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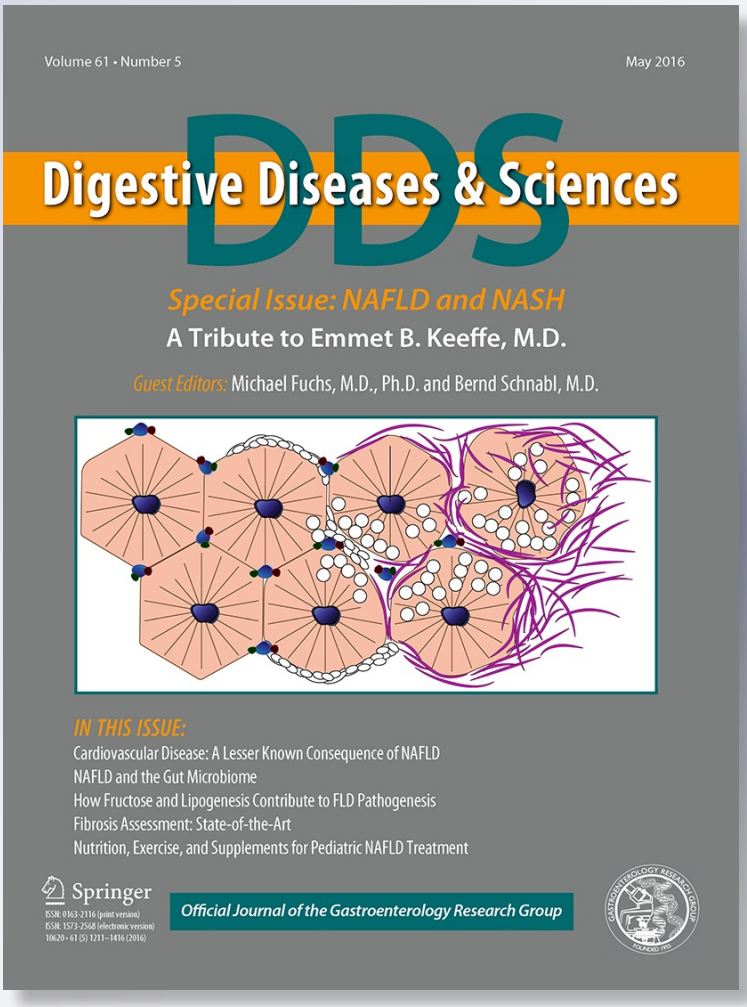

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REVIEW

Cardiovascular Disease and Myocardial Abnormalities in Nonalcoholic Fatty Liver Disease

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Abstract Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in many developed countries, affecting an estimated 30 % of the adult population. In this updated clinical review, we summarize the current knowledge regarding the strong association between NAFLD and the risk of coronary heart disease (CHD) and other functional, structural, and arrhythmic cardiac complications (e.g., left ventricular dysfunction, heart valve diseases and atrial fibrillation). We also briefly discuss the putative biological mechanisms linking NAFLD with these important extra-hepatic complications. To date, a large body of evidence has suggested that NAFLD is not simply a marker of CHD and other functional, structural, and arrhythmic cardiac complications, but also may play a part in the development and progression of these cardiac complications. The clinical implication of these findings is that patients with NAFLD may benefit from more intensive surveillance and early treatment interventions aimed at decreasing the risk of CHD and other cardiac and arrhythmic complications.

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Keywords Nonalcoholic fatty liver disease · Cardiovascular disease · Cardiac disease · Cardiac arrhythmias · Myocardial dysfunction · Heart valve diseases

Introduction

Nonalcoholic fatty liver disease (NAFLD)—defined as the entire histologic spectrum of alcohol-like hepatic conditions observed in nonalcoholic individuals—has become the most common liver disease worldwide and results in considerable liver-related mortality and morbidity [1–3]. NAFLD is the third most common indication for liver transplantation in the USA and is on a trajectory to become the most common indication within the next decade [1–3].

Over the past 10 years, it has also become increasingly clear that NAFLD is a multisystem disease that affects a variety of extra-hepatic organ systems [4, 5], including the heart and the vascular system. To date, clear evidence has indicated that coronary heart disease (CHD) is the primary cause of morbidity and mortality in patients with NAFLD [2, 4–7]. As detailed below, convincing evidence also substantiates the existence of a link between NAFLD and functional and structural myocardial alterations in both adults and children with, or without, coexisting features of the metabolic syndrome (MetS).

This article critically appraises the large body of clinical data that support a strong association between NAFLD and the risk of CHD and other cardiac (structural, functional, and arrhythmic) complications (Fig. 1). We also discuss the putative biological mechanisms by which NAFLD may be implicated in the pathophysiology of these cardiac complications.

