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Shared Mechanisms between Cardiovascular Disease and NAFLD

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Abstract

The burden of nonalcoholic fatty liver disease (NAFLD) is rising globally. Cardiovascular disease is the leading cause of death in patients with NAFLD. Nearly half of individuals with NAFLD have coronary heart disease, and more than a third have carotid artery atherosclerosis. Individuals with NAFLD are at a substantially higher risk of fatal and nonfatal cardiovascular events. NAFLD and cardiovascular disease share multiple common disease mechanisms, such as systemic inflammation, insulin resistance, genetic risk variants, and gut microbial dysbiosis. In this review, we discuss the epidemiology of cardiovascular disease in NAFLD, and highlight common risk factors. In addition, we examine recent advances evaluating the shared disease mechanisms between NAFLD and cardiovascular disease. In conclusion, multidisciplinary collaborations are required to further our understanding of the complex relationship between NAFLD and cardiovascular disease and potentially identify therapeutic targets.

Graphical Abstract

Shared mechanisms between cardiovascular disease and NAFLD

Huang, et al. *Seminars in Liver Disease*
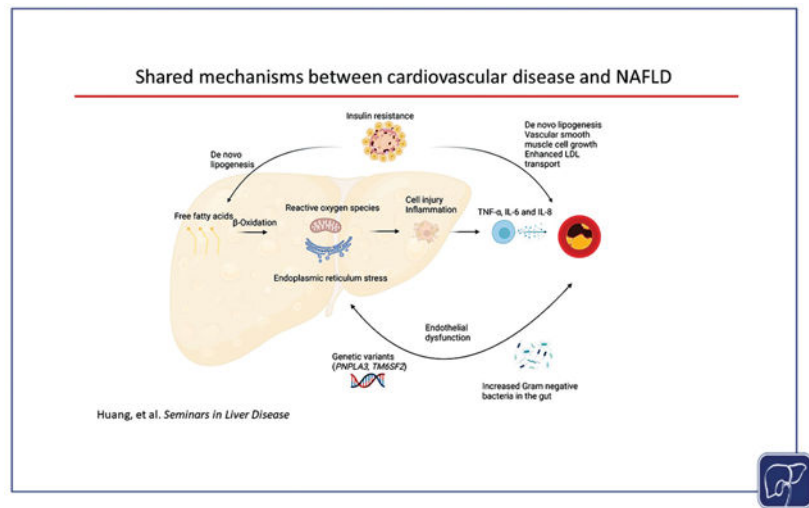
Keywords

nonalcoholic fatty liver disease; pathogenesis; atherosclerosis; coronary artery disease

One-quarter of the world's population has nonalcoholic fatty liver disease (NAFLD).[1,2] NAFLD encompasses nonalcoholic fatty liver, the benign, nonprogressive form, and nonalcoholic steatohepatitis (NASH), the progressive, inflammatory form that can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma.[3–8] With the obesity pandemic, NAFLD cases are projected to exceed 100 million in the U.S. over the next decade.[9]

NAFLD is strongly associated with obesity, insulin resistance, dyslipidemia, the metabolic syndrome, and cardiovascular disease.[10–16] Cardiovascular disease is the leading cause of death in patients with NAFLD, accounting for nearly a third of total mortality.[17–19] Even though causality has not been established, multiple studies have demonstrated that the presence and severity of NAFLD is an independent predictor for the development of cardiovascular disease and events.[12,13,20–24] Although cardiovascular disease and NAFLD share many risk factors, an individual with NAFLD is estimated to have a 57 to 69% increased risk of cardiovascular disease, independent of known common risk factors.[12,25,26] These data suggest that either NASH itself promotes cardiovascular disease, or that there are additional unidentified common risk factors. In this review, we discuss the prevalence, risk factors, and potential shared mechanisms of cardiovascular disease and NAFLD.

