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# Crosstalk between nonalcoholic fatty liver disease and cardiometabolic syndrome

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## Summary

Nonalcoholic fatty liver disease (NAFLD) is a chronic condition characterized by fat accumulation combined with low-grade inflammation in the liver. A large body of clinical and experimental data shows that increased flux of free fatty acids from increased visceral adipose tissue and de novo lipogenesis can lead to NAFLD and insulin resistance. Thus, individuals with obesity, insulin resistance, and dyslipidaemia are at the greatest risk of developing NAFLD. Conversely, NAFLD is a phenotype of cardiometabolic syndrome. Notably, researchers have discovered a close association between NAFLD and impaired glucose metabolism and focused on the role of NAFLD in the development of type 2 diabetes. Moreover, recent studies provide substantial evidence for an association between NAFLD and atherosclerosis and cardiometabolic disorders. Even if NAFLD can progress into severe liver disorders including nonalcoholic steatohepatitis (NASH) and cirrhosis, the majority of subjects with NAFLD die from cardiovascular disease eventually. In this review, we propose a potential pathological link between NAFLD/NASH and cardiometabolic syndrome. The potential factors that can play a pivotal role in this link, such as inflammation, insulin resistance, alteration in lipid metabolism, oxidative stress, genetic predisposition, and gut microbiota are discussed.

**KEYWORDS**

cardiometabolic syndrome, nonalcoholic fatty liver disease, inflammation, oxidative stress

## 1 | INTRODUCTION

### 1.1 | Prevalence of nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH)

NAFLD covers a spectrum of diseases ranging from simple steatosis to NASH, which is distinguished from the former by the presence of progressive hepatic fibrosis.[1,2] The prevalence of NAFLD or NASH in the general population varies according to the diagnostic criteria and tools used to stage the condition.[3,4] In the United States, liver biopsies performed on potential liver donors revealed that 20% of donors were ineligible for organ donation because of a high degree of steatosis (>30%).[5] A study in which liver biopsies were performed on 589 consecutive potential liver-transplant donors found an NAFLD prevalence of 51%.[6] A series of autopsies showed a broad range in the prevalence of NAFLD. The prevalence of NASH in autopsy cases of lean

**Abbreviations:** ALT, alanine aminotransferase; apoB, apolipoprotein-B; AST, aspartate aminotransferase; ChREBP, carbohydrate-responsive element-binding protein; CV, cardiovascular; ER, endoplasmic reticulum; FFA, free fatty acid; FIAF, fasting-induced adipocyte factor; GSK-3β, glycogen synthase kinase-3β; IL-6, interleukin-6; IRS1, insulin receptor substrate-1; JNK, c-Jun N-terminal kinase; LPL, lipoprotein lipase; LPS, lipopolysaccharide; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-κB; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; SCFA, short-chain fatty acid; SREBP-1, sterol regulatory element-binding protein 1; T2D, type 2 diabetes; TLR, Toll-like receptor; TNFα, tumour necrosis factor-α; VLDL, very low-density lipoprotein; WC, waist circumference; γ-GT, γ-glutamyltranspeptidase

  

individuals from Canada reported in 1990 was 3%.[7] A study in India found fatty liver in 16% of 1230 adult autopsies.[8] Another study on autopsies of cases arising from sudden death and accidents in Greece reported a prevalence of 31% and 40% for NAFLD and NASH, respectively.[9] Taken together, the global prevalence of NAFLD is estimated to be 25% to 30% with highest prevalence in the Middle East and South America and lowest in Africa.[4]

Recently, noninvasive imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography, have been used to measure fat accumulation in the liver. In the United States, a study with MRI identified an NAFLD prevalence of 31% among a multiethnic population.[10] In Spain, the prevalence of NAFLD on ultrasonography was 33% in men and 20% in women.[11] In a study in Italy that used ultrasonography, the prevalence of NAFLD was 20% in subjects without suspected liver disease.[12] The prevalence of NAFLD identified via ultrasonography in 35 519 Japanese increased from 13% to 30% over 12 years.[13] Recently, diagnosis of NAFLD in the community has increased fivefold, particularly in young adults.[14] These data suggest that the prevalence of NAFLD in the general population is 20% to 40% with minor variation by age, region, or ethnicity, and that the incidence of disease is increasing over time in many countries[4,15-22] (Table 1). A recent meta-analysis involving 35,599 patients with type 2 diabetes (T2D) reported that the pooled prevalence of NAFLD in these patients was 59.7%.[23] Thus, NAFLD is very common in patients with T2D, with an estimated prevalence of 60% to 80%.[24]

## 1.2 | The (cardio) metabolic syndrome

Metabolic syndrome indicates a constellation of components, such as abdominal obesity, high glucose, high blood pressure, high triglyceride level, and low high-density lipoprotein (HDL)-cholesterol level; all of these increase the risk of metabolic and cardiovascular diseases (CVDs).[25] In recent decades, the term "cardiometabolic syndrome" has been used in various settings.[26,27] The incidence of cardiometabolic syndrome has increased rapidly in many countries in past decades because of urbanization, economic growth, and unhealthy