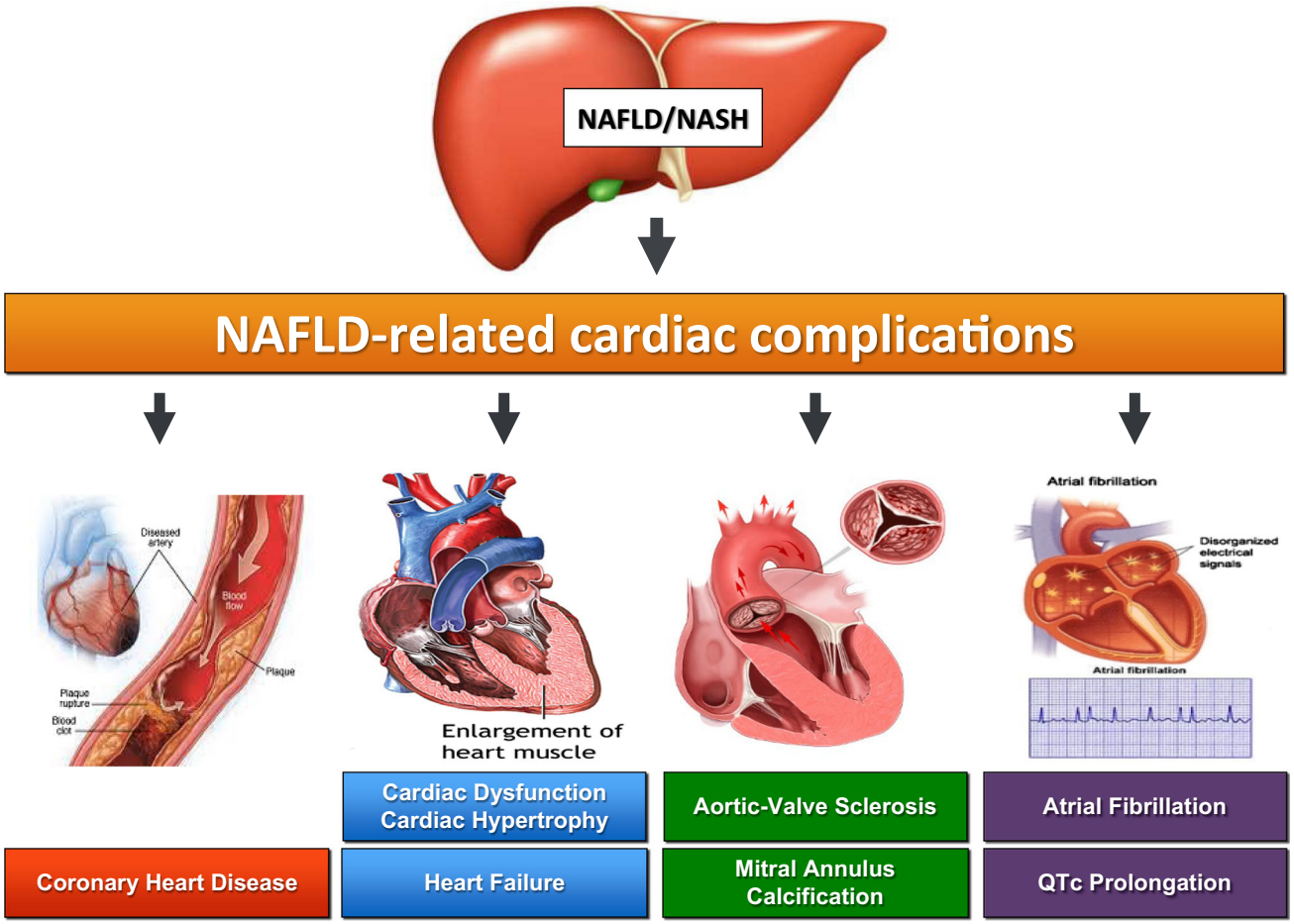

Fig. 1 Spectrum of the most important cardiac complications associated with NAFLD

Epidemiological Evidence Linking NAFLD to Altered Cardiac Structure and Function

Over the past decade, evidence of a significant relationship between NAFLD and myocardial abnormalities in both adults and children or adolescents has accumulated. This relationship appears to be significant even after adjusting for overweight/obesity, hypertension, and other coexisting MetS features.

Studies on the Effect of NAFLD on the Left Atrium and Ventricle

In a study published in 2006, Goland et al. [8] have reported that adult individuals with NAFLD in the absence of severe obesity, hypertension, and diabetes have mildly increased left ventricular (LV) mass and early features of LV diastolic dysfunction. As detailed in Table 1, after this pioneering study, several case–control studies have examined whether NAFLD (as diagnosed either by imaging or by histology) is associated with cardiac dysfunction and mildly increased LV mass, independently of coexisting cardiometabolic risk factors [8–22].

For instance, Kim et al. [14] have found that NAFLD on ultrasound was associated with LV diastolic dysfunction (as assessed by tissue Doppler imaging echocardiography) in a community-based cohort of Korean adults, independently of established cardiovascular (CVD) risk factors and MetS features. More recently, VanWagner et al. [16] have examined 2713 adult participants from the multicenter, community-based Coronary Artery Risk Development in Young Adults (CARDIA) study who underwent concurrent computed tomography quantification of liver fat and comprehensive echocardiography with myocardial strain measured by speckle tracking. Notably, these authors have reported that patients with NAFLD had lower early diastolic relaxation (e') velocity, higher LV filling pressure, larger left atrial (LA) volume, and worse absolute global longitudinal strain compared with those without NAFLD. After adjustment for established CVD risk factors, NAFLD remained significantly associated with subclinical myocardial remodeling and dysfunction, thus providing further insight into a

Table 1 Principal studies examining the association between NAFLD and alterations in cardiac structure and function in adults (ordered by publication year)

Authors (years) [Ref.]	Study characteristics	Diagnosis of NAFLD	Cardiac measures	Adjustments considered	Main findings
Goland et al. (2006) [8]	Cross-sectional: 38 non-diabetic, normotensive NAFLD patients and 25 age- and sex-matched healthy controls	Ultrasound and liver biopsy (in 11 patients)	LV structure and function (echocardiography with TDI)	Age, sex, BMI, blood pressure, metabolic, and echocardiographic variables	Patients with NAFLD have mildly altered LV geometry and early LVDD. On multivariate regression analysis, the e' wave was the only independent variable associated with NAFLD
Fallo et al. (2009) [9]	Cross-sectional: 48 newly diagnosed untreated hypertensive patients (non-obese, non-diabetic) with NAFLD and 38 without NAFLD	Ultrasound	LV structure and function (echocardiography)	Age, sex, BMI, waist circumference, triglycerides, adiponectin, insulin resistance	Patients with NAFLD had higher prevalence of LVDD (62.5 vs. 21.1 %). LVDD and HOMA-insulin resistance were independently associated with NAFLD at multivariate regression analysis
Fotbolcu et al. (2010) [10]	Cross-sectional: 35 non-diabetic, normotensive NAFLD patients and 30 age- and sex-matched healthy controls	Ultrasound	LV structure and function (echocardiography with TDI)	None	Patients with NAFLD had impaired LV systolic and diastolic function compared with healthy controls
Bonapace et al. (2012) [11]	Cross-sectional: 50 consecutive type 2 diabetic patients without CHD and hepatic diseases (64 % with NAFLD)	Ultrasound	LV structure and function (echocardiography with TDI and speckle-tracking strain analysis)	Age, sex, BMI, triglycerides, hypertension, hemoglobin A1c	NAFLD was independently associated with early LVDD. These abnormalities were worse in those with severe NAFLD on ultrasound
Mantovani et al. (2012) [12]	Cross-sectional: 116 older hypertensive patients with type 2 diabetes without history of CHD and liver diseases (53 % with NAFLD)	Ultrasound	LV hypertrophy (echocardiography)	Age, sex, BMI, systolic blood pressure, eGFR, diabetes duration, GGT, hemoglobin A1c	Patients with NAFLD had higher prevalence of LV hypertrophy than those without NAFLD (82 vs. 18 %). NAFLD was independently associated with LV hypertrophy at multivariate analysis (adjusted OR 5.94, 95 % CI 1.5–24, $P = 0.01$)
Hallsworth et al. (2013) [13]	Cross-sectional: 19 non-diabetic, overweight adults with NAFLD and 19 age-, sex- and BMI-matched healthy controls	^{1}H-MRS	LV structure and function (cardiac magnetic resonance and ^{31}P-MRS)	Age, sex, BMI	Patients with NAFLD had higher thickening of the cardiac wall, altered myocardial strains, and early LVDD. No significant differences were found in myocardial energetics between the two groups
Kim et al. (2014) [14]	Community-based study: 1886 individuals without CVD from the Korean Genome Epidemiology Study (22 % with NAFLD)	Computed tomography	LV structure and function (echocardiography with TDI)	Age, sex, BMI, MetS, heart rate, alcohol, smoking, C-reactive protein, medication use, family history of CVD	Patients with NAFLD had early LVDD compared those without NAFLD or MetS. Both NAFLD and MetS were independent predictors of LVDD ($P < 0.001$) at multivariate regression analysis
Karabay et al. (2014) [15]	Cross-sectional: 55 NAFLD patients and 21 healthy controls	Liver biopsy	LV structure and function (echocardiography with TDI and speckle-tracking strain analysis)		Patients with NAFLD had altered LV geometry and LVDD compared with controls. Speckle-tracking echocardiography showed no differences in strain among subgroup patients (simple steatosis vs. borderline NASH vs. definite NASH)
VanWagner at al. (2015) [16]	Community-based study: 2713 participants from the CARDIA study (~10 % with NAFLD)	Computed tomography	Subclinical myocardial remodeling and function (echocardiography with speckle-tracking strain analysis)	Center, age, race, sex, education, income level, alcohol, smoking, physical activity, BMI, systolic blood pressure, medication use, total cholesterol, HDL cholesterol, diabetes status, eGFR, visceral adipose tissue	Patients with NAFLD had lower early diastolic relaxation (e') velocity, higher LV filling pressure, and worse absolute peak global longitudinal strain than non-NAFLD. In multivariate regression analysis, NAFLD was independently associated with these parameters of subclinical myocardial remodeling and dysfunction