Prevalence of Coronary Heart Disease in NAFLD

A recent meta-analysis of 38 studies determined that the pooled prevalence of coronary heart disease (a continuum ranging from coronary artery atherosclerosis to coronary artery disease) among patients with NAFLD was 45%.[27] The prevalence of coronary heart disease by region ranged from 31% in Asia to 62% in North America (Fig. 1). Patients with NAFLD had increased odds of coronary heart disease (pooled odds ratio [OR] 1.3) compared

with patients without NAFLD. In addition, the prevalence of coronary heart disease was higher among NAFLD patients with moderate or severe steatosis versus those with mild steatosis (38% vs. 30%). Among patients with NAFLD who had symptoms suggestive of ischemic heart disease, the prevalence of clinical coronary artery disease was 55%, and the presence of NAFLD was associated with increased odds of clinical coronary artery disease (OR 2.2). These findings are consistent with an older meta-analysis of 16 studies, which determined that patients with NAFLD had a higher odds of fatal and/or nonfatal cardiovascular events (including ischemic heart disease and stroke) compared with patients without NAFLD.[12] In the older meta-analysis, the higher risk of cardiovascular events in NAFLD persisted even after sensitivity analyses that excluded studies with participants with diabetes, hypertension, and myocardial infarction. By contrast, a matched cohort study of population-based, electronic primary health care databases from Italy, the Netherlands, Spain, and the U.K. compared patients with a recorded diagnosis of NAFLD or NASH versus patients without a recorded diagnosis of NAFLD or NASH and did not find a significant association between NAFLD and the risk of cardiovascular events.[28] However, the prevalence of NAFLD in these databases were lower than expected (0.6% in 2007 to 1.9% in 2014), which suggested possible misclassification and underdiagnosis of NAFLD in the control group.

Taken together, these data suggest that coronary heart disease is common among patients with NAFLD and is more prevalent among those with moderate to severe steatosis. Screening for coronary heart disease among patients with NAFLD may be guided by the severity of hepatic steatosis, and identification of such patients may allow for intensive risk factor management and prevention of ischemic events.

Prevalence of Carotid Atherosclerosis and Stroke in NAFLD

A recent meta-analysis of 30 studies determined that the prevalence of carotid atherosclerosis among patients with NAFLD was 35%.[29] By region, the prevalence of carotid atherosclerosis among patients with NAFLD was lowest in the Middle East (19%) and highest in Europe (45%). The presence of NAFLD was associated with higher odds of carotid atherosclerosis (OR 3.3). The authors determined that the prevalence of stroke among NAFLD patients was 5%. Patients with NAFLD had higher odds (OR 1.9) of developing stroke compared with non-NAFLD controls. The degree of steatosis was associated with incremental odds of carotid atherosclerosis and stroke. These findings suggest that targeted screening for carotid atherosclerosis among patients with NAFLD may be guided by the severity of hepatic steatosis. The associations between NAFLD and other cardiovascular disease are summarized in Table 1.

Potential Shared Mechanisms of Disease between NAFLD and Cardiovascular Disease

The shared risk factors between NAFLD and cardiovascular disease are summarized in Fig. 2. The above-mentioned meta-analysis of NAFLD and prevalence of coronary heart disease determined that age, hypertension, and diabetes were significantly associated with coronary heart disease in NAFLD.[27] Other established shared risk factors include dyslipidemia, insulin resistance, metabolic syndrome, dietary habits, smoking, and the lack of physical

exercise.[10,30–34] A substantial proportion of patients with NAFLD and cardiovascular disease harbor the metabolic syndrome.[35,36] A study utilizing systems biology modeling demonstrated substantial overlap in disease mechanisms between NAFLD and the metabolic syndrome and suggested that multitarget therapeutic approaches may be a better strategy to treat NASH.[34] In addition, case–control studies have demonstrated that the presence of NAFLD was associated with increased levels of serum biomarkers of atherosclerosis.[37] A meta-analysis determined that patients with NAFLD have a 57 to 69% increased risk of cardiovascular disease, independent of known common risk factors, suggesting that either NASH may be an independent cause of cardiovascular disease, or there may be additional unidentified risk factors.[12] However, it is possible that this association may have confounded by undiagnosed confounders in the individual studies, such as diabetes or obesity. Due to the dynamic bidirectional relationship between NAFLD, shared metabolic risk factors, and cardiovascular disease, isolating the specific contribution of NAFLD to cardiovascular disease is challenging. In the following segment, we discuss several putative shared mechanisms of disease between NAFLD and cardiovascular disease.