**TABLE 1** Prevalence of NAFLD in different ethnic groups

| Ethnicity | Setting | Total Subjects | Definition of NAFLD | Prevalence of NAFLD | Age (y)[a]/ Male (%) | Diagnostic Tool for NAFLD | Year (Reference) |
|---|---|---|---|---|---|---|---|
| USA | White from a population-based sample | 734 | Hepatic triglyceride content >5.5% | 33.0% | 46 ± 9/51.1 | $^{1}$H-magnetic resonance spectroscopy | 2004 (Browning et al[16]) |
| | Hispanic from a population-based sample | 401 | Hepatic triglyceride content >5.5% | 45.0% | 41 ± 9/57.1 | $^{1}$H-magnetic resonance spectroscopy | 2004 (Browning et al[16]) |
| | Black from a population-based sample | 1105 | Hepatic triglyceride content >5.5% | 24.0% | 46 ± 10/ 45.2 | $^{1}$H-magnetic resonance spectroscopy | 2004 (Browning et al[16]) |
| Spanish | A multicenter, cross-sectional, populational study | 766 | Semiquantitation using increased liver echotexture compared with the kidneys | 25.8% | 53 (17-83)/ 42.0 | Ultrasound | 2010 (Caballeria et al[11]) |
| British | Birmingham and Lambeth liver evaluation testing strategies | 1118 | Semiquantitation using increased liver echotexture compared with the kidneys | 26.4% | 60 (48-70)/ 56.0 | Ultrasound | 2012 (Armstrong et al[15]) |
| Hungarian | A cross-sectional twin study | 208 | Semiquantitation using increased liver echotexture compared with the kidneys | 22.6% | 43.7 ± 16.7/ 28.4 | Ultrasound | 2012 (Tarnoki et al[21]) |
| Finnish | The Helsinki birth cohort study | 1611 | Fatty liver index >60 | 41.2% | 61.6 ± 0.2/ 48.0 | Fatty liver index | 2014 (Kanerva et al[19]) |
| Finnish | The cardiovascular risk in young Finns study | 1998 | Semiquantitation using increased liver echotexture compared with the kidneys | 18.5% | 41.9(34-49)/45.0 | Ultrasound | 2015 (Suomela et al[20]) |
| Korean | A health examination programme | 161 891 | Semiquantitation using increased liver echotexture compared with the kidneys | 27.3% | 41.6 ± 8.6/ 57.2 | Ultrasound | 2013 (Jeong et al[18]) |
| Chinese | A health examination programme | 6448 | Semiquantitation using increased liver echotexture compared with the kidneys | 33.3% | 42.2 ± 12.9/ NA | Ultrasound | 2013 (Cai et al[17]) |
| Taiwanese | A health examination programme | 6511 | Semiquantitation using increased liver echotexture compared with the kidneys | 27.2% | 70.8 ± 7.9/ NA | Ultrasound | 2014 (Shen et al[22]) |

Abbreviation: NA, not available.

[a]Mean ± SD or ranges.

diets favouring high-fat and high-calorie consumption.[28,29] These contributing factors are commonly found in people with NAFLD. Dietary carbohydrates stimulate de novo lipogenesis in the liver and increase fat accumulation.[30,31] Other evidence supports that excessive energy intake is apparently associated with fatty liver or elevated liver enzyme activities, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase (γ-GT).[32] Thus, large energy intake, particularly fructose or sucrose, induces NAFLD, a precursor of metabolic disorders as well as its consequence.

## 2 | STUDIES OF THE ASSOCIATION BETWEEN NAFLD AND CARDIOMETABOLIC DISORDERS

In a meta-analysis on 34 043 adults, where NAFLD was defined by either radiological imaging or histology, patients with NAFLD (36.3% of the whole population) had a higher risk of CVD events than those without NAFLD (odds ratio [OR] 1.64; 95% confidence interval [CI], 1.26-2.13).[33] This association with CV events was stronger in patients with severe NAFLD (OR 2.58; 95% CI, 1.78-3.75) diagnosed either by the presence of steatosis on radiological imaging plus either elevated γ-GT levels or a high NAFLD fibrosis score or by fibrosis seen in liver histology. In a retrospective cohort study of 8020 men who underwent health checkups, the age-adjusted hazard ratio was 1.23 (95% CI, 1.13-1.35) for subclinical carotid atherosclerosis in participants with persistent NAFLD, diagnosed by ultrasonography, compared with those without NAFLD.[34] In the Framingham Heart Study, fatty liver was associated with a clustering of CV risks after adjustment for other fat depots, including abdominal visceral fat.[35] Another study reported that intrahepatic lipid depot is more closely linked to CV complications than abdominal visceral fat.[36]

From this perspective, several studies have investigated the relationship between NAFLD and the incidence of CV events. Rafiq et al reported that patients with NAFLD had a significantly higher risk of developing CV events than did matched controls.[37] Of note, a 14-year follow-up study (n = 129) found that patients with biopsy-proven NAFLD died from CVDs (15.5%) more than from liver-related diseases (2.8%).[38] More directly, NAFLD has been found to be a significant predictor of adverse CV events in middle-aged populations, independent of age, gender, body mass index (BMI), smoking, alcohol consumption, lipid levels, or abnormal blood pressure.[39] Thus, much evidence supports the association of NAFLD with the incidence of CVD, independent of traditional risk factors.[40-42]

In contrast, NAFLD was not associated with an increased risk of death from all causes, CVD, cancer, or liver disease in the Third US National Health and Nutrition Examination Survey.[43] Another study with the similar data showed that NAFLD was associated independently with an increased risk of CVDs, but not CV mortality over a 14-year period.[44] Table 2 summarizes reports for the association of NAFLD with CVD. Future longitudinal studies are needed to test any independent association between NAFLD and CVD.