Table 1 continued

Authors (years) [Ref.]	Study characteristics	Diagnosis of NAFLD	Cardiac measures	Adjustments considered	Main findings
Cassidy et al. (2015) [17]	Cross-sectional: 19 adults with type 2 diabetes, 19 adults with NAFLD and 19 healthy controls matched for age and sex	^{1}H-MRS	LV structure, function, and metabolism (cardiac magnetic resonance and ^{31}P-MRS)	Age, sex, BMI, blood pressure	Changes in cardiac structure were evident in adults with diabetes and NAFLD without overt cardiac disease and without changes in cardiac energy metabolism. Only those with diabetes displayed diastolic and subendocardial dysfunction
Kocabay et al. (2015) [18]	Cross-sectional: 55 patients with NAFLD and 21 healthy controls	Liver biopsy	LA deformation parameters (echocardiography with speckle-tracking strain analysis)		LA deformation parameters were impaired in NAFLD patients with normal systolic function. There was a significant relationship between impairment in LA deformation and severity of NAFLD histology
Granér et al. (2015) [19]	Cross-sectional: 75 non-diabetic men with NAFLD	^{1}H-MRS	LV structure and function (cardiac magnetic resonance imaging and ^{1}H-MRS)	Age, BMI, waist circumference, blood pressure, heart rate, smoking status, triglycerides, HDL cholesterol, fasting glucose levels	Myocardial triglyceride content, epicardial and pericardial fat, visceral fat, and subcutaneous fat increased from lower to higher liver fat group. Hepatic fat content and visceral fat were the only two independent predictors of LVDD, whereas myocardial fat content, epicardial and pericardial fat were not associated with diastolic function measures
Mantovani et al. (2015) [20]	Cross-sectional: 222 consecutive type 2 diabetic outpatients without history of CHD, heart failure, moderate-to severe heart valve diseases, and hepatic diseases (71.2 % with NAFLD)	Ultrasound	LV structure and function (echocardiography with TDI and speckle-tracking strain analysis)	Age, sex, BMI, hypertension, diabetes duration, hemoglobin A1c, eGFR, LV mass index, LV ejection fraction	Patients with NAFLD had a greater prevalence of mild and/or moderate LVDD than those without NAFLD (71 vs. 33 %). NAFLD was associated with an increased risk of mild and/or moderate LVDD (adjusted OR 3.08, 95 % CI 1.5–6.4, $P = 0.003$)
Petta et al. (2015) [21]	Cross-sectional: 147 patients with NAFLD	Liver biopsy	LV structure and function (echocardiography)	Sex, age >50 years, visceral obesity, impaired fasting glycemia/diabetes, epicardial fat, steatosis grade 3	Diastolic posterior-wall thickness ($P = 0.01$), LV mass ($P = 0.03$), relative wall thickness ($P = 0.02$), and LA volume ($P = 0.04$), as well as lower LV ejection fraction ($P = 0.004$), lower lateral e' ($P = 0.009$), and E/A ratio ($P = 0.04$) were linked with severe hepatic fibrosis. Epicardial fat was also higher in patients with severe versus mild fibrosis
Sunbul et al. (2015) [22]	Cross-sectional: 90 consecutive patients with NAFLD and 45 age- and sex-matched controls	Liver biopsy	Right ventricular function (echocardiography with speckle-tracking strain analysis)	Age, BMI, total cholesterol, fasting glucose levels	Patients with NAFLD had impaired RV function. NASH score on biopsy independently predicted impaired RV function in patients with NAFLD

BMI body mass index, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *GGT* gamma-glutamyltransferase, *LV* left ventricular, *LVDD* left ventricular diastolic dysfunction, *MetS* metabolic syndrome, *MRS* magnetic resonance spectroscopy, *OR* odds ratio, *TDI* tissue Doppler imaging

possible link between NAFLD and the risk of new-onset heart failure [16]. In an elegant study involving non-diabetic adults who underwent magnetic resonance spectroscopy to quantify myocardial and intra-hepatic triglyceride contents and magnetic resonance imaging to assess LV function, visceral adipose tissue, epicardial and pericardial fat, Granér et al. [19] reported that only intra-hepatic triglyceride content and visceral adipose tissue were associated with significant changes in LV structure and function, whereas myocardial triglyceride content and epicardial and pericardial fat were not associated with LV diastolic dysfunction. A recent systematic review and meta-analysis of nine cross-sectional studies have confirmed that NAFLD (diagnosed on ultrasonography or histology) is associated with subclinical cardiac abnormalities [23].