NAFLD and Low-Grade Systemic Inflammation

NAFLD causes systemic inflammation through multiple complex interactions between the gut microbiome, liver, and adipose tissue.[3,38] NASH is associated with the activation of the inflammasome of multiple cell types, including both resident and infiltrating cells.[3,38,39] Free fatty acids induce hepatocytes to secrete tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8, inducing systemic inflammation.[40–42] In a study of 2,482 participants from the Framingham Heart Study, the presence of liver fat was independently associated with increased serum concentration of systemic markers of inflammation, including C-reactive protein (CRP), urinary isoprostanes, IL-6, intercellular adhesion molecule 1, and P-selectin, after adjustment for body mass index and other components of the metabolic syndrome.[43]

In a study of 3,876 participants from the Multi-Ethnic Study of Atherosclerosis, participants with NAFLD had higher serum concentrations of markers of inflammation, including LpPLA2 activity, high-sensitivity CRP, and IL-6.[44] In this study, IL-6 was independently associated with the presence and severity of subclinical atherosclerosis, defined by coronary artery calcium.

Systemic inflammation is associated with the development of incident cardiovascular disease.[45] Low-grade systemic inflammation secondary to NAFLD leads to the release of proinflammatory cytokines and may promote the development of atherogenic cardiovascular disease by inducing endothelial dysfunction and enhancing plaque formation.[46–49] Inflammation is a key determinant that links risk factors for atherosclerosis to the development of coronary artery disease, and further mechanistic studies are required to characterize the relationship between NAFLD, systemic inflammation, and cardiovascular disease.[50]

NAFLD and Epicardial Adipose Tissue

NAFLD is associated with increased epicardial adipose tissue, and a higher epicardial fat thickness is associated with more severe liver fibrosis.[51,52] Epicardial adipose tissue has close proximity with the coronary arteries and myocardium, shares a common microcirculation with the myocardium, and secretes proinflammatory cytokines, such as IL-6 and TNF-α that promote atherogenesis and heart failure by inducing infiltration of the intima and fibrosis.[53,54] In addition, the inflammatory cytokines secreted by the epicardial adipose tissue may also contribute to the activation of hepatic stellate cells and induce liver fibrosis.[55] Atherosclerotic plaques are more prevalent in regions of coronary arteries surrounded by epicardial adipose tissue, adding weight to a possible link between ectopic fat in the epicardium and coronary artery disease.[54] In a study of 147 patients with biopsy-confirmed NAFLD, epicardial fat, morphological, and functional cardiac alterations were more pronounced among patients with severe fibrosis.[52] In our opinion, these data suggest that NASH and cardiovascular disease may share synergistic mechanisms that arise from a systemic proinflammatory, proatherogenic, and profibrogenic environment maintained by ectopic adipose tissue. More studies are required to validate this hypothesis.

Insulin Resistance in NAFLD and Cardiovascular Disease

Dysregulated glucose metabolism and insulin resistance are key drivers of both NAFLD and cardiovascular disease. Skeletal muscle insulin resistance diverts glucose away from skeletal muscle glycogen synthesis and into the liver.[56,57] The increased delivery of glucose to the liver, along with hyperinsulinemia, stimulates sterol regulatory element-binding protein 1c (SREBP1c), which promotes increased expression of key hepatic enzymes that regulate de novo lipogenesis, resulting in increased very-low-density lipoprotein production, hypertriglyceridemia, and NAFLD.[3,58] Hyperinsulinemia further triggers hepatic gluconeogenesis, further increasing insulin levels, thus promoting a vicious cycle of dysregulated glucose metabolism.

Insulin resistance is a strong predictor of atherosclerotic cardiovascular disease.[59,60] High levels of insulin accelerate the atherosclerotic process by several mechanisms, including stimulating de novo lipogenesis leading to increased low-density lipoprotein (LDL) synthesis, promoting vascular smooth muscle cell growth and proliferation, increasing collagen synthesis and enhancing LDL cholesterol (LDL-C) transport into arterial smooth muscle cells.[61–65] These data reaffirm the key role of insulin resistance in the pathogenesis of both NAFLD and cardiovascular disease.