**TABLE 2** Studies of the independent association of NAFLD with cardiovascular disease (CVD)

| Study | Setting | Diagnostic Tool | Age (y)[a]/ Male (%) | Follow-up (y) | Main Findings |
|---|---|---|---|---|---|
| Rafiq et al[37] | A NAFLD cohort from the Cleveland Clinic Foundation | Liver biopsy | 50.2 ± 14.5/39.9 | 18.5 (median) | The cause of death was coronary artery disease (12.7%), followed by malignancy (8.1%) and liver-related death (6.9%) |
| Ekstedt et al[38] | Consecutive recruitment from university hospitals | Liver biopsy | 51.0 ± 12.9/67.0 | 13.7 ± 1.3 | 15.5% patients with NASH died from CVD, 5.6% from extrahepatic malignancy, 2.8% from liver-related causes |
| Pisto et al[39] | A population-based, randomly recruited cohort | Ultrasound | 46 ± 10/45.2 | 17.7 | Severe liver fat content predicted the risk for future CV events after adjusting for conventional risk factors (HR = 1.74; CI, 1.16-2.63). |
| Pais et al[40] | A retrospective single-centre study | Fatty liver index | 52 ± 11/53 | 8 ± 4 | Fatty liver predicted carotid plaque occurrence (OR = 1.63; 95% CI, 1.10-2.41), independent of conventional risk factors |
| Lazo et al[43] | US National Health and nutrition examination survey (NHANES III: 1988-1994) | Ultrasound | 43 (20-74)/49 | 14 (median) | Subjects with NAFLD showed adjusted HRs for deaths from all causes of 0.80 (0.52-1.22), from CVD of 0.59 (0.29-1.20), and from liver disease of 1.17 (0.15-8.93) compared with those without |
| Stepanova et al[44] | US National Health and Nutrition Examination Survey (NHANES III: 1988-1994) | Ultrasound | 43.7 ± 16.7/28.4 | 14.25 (median) | NAFLD was associated independently with CVD, after adjusting for major risk factors (OR = 1.23; 95% CI, 1.04-1.44) but not with CV mortality |
| Olubamwo et al[42] | Kuopio Ischaemic Heart Disease Risk Factor Study cohort | Fatty liver index | 51.6 ± 5.7/41.3 | 21.1 ± 7.6 | High fatty liver index was significant for incident CVD (HR = 1.41; 95% CI, 1.10-1.79) in the comprehensive adjusted model |

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

[a]Mean ± SD or ranges.

## 3 | PATHOLOGICAL ROLE OF NAFLD AND CARDIOMETABOLIC SYNDROME

NAFLD is a burgeoning health problem worldwide and an important risk factor for both hepatic and cardiometabolic morbidity and mortality. The hallmark features of NAFLD, such as dyslipidaemia, insulin resistance, inflammation, and oxidative and endoplasmic reticulum (ER) stress, are shared with cardiometabolic syndrome. The pathogenesis of NAFLD involves a complex interaction among environmental factors including diet and exercise, obesity, alteration in microbiota, and predisposing genetic traits.

### 3.1 | Increased inflow of free fatty acids and de novo hepatic lipogenesis are the main determinants of NAFLD

NAFLD is characterized by excess accumulation of triglycerides in the hepatocytes due to both increased inflow of free fatty acids (FFAs) and de novo hepatic lipogenesis in the face of reduced FFA elimination via very low-density lipoprotein (VLDL) assembly and β-oxidation. The development of hepatic steatosis is influenced by dietary modification.[45,46] A recent study in nondiabetic persons with obesity showed that overfeeding with saturated fat increased intrahepatic triglyceride contents.[47] Saturated fat also induced insulin resistance and endotoxaemia and significantly increased the levels of multiple plasma ceramides, which induce insulin resistance. These data suggest that saturated fat has a role in hepatic lipogenesis in nondiabetic subjects.

Dietary fructose also stimulates lipogenesis and fat accumulation in the liver.[30] A large body of evidence suggests that increased hepatic de novo lipogenesis is also a significant pathway contributing to the development of NAFLD. In an intervention study with a low-carbohydrate and high-protein diet in subjects with obesity and NAFLD, significant reduction of liver fat and improvement of cardiometabolic risk factors were found.[48] This finding was associated with decrease in hepatic de novo lipogenesis, increase in serum β-hydroxybutyrate concentrations, and alteration in microbiota. These results suggest the role of diet-microbiota interactions for treatment of NAFLD.[48]

### 3.2 | Inflammatory processes, linked with cardiometabolic syndrome, are the main determinant in progression from NAFLD to NASH

Fat accumulation in the liver stimulates the production of inflammatory cytokines (Figure 1).[49] In particular, NASH activates the pathogenesis of cardiometabolic syndrome through the systemic release of several inflammatory, prothrombotic, and oxidative stress mediators.[50,51] Nuclear factor-κB (NF-κB) and c-Jun *N*-terminal kinase