Interestingly, as shown in Table 1, a strong association between NAFLD and LV diastolic dysfunction has also been documented in patients with type 2 diabetes [11, 12, 17, 20]. For instance, in a recent cross-sectional study involving 222 consecutive type 2 diabetic patients with no previous history of CHD, heart failure, moderate-to-severe heart valve diseases or hepatic disease, who underwent transthoracic echocardiography (with speckle-tracking strain analysis), Mantovani et al. [20] have reported that NAFLD on ultrasound was associated with an approximately threefold increased risk of mild and/or moderate LV diastolic dysfunction, even after adjusting for traditional CVD risk factors, diabetes-related variables, and relevant echocardiographic parameters. In that study, patients with NAFLD also had a larger LA volume compared with those without NAFLD [20]. Similarly, other investigators have reported a significant association between NAFLD and LA enlargement or impaired LA deformation, regardless of pre-existing diabetes [16, 18].

Consistently with this line of evidence, a strong association between NAFLD and LV abnormality/dysfunction has recently been reported in pediatric population. Indeed, as shown in Table 2, numerous case–control studies have reported that overweight or obese children with NAFLD have mildly increased LV mass and early features of LV dysfunction compared with their counterparts without NAFLD [24–28]. Notably, these subclinical cardiac abnormalities are independent of coexisting cardiometabolic risk factors.

Some smaller studies that used liver biopsies to diagnose NAFLD have also shown a significant, graded relationship between LV abnormality/dysfunction and the severity of NAFLD histology in both adults and children, suggesting that hepatic inflammation and fibrosis per se might be a risk factor in the development and progression of cardiovascular damage [18, 21, 28]. However, future prospective studies in patients with biopsy-confirmed NAFLD are needed to improve our understanding of this issue.

Studies on the Effect of NAFLD on the Right Atrium and Ventricle

Very limited information exists regarding the impact of NAFLD on right ventricular (RV) function and structure (Table 1). In a two-dimensional speckle-tracking echocardiography study examining the effect of NAFLD on RV function, Sunbul et al. [22] have reported that patients with biopsy-proven NAFLD had decreased RV function as assessed by measurement of global longitudinal strain compared to age- and sex-matched healthy controls. Moreover, NAFLD patients with hepatic fibrosis had lower RV function than those without hepatic fibrosis. Logistic regression analysis revealed that higher NAS score (using the NASH Clinical Research Network scoring system) independently predicted impaired RV function among these patients [22].

Therefore, according to the evidence from published studies, it is plausible to assume that NAFLD is strongly associated with subclinical myocardial remodeling and dysfunction that may be linked to an increased risk of developing heart failure over time. Regarding this, some large population-based studies have recently shown that mildly elevated serum liver enzymes in the absence of excessive alcohol consumption (i.e., a proxy of NAFLD) are long-term, independent predictors of new-onset heart failure [29–31]. However, additional prospective studies using more accurate methods for diagnosing NAFLD are needed to examine the association between NAFLD and the risk of heart failure.

Tables 1 and 2 summarize the relevant data from the principal case–control studies that have examined the effect of NAFLD on cardiac structure and function in both adults and children.

Epidemiological Evidence Linking NAFLD to Heart Valve Diseases

As summarized in Table 3, recent studies have suggested that NAFLD is independently associated with the presence of cardiac calcification in both the aortic and mitral valves in both non-diabetic and type 2 diabetic individuals [32–34].

Aortic-valve sclerosis (AVS), defined as focal or diffuse thickening and calcification of the aortic leaflets without restriction of leaflet motion, is very common in adults >65 years of age (occurring in up to 30 % of individuals over the age of 65) [35]. AVS shares multiple risk factors with CHD and predicts all-cause and CVD mortality, independently of traditional cardiovascular risk factors, in both patients with and without type 2 diabetes [35–37]. Similarly, mitral annulus calcification (MAC) is a common finding in the elderly (approximately 15 % of adults

Table 2 Principal studies examining the association between NAFLD and alterations in cardiac structure and function in children or adolescents (ordered by publication year)

Authors (year) [Ref.]	Study characteristics	Diagnosis of NAFLD	Cardiac measures	Adjustments considered	Main findings
Sert et al. (2013) [24]	Cross-sectional: 108 obese adolescents with ($n = 97$) and without NAFLD and 68 healthy controls	Ultrasound	LV structure and function (echocardiography with TDI)	None	Patients with NAFLD had increased LV mass index, increased LA diameter, impaired diastolic function, and altered global systolic and diastolic myocardial performance
Alp et al. (2013) [25]	Cross-sectional: 400 obese children (23.2 % with NAFLD) and 150 age- and sex-matched healthy controls	Ultrasound	LV structure and function (echocardiography with TDI)	BMI, waist-to-hip ratio, total fat mass, insulin resistance index	Children with NAFLD had increased LV mass and early impairment in systolic and diastolic function. Such alterations were worse in those with severe NAFLD
Singh et al. (2013) [26]	Cross-sectional: 14 lean adolescents, 15 obese adolescents with NAFLD and 15 obese adolescents without NAFLD matched for age, sex, and Tanner stage	^{1}H-MRS	LV structure and function (echocardiography with TDI and speckle-tracking strain analysis)	Age, Tanner stage, BMI, blood pressure, percent body fat, intra-abdominal adipose tissue volume, lipids, insulin sensitivity, and b cell function indices	LV global longitudinal systolic strain and early diastolic strain rates were lower in obese than in lean subjects, as well as in obese subjects with NAFLD than in those without NAFLD ($P < 0.05$). Hepatic fat content did not independently correlate with cardiac function parameters, but it was the only independent determinant of insulin resistance indices
Fintini et al. (2014) [27]	Cross-sectional: 50 children with NAFLD	Liver biopsy	LV structure and function (echocardiography with TDI)	Age, sex, BMI	In the whole sample: prevalence of about 35 % in LV hypertrophy, 14 % of concentric remodeling, and 16 % of left atrial dilatation. Children with NAFLD (NAS score <5) showed lower cardiac alterations compared to NASH patients (NAS score >5). After adjusting for age, sex, and BMI, a positive correlation was found only between LV mass and NAS score ($P < 0.001$)
Pacifico et al. (2014) [28]	Cross-sectional: 108 obese children (54 with and 54 without NAFLD) and 18 lean healthy subjects. Moreover, 41 of the children with NAFLD underwent liver biopsy	Magnetic resonance imaging	LV structure and function (echocardiography with TDI)	Age, sex, BMI, pubertal status, blood pressure, insulin resistance, triglycerides, HDL cholesterol	Patients with NAFLD had features of LVDD. Among children with biopsy-proven NAFLD, those with definite NASH had lower e' velocity and higher E/e' than those without NASH. In multiple logistic regression analysis, NAFLD was the only statistically significant variable associated with increased E/e' (adjusted OR 3.13, 95 % CI 1.12–8.72, $P < 0.05$)