Endothelial Dysfunction in NAFLD and Cardiovascular Disease

Endothelial dysfunction is the starting point of atherogenesis.[66] An Italian study assessed endothelial function by measuring the vasodilatory response of the brachial artery in response to ischemia.[67] The study compared 52 patients with NAFLD versus 28 matched controls and determined that NAFLD was independently associated with increased endothelial dysfunction after adjustment for confounders. A study from Taiwan determined that patients with NAFLD had substantially reduced circulating bone marrow-derived

endothelial progenitor cell levels and function compared with matched controls.[68] The findings of this Taiwanese study suggested that attenuated endothelial repair capacity may contribute to atherosclerotic disease progression and increased cardiovascular risk in NAFLD patients. In addition, patients with NAFLD are known to have higher levels of homocysteine, which further promotes atherogenesis by inducing oxidative stress and endothelial dysfunction.[69–71] In a case–control study of patients with NASH, simple steatosis, and controls, the presence of NASH was associated with a higher expression of mediators of atherogenesis and endothelial damage (*ACE*, *CSF2*, *IL1A*, *LIF*, *MMP1*, and *TGFβ1*).[72] These emerging data suggest that endothelial dysfunction may play an important role in the development of cardiovascular disease among individuals with NAFLD.

PPARs in NAFLD and Cardiovascular Disease

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors and comprise three isoforms (PPARα, PPARβ/δ, and PPARγ).[73] PPARs are centrally involved in the regulation of genes that influence the metabolism of triglycerides, glucose, lipogenesis, fatty acid transport, inflammation, fibrosis, and atherosclerosis.[74,75] A randomized, placebo-controlled phase 2 trial of saroglitazar, a dual PPAR-α/γ agonist in patients with NAFLD/NASH, determined that saroglitazar was associated with reductions in alanine aminotransferase, liver fat content, atherogenic lipids, and lipotoxic lipid species.[76] These data suggest that saroglitazar has the potential to improve both NAFLD and cardiovascular disease, but a phase 3 trial, which is ongoing, is required to confirm this (Clinical-Trials.gov NCT04193982). The NATIVE trial was a phase 2b, randomized, placebo-controlled trial of a pan-PPAR (lanifibranor) agonist for the treatment of NASH.[77] In this study, participants who received 1200 mg of lanifibranor daily had a greater proportion with a decrease in at least two points in the Steatosis, Activity, Fibrosis score compared with those who received placebo (55% vs. 33%, $p = 0.007$). These data prompted the initiation of a phase 3 study which is ongoing (Clinical-Trials.gov NCT04849728). By contrast, a randomized, phase 2 trial of selective PPAR-α modulator (SPPARMα), pemafibrate, in patients with NAFLD did not meet the primary endpoint of reduction in liver fat content, although it was associated with reduction in liver fibrosis and LDL-C.[78] A randomized trial of pioglitazone, a PPAR-γ/PPAR-α agonist, in patients with NASH and diabetes or prediabetes, determined that long-term treatment with pioglitazone was associated with NASH resolution and improvements in insulin resistance and lipid profile.[79] Taken together, these data suggest that targeting the PPAR isoforms may be a potential strategy for treating both NAFLD and cardiovascular disease.

Gut Microbial Dysbiosis and Systemic Inflammation

NAFLD is associated with disruption of intestinal enterocyte intercellular tight junctions, resulting in increasing gut permeability and translocation of gut bacteria and lipopolysaccharides.[80,81] A prospective study conducted using whole-genome shotgun sequencing of deoxyribonucleic acid extracted from the stool of participants with biopsy-confirmed NAFLD determined that advanced fibrosis was associated with an increased abundance of proinflammatory Gram-negative Proteobacteria (including *Escherichia coli*).[82] Another study evaluated 16S gut-microbiome compositions of 203 well-characterized

participants, including 26 with NAFLD cirrhosis, and similarly found that participants with NAFLD and advanced liver disease were enriched in Gram-negative bacterium such as Enterobacteriaceae and Gallibacterium.[83] In a metagenome-wide association study of participants with atherosclerotic cardiovascular disease compared with healthy controls, Gram-negative bacteria (including *E. coli*) were elevated among participants with atherosclerotic cardiovascular disease.[84] Likewise, a case–control study sequencing the 16S rRNA V4 tag compared patients with large artery atherosclerotic ischemic stroke and transient ischemic attacks against healthy controls and identified increased Gram-negative bacteria (including Enterobacteriaceae and Proteobacteria) among cases.[85] These data suggest that gut microbial dysbiosis in patients with NAFLD contributes to systemic inflammation and may potentiate cardiovascular disease.[47,86–88]

