**:104-8.

75 Witkowski M, Weeks TL, Hazen SL. Gut Microbiota and Cardiovascular Disease. Circ Res 2020;**127**:553-70.

76 Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ, MacFadyen JG, Nissen SE*, et al.* Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. Lancet 2023;**401**:1293-301.

77 Verma S, Mazer CD, Connelly KA. Inflammation and cholesterol at the crossroads of vascular risk. Cell Metab 2023;**35**:1095-8.

78 Huang J, Wang M, Wu Y, Kumar R, Lin S. Serum high-sensitive C-reactive protein is a simple indicator for all-cause among individuals with MAFLD. Front Physiol 2022;**13**:1012887.

79 Hendrikx T, Walenbergh SM, Jeurissen ML, Houben T, van Gorp PJ, Lindsey PJ*, et al.* Plasma IL-1 receptor antagonist levels correlate with the development of non-alcoholic steatohepatitis. Biomark Med 2015;**9**:1301-9.

80 Tacke F, Puengel T, Loomba R, Friedman SL. An integrated view of anti-inflammatory and antifibrotic targets for the treatment of NASH. J Hepatol 2023;**79**:552-66.

81 Vitale A, Svegliati-Baroni G, Ortolani A, Cucco M, Dalla Riva GV, Giannini EG*, et al.* Epidemiological trends and trajectories of MAFLD-associated hepatocellular carcinoma 2002-2033: the ITA.LI.CA database. Gut 2023;**72**:141-52.

82 Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG*, et al.* Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 2010;**140**:197-208.

83 He G, Karin M. NF-kappaB and STAT3 - key players in liver inflammation and cancer. Cell Res 2011;**21**:159-68.

84 He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y*, et al.* Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. Cell 2013;**155**:384-96.

85 Sakurai T, He G, Matsuzawa A, Yu GY, Maeda S, Hardiman G*, et al.* Hepatocyte necrosis induced by oxidative stress and IL-1 alpha release mediate carcinogen-induced compensatory proliferation and liver tumorigenesis. Cancer Cell 2008;**14**:156-65.

86 Boslem E, Reibe S, Carlessi R, Smeuninx B, Tegegne S, Egan CL*, et al.* Therapeutic blockade of ER stress and inflammation prevents NASH and progression to HCC. Sci Adv 2023;**9**:eadh0831.

87 Umemura A, Park EJ, Taniguchi K, Lee JH, Shalapour S, Valasek MA*, et al.* Liver damage, inflammation, and enhanced tumorigenesis after persistent mTORC1 inhibition. Cell Metab 2014;**20**:133-44.

88 Liang S, Ma HY, Zhong Z, Dhar D, Liu X, Xu J*, et al.* NADPH Oxidase 1 in Liver Macrophages Promotes Inflammation and Tumor Development in Mice. Gastroenterology 2019;**156**:1156-72 e6.

89 Yahoo N, Dudek M, Knolle P, Heikenwalder M. Role of immune responses in the development of NAFLD-associated liver cancer and prospects for therapeutic modulation. J Hepatol 2023;**79**:538-51.

90 Dudek M, Pfister D, Donakonda S, Filpe P, Schneider A, Laschinger M*, et al.* Auto-aggressive CXCR6(+) CD8 T cells cause liver immune pathology in NASH. Nature 2021;**592**:444-9.

91 Pfister D, Nunez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M*, et al.* NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;**592**:450-6.

92 Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. J Hepatol 2021;**75**:1476-84.

93 Ebrahimi F, Hagström H, Sun J, Bergman D, Shang Y, Yang W*, et al.* Familial coaggregation of MASLD with hepatocellular carcinoma and adverse liver outcomes: Nationwide multigenerational cohort study. J Hepatol 2023;**79**:1374-84.

94 Roderburg C, Kostev K, Mertens A, Luedde T, Loosen SH. Non-alcoholic fatty liver disease (NAFLD) is associated with an increased incidence of extrahepatic cancer. Gut 2022.

95 Carlsson LMS, Sjoholm K, Jacobson P, Andersson-Assarsson JC, Svensson PA, Taube M*, et al.* Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study. N Engl J Med 2020;**383**:1535-43.

96 Hardvik Akerstrom J, Santoni G, von Euler Chelpin M, Chidambaram S, Markar SR, Maret-Ouda J*, et al.* Decreased Risk of Esophageal Adenocarcinoma After Gastric Bypass Surgery in a Cohort Study From 3 Nordic Countries. Ann Surg 2023;**278**:904-9.

97 Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;**6**:772-83.

98 Stadlmayr A, Aigner E, Steger B, Scharinger L, Lederer D, Mayr A*, et al.* Nonalcoholic fatty liver disease: an independent risk factor for colorectal neoplasia. J Intern Med 2011;**270**:41-9.

99 Kaklamani VG, Wisinski KB, Sadim M, Gulden C, Do A, Offit K*, et al.* Variants of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes and colorectal cancer risk. JAMA 2008;**300**:1523-31.

100 An W, Bai Y, Deng SX, Gao J, Ben QW, Cai QC*, et al.* Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. Eur J Cancer Prev 2012;**21**:126-33.

101 Fujisawa T, Endo H, Tomimoto A, Sugiyama M, Takahashi H, Saito S*, et al.* Adiponectin suppresses colorectal carcinogenesis under the high-fat diet condition. Gut 2008;**57**:1531-8.

102 Kaser S, Moschen A, Cayon A, Kaser A, Crespo J, Pons-Romero F*, et al.* Adiponectin and its receptors in non-alcoholic steatohepatitis. Gut 2005;**54**:117-21.

103 Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ*, et al.* 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;**140**:e563-e95.

104 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA*, et al.* Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and international association for the Study of Obesity. Circulation 2009;**120**:1640-5.

105 Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ*, et al.* 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;**140**:e596-e646.

106 CVD risk assessment and management. <https://cksniceorguk/topics/cvd-risk-assessment-management/> 2023.

107 group S-Ow, collaboration ECr. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. European Heart Journal 2021;**42**:2455-67.

108 Group S-DW, Collaboration tECR. SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe. European Heart Journal 2023;**44**:2544-56.

109 group Sw, collaboration ECr. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. European Heart Journal 2021;**42**:2439-54.

110 Åberg F, Byrne CD, Pirola CJ, Männistö V, Sookoian S. Alcohol consumption and metabolic syndrome: Clinical and epidemiological impact on liver disease. J Hepatol 2023;**78**:191-206.

111 Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L*, et al.* Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. The lancet Diabetes & endocrinology 2019;**7**:344-55.