BMI body mass index, *LV* left ventricular, *LVDD* left ventricular diastolic dysfunction, *MetS* metabolic syndrome, *MRS* magnetic resonance spectroscopy, *TDI* tissue Doppler imaging

Table 3 Principal studies examining the association between NAFLD and the risk of heart valve disease or cardiac arrhythmias

Authors (years) [Ref.]	Study characteristics	Diagnosis of NAFLD	Cardiac measures	Adjustments considered	Main findings
Heart valve calcification					
Markus et al. (2013) [32]	Community-based study of 2022 middle-aged individuals from the SHIP study (39.7 % with NAFLD)	Ultrasound	Prevalence of AVS (echocardiography)	Age, sex, waist-to-height ratio, smoking, alcohol, physical activity, systolic blood pressure, total/HDL cholesterol ratio, hemoglobin A1c, medication use, eGFR, C-reactive protein, ferritin, white blood cells	NAFLD was independently associated with an increased prevalence of AVS (adjusted OR, 1.32, 95 % CI 1.04–1.66, $P < 0.05$)
Bonapace et al. (2014) [33]	Cross-sectional: 180 consecutive type 2 diabetic outpatients without history of CHD and hepatic diseases (66.7 % with NAFLD)	Ultrasound	Prevalence of AVS (echocardiography with TDI)	Age, sex, diabetes duration, BMI, hypertension, eGFR, dyslipidemia, hemoglobin A1c	NAFLD was independently associated with an increased prevalence of AVS (adjusted OR 3.04, 95 % CI 1.3–7.3, $P = 0.01$)
Mantovani et al. (2015) [34]	Cross-sectional: 247 consecutive type 2 diabetic outpatients without history of heart failure, moderate-severe valvular diseases, and hepatic diseases (70.8 % with NAFLD)	Ultrasound	Prevalence of AVS or MAC (echocardiography with TDI)	Age, sex, waist circumference, smoking, blood pressure, hemoglobin A1c, lipids, eGFR, medication use, prior CHD, echocardiographic variables (E/e' ratio, LV mass or LA volume)	Prevalence of NAFLD was higher in patients with AVS and MAC compared with in those with either one valve affected (AVS or MAC) or no heart valve calcification (86.1 vs. 83.1 vs. 60.4 %, respectively; $P < 0.001$). NAFLD was significantly associated with an increased risk of prevalent AVS and/or MAC (adjusted OR 2.70, 95 % CI 1.2–7.4, $P < 0.01$)
Cardiac arrhythmias					
Sinner et al. (2013) [41]	Community-based cohort study of 3744 adult participants free of clinical HF from the Framingham Heart Study Original and Offspring cohorts, free of clinical heart failure. Mean follow-up: 10 years	Liver enzymes	Incidence of AF (ECG)	Age, sex, BMI, blood pressure, anti-hypertensive treatment, smoking, diabetes, VHD, electrocardiographic PR interval, alcohol consumption	Mildly elevated aminotransferase levels were independently associated with a higher risk of incident AF [hazard ratio (HR) expressed per standard deviation of natural logarithmically transformed biomarker: HR 1.19, 95 % CI 1.07–1.32 for ALT; HR 1.12, 95 % CI 1.01–1.24 for AST, $P < 0.005$]
Alonso et al. (2014) [42]	Community-based cohort study of 9333 individuals free of AF, participating in the atherosclerosis risk in communities study. Mean follow-up: 12 years	Liver enzymes	Incidence of AF (ECG)	Age, sex, race, study site, BMI, education level, diabetes status, alcohol intake, smoking, systolic blood pressure, medication use, prior CHD, atrial natriuretic peptide	Mildly elevated serum liver enzymes, mainly GGT, were independently associated with an increased risk of incident AF
Targher et al. (2013) [43]	Hospital-based sample of 702 type 2 diabetic patients without history of hepatic diseases and excessive alcohol intake (73 % with NAFLD)	Ultrasound	Prevalence of persistent/permanent AF (ECG)	Age, sex, systolic blood pressure, HbA1c, eGFR, total cholesterol, electrocardiographic LV hypertrophy, COPD and prior history of HF, VHD, hyperthyroidism	Patients with NAFLD had higher prevalence of persistent/permanent AF than those without NAFLD (88 vs. 71 %, $P < 0.001$). In multivariate analysis, NAFLD was independently associated with an increased risk of prevalent AF (adjusted OR 5.88, 95 % CI 2.7–12.7, $P < 0.001$)

Table 3 continued

Authors (years) [Ref.]	Study characteristics	Diagnosis of NAFLD	Cardiac measures	Adjustments considered	Main findings
Targher et al. (2013) [44]	Longitudinal cohort: 400 randomly selected type 2 diabetic outpatients without AF, moderate-to-severe VHD, and liver diseases at baseline (70 % with NAFLD). Mean follow-up: 10 years	Ultrasound	Incidence of AF (ECG)	Age, sex, BMI, electrocardiographic LV hypertrophy, PR interval, systolic blood pressure, anti-hypertensive treatment, prior history of HF	Patients with NAFLD had a higher incidence of AF than those without NAFLD. In multivariate regression analysis, NAFLD was independently associated with an increased risk of incident AF (adjusted OR 4.96, 95 % CI 1.4–17, $P = 0.01$)
Käräjämäki et al. (2015) [45]	Cohort of 958 middle-aged hypertensive subjects and age- and sex-matched controls (without excessive alcohol consumption) participating in the OPERA study (26 % with NAFLD). Mean follow-up: 16.3 years	Ultrasound	Incidence of AF (ECG)	Age, sex, diabetes status, CHD, BMI, waist circumference, alcohol consumption, smoking, serum alanine aminotransferase, systolic blood pressure, insulin resistance, plasma atrial natriuretic peptide and C-reactive protein, LV mass index, LA diameter	Patients with NAFLD had a higher incidence of AF than those without NAFLD. In multivariate regression analysis, NAFLD was independently associated with an increased risk of incident AF (adjusted hazard ratio 1.88, 95 % CI 1.03–3.5, $P < 0.05$)
Targher et al. (2014) [49]	Cross-sectional: 400 randomly selected type 2 diabetic outpatients without pre-existing AF, moderate-to-severe VHD, hepatic diseases, excessive alcohol consumption (70 % with NAFLD)	Ultrasound	Prevalence of QTc interval ≥416 ms (ECG)	Age, sex, diabetes duration, peripheral artery disease, sensory neuropathy, BMI, alcohol, smoking, hemoglobin A1c, electrocardiographic LV hypertrophy, CHD, kidney dysfunction	Mean QTc interval duration and the proportion of patients with prolonged QTc interval increased steadily with the severity of NAFLD. NAFLD was independently associated with prolonged QTc interval (adjusted OR 2.26, 95 % CI 1.4–3.7, $P < 0.001$)
Hung et al. (2015) [50]	Community-based study of 31,116 adult participants (41.5 % with NAFLD)	Ultrasound	Prevalence of prolonged QTc interval (ECG)	Age, sex, diabetes, hypertension, lipids, AST, BMI, LV hypertrophy, hypokalemia, eGFR, C-reactive protein, smoking, presence of the MetS	QTc intervals increased sharply with the severity of NAFLD. Mild, moderate, and severe NAFLD were independently associated with an increased risk of prolonged QTc interval