Genetic Determinants of NAFLD and Cardiovascular Disease

Multiple studies have shown that hepatic steatosis and fibrosis are heritable traits.[89,90] The most well-studied single-nucleotide polymorphism (SNP) in NAFLD is the patatin-like phospholipase domain-containing 3 (*PNPLA3*) c.444 C > G SNP, which encodes the I148M variant and has been strongly linked to an increased risk of liver-related mortality in NAFLD.[91–93] *PNPLA3* is a multifunctional enzyme implicated in the regulation of lipids and retinyl ester activity.[94] The *TM6SF2* rs58542926 C > T polymorphism codes for an E to K substitution at position 167 that results in loss of function and is associated with reduced hepatic *TM6SF2* messenger ribonucleic acid (RNA) and protein expression, higher levels of alanine transaminase, and lower levels of LDL-C.[95,96] A large exome-wide association study of plasma lipids in more than 300,000 participants determined that variants in *PNPLA3* and *TM6SF2* were associated with higher liver fat and a greater risk for diabetes, but lower blood lipid levels and a lower risk for coronary artery disease.[97] A meta-analysis of 10 studies (101,326 individuals) determined that carriers of the *TM6SF2* variant had lower levels of total cholesterol, LDL, and triglycerides, along with a higher risk of NAFLD.[98] Another study that included 60,801 cases with coronary artery disease and 123,504 controls determined that the *TM6SF2* variant was protective against coronary artery disease, while the cardioprotective effect of the *PNPLA3* was only modest.[99] Similarly, the impact of the *TM6SF2* E167K variant was assessed in 1,819 Swedish individuals and was found to be associated with a lower incidence of cardiovascular events.[100] A prospective study of 270 patients undergoing coronary angiography determined that the *PNPLA3* variant was associated with lower LDL-C and a lower risk of coronary heart disease after adjusting for confounders.[101] Taken together, these data indicate that variants in *PNPLA3* and *TM6SF2* are associated with an increased risk of NAFLD, but a reduced risk of coronary artery disease, possibly due to lower serum lipid levels.

Implications for Future Drug Development

Continued research into the shared mechanisms and distinctions, between NAFLD and cardiovascular disease may help tailor NAFLD drug development toward the treatment of both NAFLD and cardiovascular disease and avoid adding to cardiovascular risk. The challenges faced with the use of the first-generation steroidal farnesoid X receptor (FXR) agonist obeticholic acid in the treatment of patients with NASH are an example of how

the interplay between NAFLD and cardiovascular disease may influence side effect profiles. The phase 2b, randomized, placebo-controlled trial of obeticholic acid performed in patients with NASH determined that obeticholic acid improved the histological features of NASH, but was associated with increases in total serum cholesterol and LDL-C, and a decrease in high-density lipoprotein (HDL) cholesterol.[102] Similarly, the interim analysis of the phase 3 trial of obeticholic acid showed that LDL-C increased in the initial months after treatment initiation but fell with time and approached baseline by month 18.[103] The impact of obeticholic acid on LDL is related to an FXR-specific effect, which downregulates an LDL-C receptor and increases transfer cholesteryl ester transfer protein, leading to increased LDL-C and reduced HDL cholesterol. Future drug developmental efforts in NASH should be guided by greater efforts to understand the complex interactions between NAFLD and cardiovascular disease.

Future Directions

The formation of cross-disciplinary collaborations and consortiums with prospective studies are essential to untangle the complex relationship between NAFLD and cardiovascular disease. In addition, as analytical technologies progress and allow for a deeper understanding of the complex pathways between NAFLD and cardiovascular disease, these may give rise to the identification of shared therapeutic targets. As an example, single-cell RNA sequencing technologies are currently enabling characterization of the molecular phenotypes of the various cell types of normal and diseased tissues. These methods have recently been applied to examine the resident nonparenchymal cell types in normal versus cirrhotic human livers[104] and the composition of cells within human atherosclerotic lesions.[105] In each case, striking disease-specific variation was observed both in cellular population structure and in gene expression within specific cell types. There are hints of dysregulation of common pathways that may account for these findings, but analysis of these types of data has not yet begun in a systematic manner. Importantly, application of single-cell RNA sequencing technologies will provide an important additional tool in analyzing responses to therapeutic interventions in preclinical models.

Conclusion

There is a high prevalence of cardiovascular disease in NAFLD, and patients with NAFLD are at increased risk of cardiovascular-related morbidity and mortality. NAFLD and cardiovascular disease share many common disease mechanisms, including low-grade systemic inflammation, endothelial dysfunction, insulin resistance, gut microbial dysbiosis, and genetic risk alleles (Fig. 3). Multidisciplinary collaborations are required to further our understanding of the complex relationship between NAFLD and cardiovascular disease.