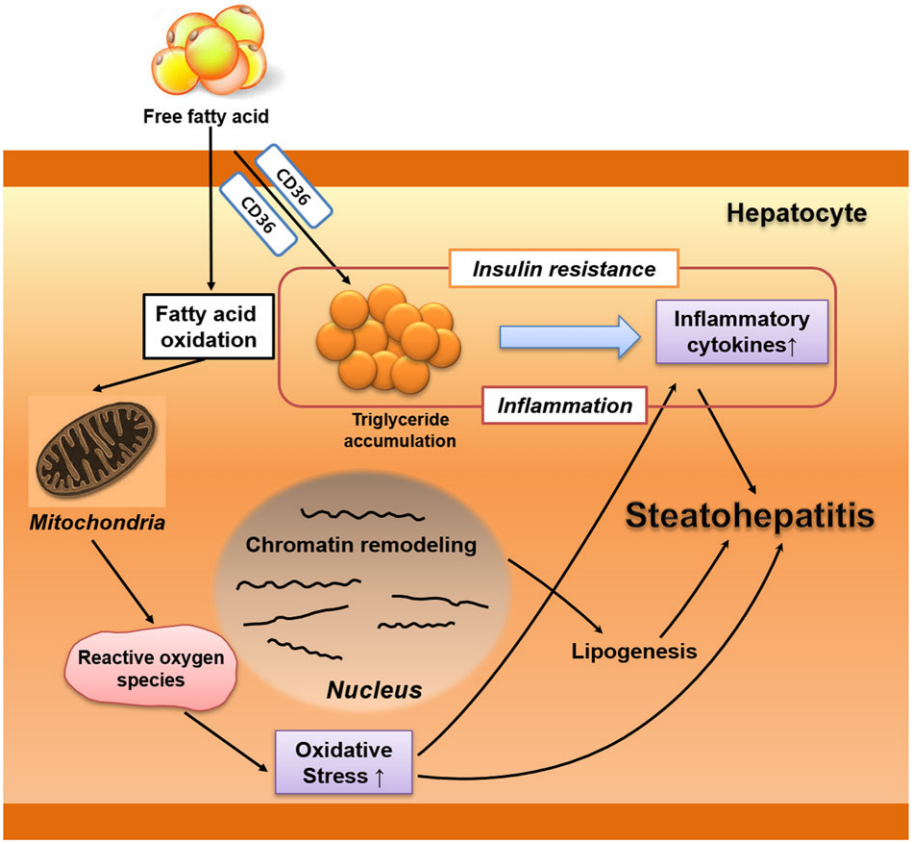


**FIGURE 1** Role of inflammation and oxidative stress in the pathogenesis of NAFLD/NASH. Under conditions of insulin resistance, free fatty acids (FFAs) released from adipose tissues are influenced by inflammation. Simultaneously, FFAs taken up in the liver decrease the activity of antioxidant systems and produce reactive oxygen species (ROS), thereby inducing oxidative stress [Colour figure can be viewed at wileyonlinelibrary.com]

(JNK) are the main intracellular signalling pathways involved in the mechanistic link between NAFLD and inflammation. The activation of the NF-κB pathway in the liver of patients with NAFLD leads to steatosis, which in turn enhances the transcription of several genes, such as those for the intercellular adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1). These molecules are associated with the development or progression of atherosclerosis.[52] In a different context, JNK aggravates insulin resistance via the phosphorylation and degradation of insulin receptor substrate-1 (IRS-1) and contributes to the inhibition of the intracellular signalling pathway downstream of the insulin receptor.[53]

Elevated liver enzyme activity may reflect inflammation, which impairs insulin signalling both locally and systemically (Figure 2).[54] Furthermore, increased levels of inflammatory cytokines, such as C-reactive protein (CRP), were observed in patients with NAFLD.[55] In a Japanese study, elevated ALT concentration was found to be an independent marker of the activation of systemic inflammation and increased oxidative stress.[56] We also showed that individuals in the top ALT quartile had the highest levels of hsCRP, which was also an independent predictor of T2D.[57]

Recent studies have shown novel roles for inflammatory mediators in the link between NAFLD/NASH and inflammation. In the Multi-Ethnic Study of Atherosclerosis, which is a longitudinal, population-based study of four ethnic groups free of CVD at baseline, levels of interleukin-6 (IL-6) were significantly associated with liver fat assessed via CT after adjusting for other risk factors for atherosclerosis.[58] Toll-like receptors (TLRs), which are well-characterized immune receptors,[59] activate proinflammatory pathways.[60] Among TLRs, TLR2 and TLR4 induce insulin resistance, which is pivotal in the pathogenesis of NAFLD, obesity, and metabolic syndrome.[61] TLR4 is activated by fatty acids and endotoxaemia, resulting in the activation of NF-κB and increased release of inflammatory cytokines, such as IL-6, IL-1β, TNFα, and MCP-1, which play a critical role in the pathophysiology of cardiometabolic syndrome.[62]

### 3.3 | Lipotoxicity is involved in development of NAFLD

Lipotoxicity-related mechanism of NAFLD is linked to the "double-hit" theory. In the "first hit," the hepatic concentrations of diacylglycerols (DAGs) lead to increase in saturated fat content in liver. Activities of mitochondrial respiratory chain complexes are decreased in liver tissue of patients with NASH. Furthermore, lipoapoptosis in hepatocytes is a critical feature of NASH. In a "second hit," reduced glutathione levels caused by oxidative stress lead to overactivation of c-JNK/c-Jun signalling that induces cell death in NASH.[63] The ER has oxidation machinery and ER oxidoreductin-1 (Ero1) is an essential component of this.[64] Activation of oxidative stress is caused by the abnormal cycling of Ero1 at the mitochondrial inner membrane.[65] Insulin resistance along with a deficiency in IRS-2-associated phosphatidylinositol 3-kinase (PI3K) activity directs FFA flux to pathways that serve to increase metabolites, such as DAG and ceramides.[66] Thus, metabolic oxidative stress and inflammation induce NASH progression.