AF atrial fibrillation, *AVS* aortic-valve sclerosis, *BMI* body mass index, *CHD* coronary heart disease, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *ECG* electrocardiogram, *eGFR* estimated glomerular filtration rate, *GGT* gamma-glutamyltransferase, *HF* heart failure, *LV* left ventricular, *MAC* mitral annulus calcification, *MetS* metabolic syndrome, *OR* odds ratio, *TDI* tissue Doppler imaging, *VHD* valvular heart diseases

>65 years have MAC on echocardiography) and is also associated with adverse CVD outcomes [37, 38].

In a large community-based study including 2212 German men and women (aged 45–81 years), Markus et al. [32] have shown, for the first time, that NAFLD diagnosed on ultrasound was associated with an increased prevalence of AVS independent of multiple cardiometabolic risk factors. Bonapace et al. [33] have found that NAFLD and AVS were strictly interrelated after adjustment for major confounding factors in a sample of 180 consecutive type 2 diabetic patients. Moreover, Mantovani et al. [34] have recently conducted a cross-sectional study of 247 consecutive type 2 diabetic patients with no previous history of heart failure, moderate-to-severe heart valve diseases, or known hepatic diseases. In this study, 26.3 % of patients had isolated AVS or isolated MAC, and both valves were affected in 17.4 % of patients. NAFLD was associated with a 3.5-fold increased rate of AVS, MAC, or both. Adjustments for age, sex, waist circumference, smoking, blood pressure, hemoglobin A1c, lipids, kidney function parameters, medication use, CHD, and echocardiographic parameters did not appreciably weaken this association. Notably, when the relationships between NAFLD and AVS or between NAFLD and MAC were analyzed separately, NAFLD remained associated with a 2.5-fold to 3-fold higher rate of either AVS or MAC after adjustment for potential confounding variables.

Although further studies are needed, these findings collectively suggest that valvular calcification of the aortic and mitral valves might represent a further link underpinning the increased risk of CVD events observed among patients with NAFLD.

Epidemiological Evidence Linking NAFLD to Cardiac Arrhythmias

NAFLD and Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia observed in clinical practice, and its prevalence is expected to substantially increase over the next few decades because of an aging population and improvements in cardiovascular treatments [39].

Although the first description of the concurrence of peripheral artery disease and AF in a patient with type 2 diabetes and fatty liver was reported in the early 1950s [40], some population-based cohort studies have recently examined the impact of NAFLD on the risk of incident AF [41, 42]. The Framingham Heart Study investigators have shown that impaired liver function, as assessed by elevation of serum transaminases, was independently associated with an increased risk of incident AF over 10 years of follow-up among 3744 white adults who were free of AF at baseline [41]. Similar findings have been reported in another population-based study, which involved more than 9000 adults followed up for a mean period of 12 years [42].

Recently, in two subsequent observational studies, Targher et al. [43] have reported that patients with type 2 diabetes and NAFLD on ultrasound had an increased prevalence of permanent or persistent AF and were also more likely to develop incident AF over a 10-year follow-up period compared with those without NAFLD [44]. Interestingly, the association between NAFLD and the risk of AF in these two studies remained significant even after adjustment for multiple AF risk factors [43, 44].

Finally, in a prospective study involving approximately 1000 middle-aged Finnish individuals, who were followed up for a mean period of 16.3 years, Käräjämäki et al. [45] have reported that NAFLD on ultrasound was associated with an approximately twofold increased risk of incident AF, independently of age, sex, body mass index, waist circumference, alcohol consumption, smoking, blood pressure, diabetes status, serum alanine aminotransferase (ALT) levels, insulin resistance, atrial natriuretic peptide levels, C-reactive protein levels, and echocardiographic parameters.

To date, detailed information regarding the underlying mechanisms of increased AF risk among patients with NAFLD is lacking. Although impaired atrial conduction plays a role in the pathophysiology of AF, there is only one small study to date that has investigated atrial conduction properties in NAFLD. In this pilot case–control study, NAFLD patients without clinical diagnosis of hypertension, diabetes, or cardiac diseases had longer interatrial and intra-atrial electromechanical delay intervals (by tissue Doppler echocardiography) and higher P-wave dispersion (by a standard 12-lead electrocardiogram) compared with healthy controls [46].

NAFLD and Ventricular Arrhythmias

To date, there is a lack of published data regarding the association between NAFLD and the risk of ventricular arrhythmias, which are established risk factors for sudden cardiac death. Heart rate variability and heart rate-corrected QT (QTc) interval prolongation on standard electrocardiogram have been proposed as useful tools for identifying patients at risk of sudden cardiac death. For instance, it is known that QTc interval prolongation is a powerful risk factor for ventricular arrhythmias, and is also associated with increased cardiac mortality in both patients with and without diabetes [47, 48].

In a recent study involving 400 outpatients with type 2 diabetes without a documented history of AF, moderate-to-severe heart valve diseases, hepatic disease, or excessive

alcohol consumption [49], the presence and severity of ultrasonographic NAFLD were found to be associated with a 2.2-fold increased rate of prolonged QTc interval duration, independently of age, sex, hypertension, diabetes-related variables, and other comorbid conditions. Of note, the exclusion of those with established CHD from the analysis did not appreciably weaken this association [49].

More recently, Hung et al. [50] have examined whether the association between NAFLD and QTc interval prolongation was also observed in the general population. The authors found that the severity of NAFLD on ultrasound was associated with a higher risk of QTc interval prolongation, independently of many cardiometabolic risk factors. Notably, such association was consistent in all subgroups of patients examined.