Funding

Conflict of Interest

R.L. serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals, and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes, and Terns Pharmaceuticals. Co-founder of LipoNexus Inc.

D.H. receives funding support from Singapore Ministry of Health's National Medical Research Council under its NMRC Research Training Fellowship (MOH-000595-01). In addition, he has served as an advisory board member for Eisai.

J.L.W. holds patents related to the use of oxidation specific antibodies held by UCSD. He is cofounder of Oxitope and Kleanthi Diagnostic and is a consultant to Ionis Pharmaceuticals.

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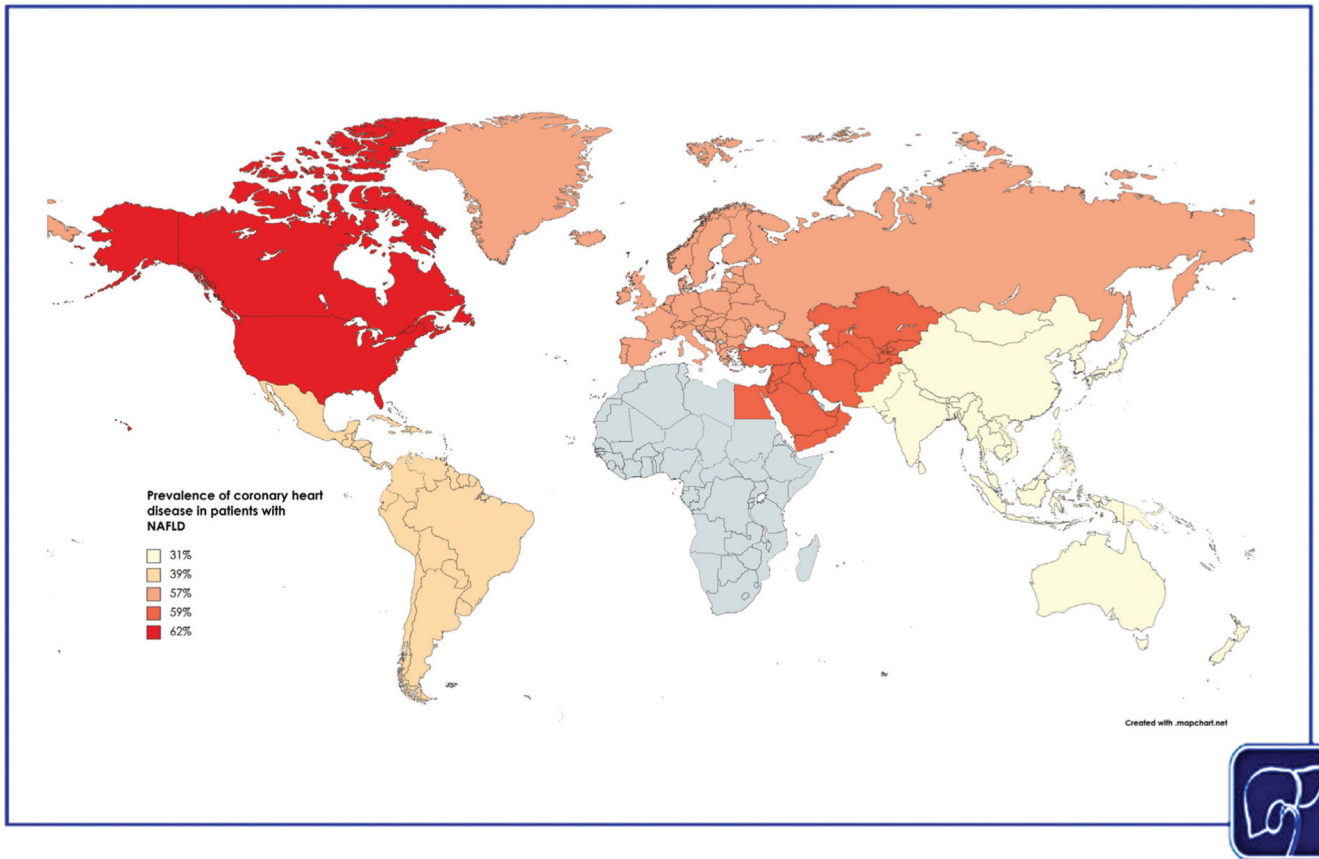
Fig. 1.
Estimated global prevalence of coronary heart disease, by World Health Organization
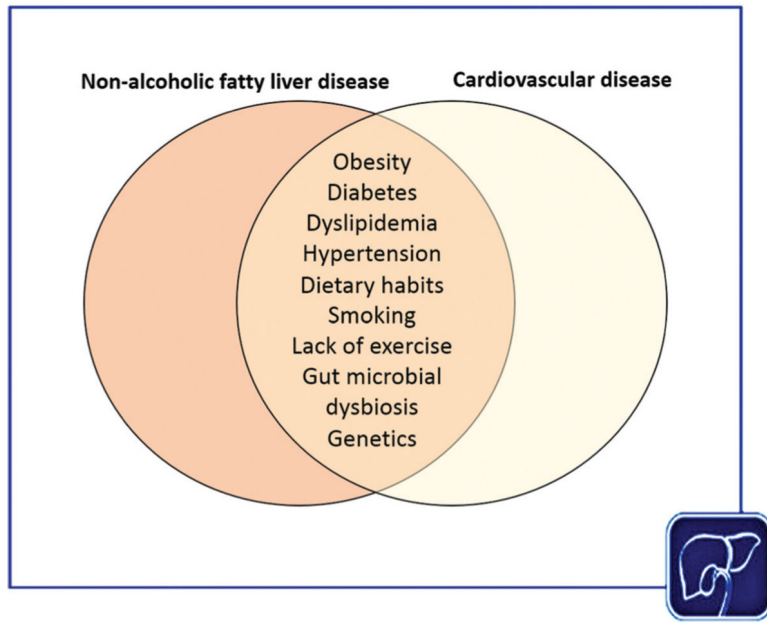(WHO) region.