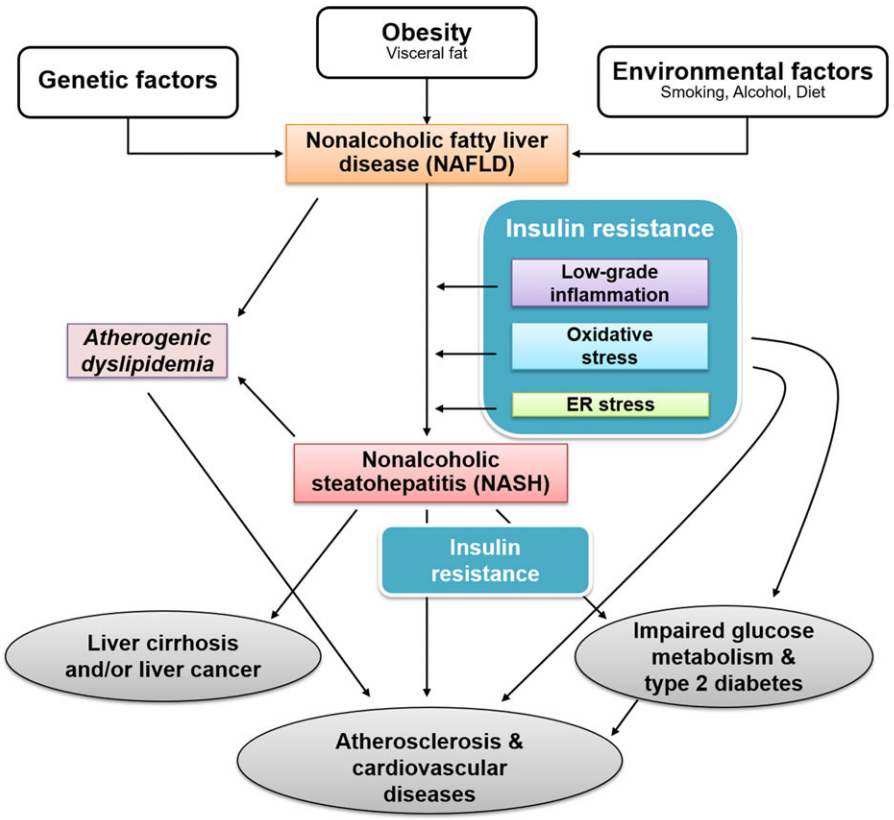


**FIGURE 2** Contributing factors linking NAFLD/NASH with cardiometabolic syndrome. ER, endoplasmic reticulum [Colour figure can be viewed at wileyonlinelibrary.com]

### 3.4 | Role of insulin resistance in the development of NAFLD and cardiometabolic syndrome

Hepatic insulin resistance is a key pathophysiological mechanism of NAFLD (Figure 1). Recently, liver enzyme activities, which are associated with insulin resistance, have attracted much attention, as hepatic dysfunction resulting from intrahepatic lipid deposition contributes to the development of T2D. Levels of ALT, AST, and γ-GT are known indicators of hepatocellular health, and abnormal hepatocellular function is associated with the onset of T2D. Many prospective studies have shown that elevated liver enzymes, including ALT, AST, and γ-GT, are predictors of the development of insulin resistance, metabolic syndrome, and T2D in Western populations.[67,68] Similarly, serum γ-GT level is an important predictor of the development of metabolic syndrome and T2D in middle-aged Japanese men.[69] In a prospective community-based study conducted in Korea, we found that increased activity of ALT was associated with a twofold increase in the risk of T2D, independent of conventional risk factors.[57]

In a study of NAFLD patients without obesity and control individuals closely matched for age and body composition, the pattern of metabolic defects observed in NAFLD patients was consistent with whole body insulin resistance involving the liver, adipose tissue, and skeletal muscle.[70] Even as low as 1.5% triglyceride accumulation in the liver leads to hepatic insulin resistance, assessed by hyperinsulinaemic-euglycaemic clamping.[71] In line with this, insulin-stimulated glucose disposal assessed by insulin clamping was lower in patients with NAFLD and T2D than in control subjects.[72] Compared with individuals with simple fatty liver, those with NASH had higher levels of sphingolipids, which are associated with oxidative stress, inflammation, and insulin resistance assessed by insulin clamping.[73]

In addition, it has been reported that elevated hepatic DAG levels are associated with insulin resistance. Specifically, increased DAG levels lead to the activation of protein kinase Cε (PKCε), which impairs insulin-stimulated tyrosine phosphorylation of IRS-1 and IRS-2 and obstructs activation of PI3K downstream of insulin signalling.[74,75] These results suggest that increased hepatic DAG levels play a pivotal role in the development of NAFLD through deterioration in insulin signalling.[75,76] Other studies have suggested that an increase in hepatic ceramide content is the major mediator of lipid-induced hepatic insulin resistance in the context of NAFLD.[77,78] However, the mechanisms by which ceramides cause hepatic insulin resistance have not been clearly determined. Thus, fatty acid accumulation in the liver induces insulin resistance, which contributes to increases in endogenous glucose production.[79] This acts as a stimulus for further increased whole-body insulin resistance, leading to accelerated atherosclerosis.[80] Taken together, as NAFLD is associated with insulin resistance but also enables the production of a plethora of cardiometabolic risk factors, the relationship between NAFLD and cardiometabolic risks seems to be bidirectional and the cause/consequence relationship is difficult to separate.[81]

Peripheral insulin resistance contributes to the development of NAFLD/NASH by aggravating glucose and lipid metabolism (Figure 2). In healthy people, increased DAG by lipid infusions in skeletal muscle was linked with insulin resistance through protein kinase C-θ activation.[82] Conversely, weight loss with diet or bariatric surgery effectively treats NAFLD.[83]

In a different context, sarcopenia, loss of muscle mass, is associated with NAFLD and diabetes.[84,85] People with sarcopenia had a twofold to threefold increased risk of NAFLD.[84] Skeletal muscle secretes myokines, such as irisin, that can affect other metabolic organs or tissues.[86] Irisin level was inversely associated with the degree of fat accumulation in liver in people with obesity.[87] Irisin alleviates insulin resistance by increasing total body energy expenditure.[88] Irisin also involves peroxisome proliferator-activated receptor (PPAR)-α signalling,[87] which plays a crucial role in fatty acid β-oxidation in the liver.[89]

Thus, NAFLD is emerging as a component of cardiometabolic syndrome based on hepatic and peripheral insulin resistance.[83,90] Taken together, these findings suggest that fat accumulation in the liver is a critical determinant of metabolic flux and inflammatory processes, thereby representing an important therapeutic target in insulin resistance and T2D.