Collectively, although the arrhythmogenic potential of NAFLD requires further confirmation in future follow-up studies, we believe that this field of research is promising, and that the pathophysiological pathways that involve the contribution of NAFLD to chronic inflammation, hypercoagulation, and insulin resistance might provide potential therapeutic targets for the prevention and treatment of myocardial remodeling and electrophysiological abnormalities of the myocardium in patients with NAFLD [43, 44, 51].

Table 3 summarizes the principal studies that have examined the association between NAFLD and the risk of cardiac arrhythmias (mainly atrial fibrillation).

Epidemiological Evidence Linking NAFLD to Coronary Heart Disease

The negative impact of NAFLD on the risk of CHD/CVD has generated intense scientific interest over the past decade [2, 4–7]. This risk deserves particular attention because it has important clinical implications for screening and surveillance strategies for the growing number of patients with NAFLD. In addition, the increased CVD risk in patients with NAFLD is the aspect of the condition that is most amenable to medical management that could improve clinical outcomes of these patients.

Prevalence of Subclinical CHD

Several cross-sectional studies have shown that NAFLD is associated with an increased coronary artery calcium (CAC) score, which is a marker of early atherosclerosis and a powerful predictor of CVD events [7, 52]. NAFLD has been consistently associated with increasing CAC scores beyond traditional risk factors in Asians [53–55], African-Americans [56], and American volunteers [57]. A recent meta-analysis of 27 cross-sectional studies has reported a strong association of NAFLD not only with CAC score but also with other markers of subclinical atherosclerosis, such as increased carotid intima-media thickness, reduced flow-mediated vasodilation, and increased arterial stiffness. All of these associations are independent of traditional cardiovascular risk factors and MetS features across a wide range of patient populations [58].

Moreover, some studies have also shown that coronary flow reserve, an index of coronary microcirculation, is reduced in patients with NAFLD, independently of multiple potential confounders [59–61].

Prevalence of Clinical CHD

Two Italian studies of type 2 and type 1 diabetic outpatients [62, 63] as well as a community-based study from Taiwan [64] have found that NAFLD on ultrasound was associated with an increased prevalence of clinically manifest CHD, independently of multiple CVD risk factors. Similarly, the Framingham Heart Study investigators reported a significant association of NAFLD with subclinical CVD outcomes (CAC and abdominal artery calcium scores), independent of many metabolic diseases/traits, with a trend toward association between NAFLD and prevalent clinical CVD [65]. Conversely, ultrasonography-diagnosed NAFLD was not found to be associated with prevalent CHD among diabetic patients in a multiracial Asian hospital clinic population [66].

Many cross-sectional studies have shown that patients with NAFLD have an increased rate of CHD at coronary angiography, independently of traditional cardiovascular risk factors [67–71]. The existence of an independent association between NAFLD and increased CHD prevalence has further been confirmed by a recent meta-analysis [72]. Moreover, evidence has also supported a strong, graded relationship between NAFLD and the angiographic severity of CHD [70, 73–75]. Worryingly, NAFLD has also been independently associated with the presence of high-risk coronary atherosclerotic plaques [76–78], impaired myocardial perfusion, and adverse outcomes following primary percutaneous coronary interventions [79], which can be attributed to an increased risk of in-stent restenosis after bare metal stenting in native coronary arteries [80].

Incidence of Clinical CHD

In this review, we have not discussed the large number of population-based cohort studies that used elevated serum liver enzymes to diagnose NAFLD. These studies have consistently shown a strong association between mildly elevated serum liver enzyme levels (mainly serum gamma-glutamyltransferase [GGT]) and the subsequent risk of CVD events and mortality in both men and women [7, 81–83].

In patients with NAFLD diagnosed with imaging techniques (Table 4), several prospective studies have reported that NAFLD is associated with an increased risk of fatal and non-fatal CVD events, independently of multiple cardiometabolic risk factors, both in patients with and without type 2 diabetes [84–97]. A study addressing CHD as a prespecified outcome has also shown that patients with NAFLD have a higher 10-year risk of CHD as calculated by the Framingham risk score than the matched control population, thus proving the clinical utility of the Framingham risk score in this group of patients [91].

Moreover, the severity of NAFLD (as diagnosed by imaging) appears to be associated with higher risk of adverse CVD outcomes. A prospective population-based Finnish study with a relatively long follow-up period has reported that severe ultrasonographic NAFLD was independently associated with an increased risk of fatal and non-fatal CVD events [94]. A large retrospective study has also found that moderate-to-severe NAFLD diagnosed on computed tomography was associated with an increased risk of CVD events over a 7-year follow-up period; however, this association disappeared after adjustment for coexisting CVD risk factors [95].

Other recent prospective studies examining the association between NAFLD and incident CVD events have provided conflicting results. Data from the Third National Health and Examination Survey (NHANES-III) database, whose significance is limited by the inclusion of individuals with mild hepatic steatosis within the control arm, have shown that NAFLD on ultrasound did not significantly predict the risk of all-cause and cause-specific (CVD, liver, and cancer) mortality in US adults during a mean follow-up period of 14 years [88, 89]. Interestingly, the latest analysis of the same NHANES-III cohort found that patients with NAFLD and advanced hepatic fibrosis (as estimated by NAFLD fibrosis score and other noninvasive score systems) as well as those with NAFLD and MetS were indeed at increased risk of all-cause and CVD mortality [92, 93]. Surprisingly, a recent retrospective cohort study has reported that NAFLD on ultrasound was significantly associated with a 5-year lower risk of adverse CVD outcomes in a cohort of 612 patients with clinical indications for a coronary angiogram [96]. However, it is plausible to assume that the modality of cardiac interventions (percutaneous coronary intervention or coronary artery bypass) and changes in lipid-lowering drugs or other potentially cardioprotective drugs over the follow-up period may have markedly modified the clinical outcome of patients with NAFLD (most of whom had a greater severity of CHD and a worse cardiovascular risk profile at the baseline) [98].

In patients with NAFLD diagnosed by histology (Table 4), a number of retrospective natural history studies with reasonably long follow-up have clearly shown that all-cause, CVD-related, and liver-related mortality is higher in patients with NAFLD than in the matched control population [99–106]. These studies have also shown that the severity of hepatic fibrosis is the main determinant of all-cause and cause-specific mortality, and that CVD is the leading cause of mortality among these patients [101–106]. Interestingly, although two of these studies have also shown that patients with NASH, but not those with simple steatosis, were at higher risk of all-cause and CVD mortality compared with the reference population [102, 104], this finding was not confirmed by a recent meta-analysis that concluded that patients with NAFLD had a higher risk of major CVD events than the matched control population, but that the severity of NAFLD histology did not further increase CVD mortality [81]. However, further prospective studies in patients with biopsy-confirmed NAFLD are needed to improve understanding of this issue.