Fig. 2.
Established shared risk factors between nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease.
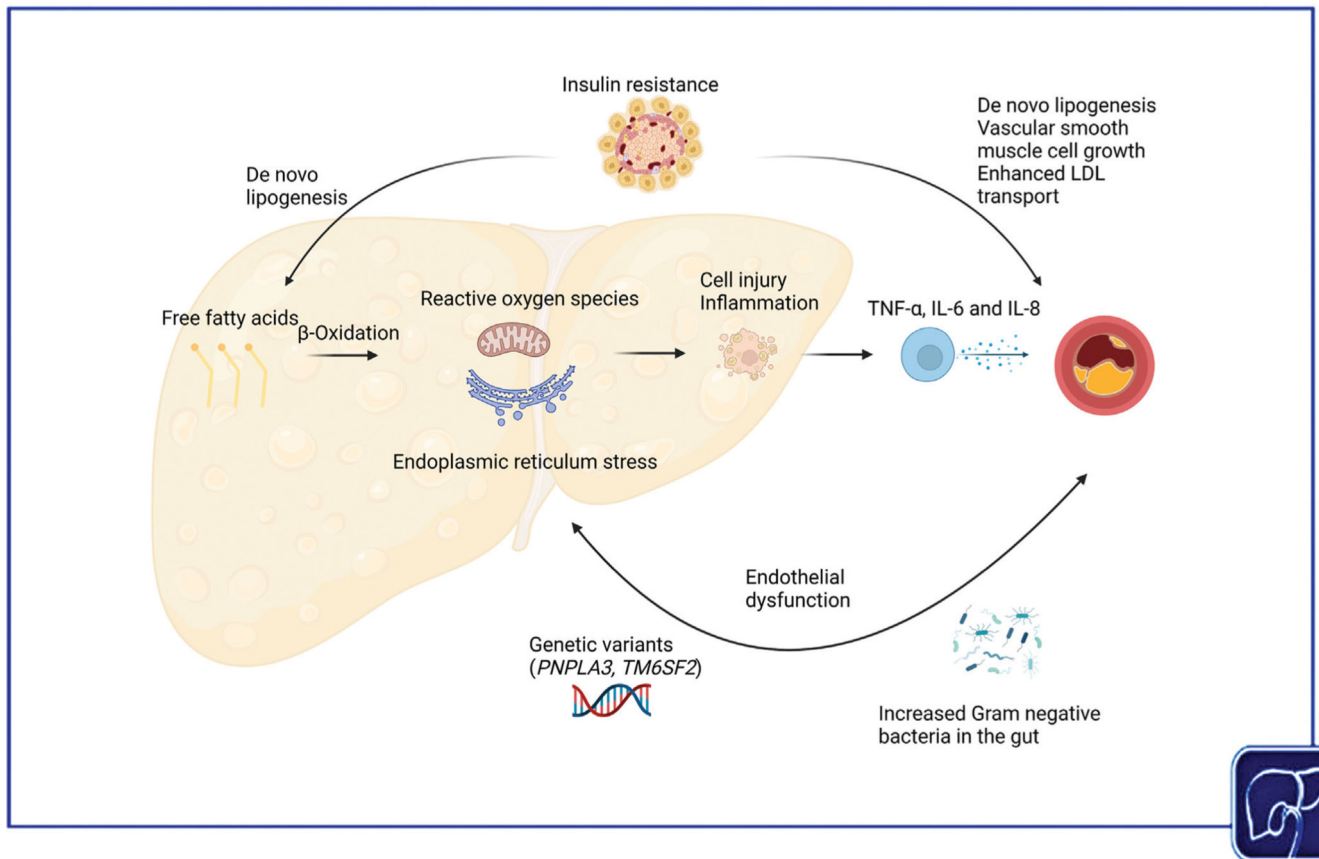
Fig. 3.
Putative shared disease mechanisms between cardiovascular disease and nonalcoholic fatty liver disease (NAFLD). In NAFLD, there is increased production of proinflammatory cytokines, which promotes atherosclerosis. Individuals with NAFLD and cardiovascular disease have endothelial dysfunction, which may be mediated by early atherosclerosis. Insulin resistance is a key driver of both NAFLD and cardiovascular disease. With more advanced hepatic and cardiovascular disease, there is increased abundance of proinflammatory Gram-negative bacteria in both NAFLD and cardiovascular disease. Genetic variants in *PNPLA3* and *TM6SF2* promote hepatic steatosis and advanced fibrosis but reduce systemic lipid levels and may be cardioprotective.