### 3.5 | Alterations in lipid metabolism in NAFLD/NASH

The liver plays an important role in lipid synthesis, storage, and release and is an important site for insulin clearance.[91] FFAs overflow to the liver, either from dietary intake or driven by visceral adipose tissue, and impaired hepatic elimination of FFAs leads to fat accumulation in the liver and insulin resistance.[92,93] Many clinical and experimental data show that increased levels of FFAs and their metabolites play key roles in the onset and progression of lipotoxic liver injury, resulting in NASH.[94]

Hepatocytes contain lipid droplets in the lumen of the ER where VLDL particles are assembled.[95,96] Kinetically, FFAs impair insulin-induced VLDL1 suppression and this impairment enhances the secretion of triglyceride-rich VLDL1 particles in individuals with NAFLD or insulin resistance.[97] This increased VLDL1 formation reduces the amounts of VLDL precursors and decreases the degradation of apolipoprotein-B (apoB).[98] FFAs also increase basal hepatic glucose production and induce hepatic insulin resistance through increasing glucose-6-phosphatase activity.[99] In addition, an increased FFA level in hepatocytes reduces the post-translational degradation of apoB. FFAs also appear to induce JNK activation, which leads to insulin resistance via IRS-1 and IRS-2 serine phosphorylation.[100] In another context, sterol regulatory element-binding protein-2 (SREBP-2), an important transcription factor in lipid homeostasis, is linked to autophagic function,[101] which is impaired in lipid-overloaded human hepatocytes or in those with NAFLD.[102] Thus, increased FFAs and subsequent VLDL1 formation are key pathological mechanisms in altering lipid metabolism found in subjects with NAFLD or insulin resistance.[103]

A recent study showed that people with NAFLD have lower metabolic adaptability throughout metabolic functions related to gluconeogenesis and ureagenesis compared with those with lower liver fat.[104] Thus, aberrant lipid metabolism and dysfunctional adipocytes in the liver recruit multiple cell populations, including macrophages and other immune cells,[105] which contribute to the development of CVDs.

### 3.6 | Oxidative stress is another critical factor in NAFLD and cardiometabolic syndrome

Many clinical studies have found that markers of oxidative stress, such as thiobarbituric acid reactive substances, carboxymethyl lysine, and 8-hydroxy-deoxyguanosine, are increased in systemic circulation and liver in patients with NAFLD.[106,107] Other markers of oxidative stress including serum sNOX2-dp, a NADPH oxidase isoform involved in generation of oxidative stress[108] and urine 8-iso-prostaglandin F2α, from the nonenzymatic oxidation of arachidonic acid,[109] are increased in patients with NAFLD. There is also evidence in support of the activation of oxidative stress[110] and increased levels of homocysteine in NAFLD.[111] In addition to insulin resistance and inflammation, elevated ALT and γ-GT activity may result from increased oxidative stress caused by increased delivery of FFAs to the liver.[112,113]

Oxidative stress induces endothelial dysfunction,[114] which is likely to predispose people with NAFLD to develop CV events. Thus, NAFLD may amplify oxidative stress and systemic inflammation, thus turning on the switch for the initiation of T2D and CVD.

### 3.7 | Other factors related to NAFLD and CVDs

Patients with NAFLD exhibit low levels of adiponectin, which are associated with insulin resistance, endothelial dysfunction, atherosclerosis, and CV events.[115] An in vitro study showed that full-length adiponectin treatment suppressed palmitate-induced fetuin-A via the AMPK pathway and improved steatosis.[116] In an animal model of diabetes, treatment with recombinant adiponectin alleviated hepatic fat accumulation.[117] Further studies are needed to determine whether the modulation of adiponectin is beneficial in the management of NAFLD and cardiometabolic syndrome.

ER stress is also associated with the development of NAFLD/NASH.[118] ER stress is defined as a condition in which the protein-processing capacity of the ER is exceeded by nascent proteins, resulting in the accumulation of unfolded or misfolded proteins.[119] Accumulating evidence supports a causative role for ER stress in the development or progression of atherosclerosis.[120] Elevated levels of diagnostic markers of ER stress and increased glycogen synthase kinase-3β (GSK-3β) activity were also found in the livers and atherosclerotic lesions in various animal models.[118] These data support a role for ER stress-induced GSK-3β activity in the accelerated development of hepatic steatosis and atherosclerosis. ER stress can also activate caspases and promote the apoptosis of vascular endothelial cells.[121]

Factors that are related to fibrinolysis and haemostasis (eg, fibrinogen, tissue plasminogen activator, and plasminogen activator inhibitor-1 [PAI-1]) are strongly associated with NAFLD.[122] Interestingly, plasma PAI-1 levels are more closely associated with fat accumulation in the liver than in adipose tissue, suggesting that fat deposition in the liver is an important source of PAI-1 production.[123]

Taken together, ectopic fat accumulation in the liver and the subsequent alteration of metabolic pathways including inflammation, lipid metabolism, glucose homeostasis, and oxidation, cause biological dysfunction in vital organs and tissues related to cardiometabolic syndrome.[105,124]

## 4 | GENETIC ASSOCIATION BETWEEN NAFLD/NASH AND CARDIOMETABOLIC SYNDROME

NAFLD has a complex disease trait with interactions between the environment and susceptible genes.[125,126] NAFLD/NASH and cardiometabolic syndrome share several common genes. Genetic polymorphisms in the gene for patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) are associated with the development of fatty liver and with disease severity.[127,128] *PNPLA3* encodes the protein adiponutrin, a triacylglycerol lipase that involves triacylglycerol hydrolysis.[129] The gene for transmembrane 6 superfamily 2 (*TM6SF2*), which regulates plasma lipid levels and hepatic fat contents, is also associated with NAFLD susceptibility.[130] Moreover, *TM6SF2* polymorphism affects glucose homeostasis including pancreatic β-cell function.[131] Furthermore, polymorphisms of *PNPLA3* and *TM6SF2* suggest a link with CVDs.[132] The gene for membrane-bound O-acyltransferase domain-containing 7 (*MBOAT7*), which regulates hepatic fat contents, is also linked to the development and severity of NAFLD and metabolic derangement.[133]

Microsomal triglyceride transfer protein (MTP), a lipid transfer protein, is an essential molecule for the transportation of triglycerides from the liver to apoB.[134] Polymorphisms (−493 G/T) in *MTP* are related to the phenotype of NAFLD and insulin resistance.[135,136] Several studies have shown significant associations between *apolipoprotein-C3 (APO-C3)* gene variants and the hepatic fat accumulation.[137,138] APO-C3 is an apolipoprotein that inhibits lipoprotein lipase (LPL) and plays a crucial role in lipid metabolism.[139] An *APO-C3* gain-of-function variant associates with the risks of atherosclerotic diseases including ischaemic stroke and coronary heart disease.[140,141] However, other studies failed to show any significant association between variants in *APO-C3* and NAFLD.[142,143]

In a study with 702 patients with biopsy-proven NAFLD, the presence of the ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1)121Gln and IRS-1 972Arg polymorphisms was independently associated with hepatic fibrosis in patients with obesity.[144] Polymorphisms in the genes for both proteins are associated with a marked reduction in AKT activation, reflecting insulin resistance and disease severity. A recent study found that hepatic lipid synthesis from polyunsaturated fatty acids is impaired and intrahepatic triglyceride accumulation increased in the transmembrane 6 superfamily member-2 E167K gene variant.[145] Thus, several genes are proposed as candidates for NAFLD, but the effects of these genetic abnormalities on NAFLD appear to differ between study groups and remain controversial.[146,147]

Of note, there is no evidence of any association between these genetic variations for NAFLD and CVD.[148] In a cohort study of the Danish general population utilizing Mendelian randomization, a variant in the gene encoding the *PNPLA3*, I148M (rs738409) was associated with NAFLD (OR 2.03; 95% CI, 1.52-2.70; $P = 3 \times 10^{-7}$), but not associated with ischaemic heart disease (OR 0.95; 95% CI, 0.86-1.04; $P = 0.46$).[148] Therefore, more comprehensive studies aimed at finding genes that are associated with pathogenesis in the development of NAFLD related with cardiometabolic syndrome are warranted.

## 5 | CONTRIBUTION OF GUT MICROBIOTA IN CROSSTALK BETWEEN NAFLD AND CARDIOMETABOLIC SYNDROME

The liver is closely related to the gut both anatomically and functionally; thus, environmental changes in the gut influence the liver via portal circulation. Recent evidence has linked gut dysbiosis, or compositional shift, to the pathogenesis of NAFLD and cardiometabolic disorders.[149,150] People with obesity have a higher pathological bacterial overgrowth in the small intestine, which contributes to the development of NAFLD.[151] More specifically, microbiota samples from patients with NAFLD or NASH have a lower proportion of the family *Ruminococcaceae* than those from healthy counterparts.[152] Patients with NASH have a significantly higher percentage of *Clostridium coccoides*, but lower *Bacteriodes*, than healthy controls or patients with a simple fat depot in the liver.[153]

In a whole-genome shotgun sequencing of fecal samples obtained from Finnish participants (17.5 million paired-end reads), *Streptococcus*, *Lactococcus*, and *Eggerthella* counts were increased after low carbohydrate and high protein diet, whereas the carbohydrate-degrading bacteria *Ruminoccocus*, *Eubacterium*, *Clostridium*, and *Bifidobacterium* were decreased, suggesting that dietary intervention rapidly alters the gut microbiota.[48] Furthermore, compositional differences in gut microbiota were observed according to the degree of intrahepatic triglyceride content, both in human and animal studies.[154,155]

Several mechanistic pathways link NAFLD, metabolic disturbance, and microbiota. First, short-chain fatty acids (SCFAs), the major products of carbohydrate fermentation by the gut microbiome, have diverse roles in energy metabolism and are major precursors in hepatic lipogenesis and gluconeogenesis.[156] SCFAs shorten bowel transit time, increase nutrition absorption rates, and transfer of energy sources to the liver and thereby regulate hepatic lipogenesis and gluconeogenesis.[157] The types and amounts of SCFAs synthesized in the gut are influenced by gut dysbiosis and are expected to affect obesity-related disorders and NAFLD.[158] Second, fasting-induced adipocyte factor (FIAF) is a protein that is produced in intestinal L-cells and inhibits LPL activity. Gut dysbiosis inhibits this intestinal FIAF secretion and leads to LPL activation, thus promoting fat storage in adipocytes and the liver.[159] Inhibiting FIAF also promotes hepatic production of carbohydrate-responsive element-binding protein (ChREBP) and SREBP-1 and further stimulates fat accumulation in the liver.[159] Third, choline, a water-soluble essential nutrient, plays crucial roles in lipid metabolism and promotes lipid transport from the liver.[160] A methionine-choline deficient diet aggravated gut microbiota dysbiosis and induced NASH in an animal model.[161] Fourth, dysbiosis of gut microbiota influences TLR4- and TLR9-mediated low-grade inflammation in the liver.[162] TLR4 mRNA expression and plasma levels of LPS, a bacterial-derived ligand of TLR4, were increased in biopsy specimen of liver in patients with NASH.[163] Fifth, increase in intestinal permeability and alteration in tight junctions caused by gut dysbiosis are also observed in patients with NAFLD.[164]