Table 1

Selected meta-analyses that examined the association between nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease

Author, publication year	Cardiovascular disease	Number of included studies	Main findings	Strength of association
Toh et al,[27] 2021	Coronary heart disease	38	The pooled prevalence of coronary heart disease was 44.6% (95% CI, 36.0–53.6%) among 67,070 patients with NAFLD with an odds ratio of 1.33 (95% CI, 1.21–1.45%; $p < 0.0001$), compared with patients without NAFLD	Moderate to strong
Tang et al,[29] 2022	Carotid atherosclerosis and stroke	30	35.02% (CI, 27.36–43.53%) of patients with NAFLD had carotid atherosclerosis, with an odds ratio of 3.20 (95% CI, 2.37–4.32; $p < 0.0001$) compared with patients without NAFLD. The prevalence of stroke was 5.04% (95% CI, 2.74–9.09%) among patients with NAFLD with an odds ratio of 1.88 (95% CI, 1.23–2.88; $p = 0.02$) compared with patients without NAFLD	Moderate to strong
Yong et al,[106] 2022	Echocardiographic-derived cardiac function and structural characteristics	41	Patients with NAFLD had poorer systolic indices with lower ejection fraction (mean difference: −0.693; 95% CI: −1.112 to −0.274; $p = 0.001$), and worse diastolic indices with higher E/e' (mean difference: 1.575; 95% CI: 0.924–2.227; $p < 0.001$) compared with non-NAFLD patients The presence of NAFLD was associated with increased left ventricular mass (mean difference: 34.484; 95% CI: 26.236–42.732; $p < 0.001$) and epicardial adipose thickness (mean difference:0.1343; 95%CI: 0.055–0.214; $p = 0.001$)	Moderate to strong
Mantovani et al,[107] 2019	Atrial fibrillation	9	NAFLD was associated with an increased risk of prevalent atrial fibrillation (odds ratio 2.07, 95% CI 1.38–3.10)	Moderate
Ciardullo et al,[108] 2022	Hypertension	11	The presence of NAFLD was associated with an increased risk of incident hypertension (hazard ratio 1.66; 95% confidence interval [CI], 1.38–2.01; $p < 0.001$)	Moderate

Abbreviations: CI, confidence interval; NAFLD, nonalcoholic fatty liver disease.