Recent data indicate that an imbalance in intestinal microbiota or dysbiosis influences not only NAFLD but also CKD.[165] Dysbiosis leads to an increase in lipopolysaccharide (LPS) levels and bile acids productions, which are linked to chronic inflammation. The intestinal microbiota also generates trimethylamine oxide, which promotes atherosclerotic vascular disease.[166] Dysbiosis reduces the levels of

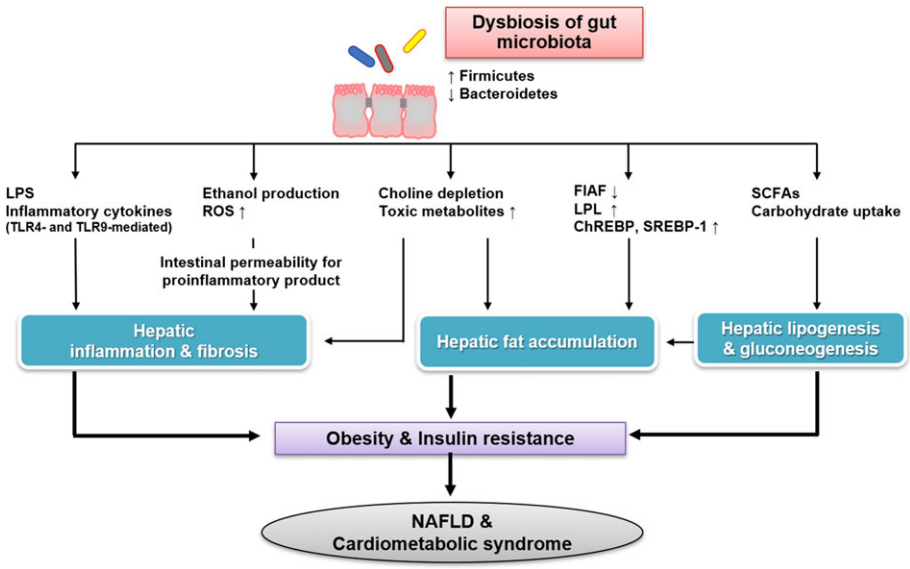


**FIGURE 3** Roles of gut microbiota in NAFLD and cardiometabolic syndrome. Gut dysbiosis increases the lipopolysaccharide (LPS) production and subsequent TLR4- or TLR9-mediated proinflammatory cytokines, thereby promoting hepatic inflammation and fibrosis. Compositional changes of gut microbiota produce ethanol and ROS, and then contribute to increased intestinal permeability and transport of proinflammatory products into the liver. Enhanced cleavage of choline resulting in the levels of its toxic metabolites, including trimethylamine, cause liver steatosis and inflammation. Decreased fasting-induced adipocyte factor (FIAF) levels enhance lipoprotein lipase (LPL) activity and ChREBP and SREBP-1 transactivation, and lead to increased hepatic fat accumulation. SCFAs produced by the gut microbiota are substrates for hepatic lipogenesis and gluconeogenesis, and increased energy delivery in the form of SCFAs or carbohydrate results in hepatic steatosis. Increased hepatic fat accumulation and inflammation by gut dysbiosis promote obesity and insulin resistance, resulting in risks of NAFLD and cardiometabolic syndrome [Colour figure can be viewed at wileyonlinelibrary.com]

SCFAs and this serves to reduce lipogenesis and to increase gluconeogenesis, leading to insulin resistance.[167]

A recent meta-analysis revealed that treatment with probiotics significantly decreased common risk factors of NAFLD and cardiometabolic syndrome.[168] It is obvious that there is a robust association between microbiota changes and the development of NAFLD and possibly cardiometabolic syndrome via sharing common pathways including systemic low-grade inflammation.[169] Possible pathological links between NAFLD and cardiometabolic syndrome are displayed in Figure 3.

## 6 | CONCLUSIONS

NAFLD is a chronic condition that is characterized by fat accumulation or inflammation in the liver, or both. Individuals with obesity, insulin resistance and dyslipidaemia are at the greatest risk of developing NAFLD. NAFLD is considered a phenotype of cardiometabolic syndrome. NAFLD/NASH plays a crucial role in the pathogenesis of T2D and CVDs via the systemic release of several inflammatory, prothrombotic, and oxidative stress mediators. NAFLD is linked with insulin resistance and contributes to atherogenic dyslipidaemia directly (Figure 2).

Currently, four agents—obeticholic acid, elafibranor, apoptosis signalling kinase-1 inhibitor, and cenicriviroc—are being evaluated in phase 3 trials for the treatment of NASH or NAFLD.[170] Before these medications are available generally (if approved), maintaining a healthy lifestyle is a fundamental way to prevent or delay the development of cardiometabolic disease and possibly reverse it in people with existing NAFLD. Future studies focusing on the molecular mechanism and signal transduction of the common denominators of NAFLD and cardiometabolic syndrome may allow the development of new therapeutic agents for NAFLD and cardiometabolic disorders.

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### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

### AUTHOR CONTRIBUTION

SL performed the literature review and prepared the manuscript. MT and JB contributed intellectual input and edited the manuscript.

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