Together, the findings from all of these retrospective and prospective studies support the assertion that NAFLD, regardless of the diagnostic technique, is significantly associated with increased CHD/CVD mortality and morbidity in patients either with or without type 2 diabetes. Some uncertainty, however, remains as to whether NAFLD is associated with an increased risk of CVD outcomes beyond the known risk factors. Additional large-scale prospective studies of a more extensive panel of known CVD risk factors are needed to draw firm conclusions about any independent hepatic contribution to the increased CVD risk observed among patients with NAFLD.

Table 4 summarizes the principal prospective and retrospective studies that have examined the association between NAFLD (diagnosed either by imaging or by histology) and the risk of CHD/CVD events and mortality.

Putative Biological Mechanisms Linking NAFLD with Cardiovascular and Cardiac Complications

The pathophysiological mechanisms linking NAFLD with vascular, structural, and arrhythmic cardiac complications are not completely understood. NAFLD is associated with multiple cardiometabolic risk abnormalities, including abdominal obesity, ectopic fat accumulation, dysglycemia, insulin resistance, atherogenic dyslipidemia, hypertension, and altered hormonal and cytokine profiles, which collectively result in the development of a pro-inflammatory, pro-atherogenic, and pro-thrombotic milieu [2, 4, 6, 7, 107–110]. Although further research is needed, recent data also suggest that specific genetic traits (e.g., patatin-like phospholipase domain-containing protein 3 [PNPLA3] and transmembrane six superfamily member 2 [TM6SF2] gene variants) may predispose individuals to hepatic as opposed

Table 4 Principal prospective and retrospective studies examining the association between NAFLD and increased risk of CVD events and mortality (ordered by both methodology used for diagnosis of NAFLD and publication year)

Authors (year) [Ref.]	Study characteristics	Years of follow-up	Diagnosis of NAFLD	Study outcomes	Main findings
Jepsen et al. (2003) [84]	Population-based cohort, $n = 1804$ inpatients with NAFLD (Danish national registry)	6.5	Ultrasound	All-cause and cause-specific mortality	Increased rates of all-cause, CVD and liver-related mortality in NAFLD, independently of sex, diabetes and cirrhosis at baseline
Targher et al. (2007) [85]	Outpatient cohort, $n = 2103$ type 2 diabetic patients (Valpolicella Heart Diabetes Study)	6.5	Ultrasound	Fatal and non-fatal CVD (myocardial infarction, ischemic stroke, coronary revascularization procedures, CVD mortality)	Increased rates of fatal and non-fatal CVD events in NAFLD, independently of age, sex, smoking, diabetes duration, hemoglobin A1c, LDL-cholesterol, medication use, and presence of the MetS
Hamaguchi et al. (2007) [86]	Community-based cohort, $n = 1637$ healthy Japanese	5	Ultrasound	Non-fatal CVD events	Increased rates of non-fatal CVD events in NAFLD, independently of age, sex, BMI, alcohol intake, smoking, LDL-cholesterol, MetS features
Haring et al. (2009) [87]	Population-based cohort, $n = 4160$ German subjects (Study of Health in Pomerania)	7.2	Ultrasound and liver enzymes	All-cause and CVD mortality	NAFLD was associated with increased all-cause and CVD mortality in men, independently of age, sex, waist circumference, alcohol intake, physical exercise, civil status, equalized income, functional comorbidity index, blood pressure, diabetes status
Lazo et al. (2011) [88]	Population-based cohort, $n = 11371$ US adults (NHANES-III)	14.5	Ultrasound	All-cause and cause-specific mortality	NAFLD was not associated with increased all-cause and cause-specific (CVD, cancer, and liver) mortality
Stepanova et al. (2012) [89]	Population-based cohort, $n = 11613$ US adults (NHANES-III)	14.5	Ultrasound	All-cause and cause-specific mortality	NAFLD was independently associated with increased CVD prevalence, but not with increased risk of all-cause and CVD mortality
Zhou et al. (2012) [90]	Community-based cohort, $n = 3543$ Chinese individuals	4	Ultrasound	All-cause and CVD mortality	Increased rates of all-cause and CVD mortality in NAFLD
Treeprasertsuk et al. (2012) [91]	Retrospective community-based cohort, $n = 309$ US patients with NAFLD	11.5	Ultrasound and computed tomography	Fatal and non-fatal IHD	NAFLD patients had a higher 10-year CHD risk by Framingham risk score (FRS) than the general population of the same age and sex. Almost identical number of FRS-predicted and actual new CHD events
Younossi et al. (2013) [92]	Population-based cohort, $n = 6709$ US adults (NHANES-III)	14.2	Ultrasound	All-cause and cause-specific mortality	NAFLD was independently associated with increased all-cause, CVD-related, and liver-related mortality only in the subgroup of NAFLD patients with the MetS

Table 4 continued

Authors (year) [Ref.]	Study characteristics	Years of follow-up	Diagnosis of NAFLD	Study outcomes	Main findings
Kim et al. (2013) [93]	Population-based cohort, $n = 11154$ (NHANES-III)	14.5	Ultrasound	All-cause and cause-specific mortality	NAFLD was not associated with increased all-cause mortality. However, NAFLD with advanced hepatic fibrosis (defined by NAFLD fibrosis score or other noninvasive clinical scores) was independently associated with increased all-cause and CVD mortality
Pisto et al. (2014) [94]	Population-based cohort of 988 middle-aged Finnish participants (OPERA study)	19	Ultrasound	Fatal and non-fatal CVD	Severe NAFLD predicted the risk of CVD events after adjustment for age, sex, study group, smoking, alcohol intake, LDL-cholesterol, BMI, systolic blood pressure. Statistical significance disappeared after additional adjustment for insulin resistance
Pickhardt et al. (2014) [95]	Retrospective cohort study of consecutive adults undergoing abdominal computed tomography: 282 NAFLD and 768 control patients after exclusions	7	Computed tomography	CVD events (myocardial infarction, stroke, transient ischemic attacks, or coronary bypass or stent)	Moderate-to-severe NAFLD was not associated with CVD events after adjustment for BMI and diabetes status
Wong et al. (2015) [96]	612 consecutive patients undergoing a coronary angiogram (58.2 % NAFLD)	5	Ultrasound	Fatal and non-fatal CVD, heart failure, or secondary interventions	NAFLD was associated with significant CHD needing percutaneous coronary interventions at baseline, but NAFLD was associated with a significantly lower risk of cardiovascular outcomes and mortality
Moon et al. (2015) [97]	Retrospective cohort of 815 consecutive asymptomatic participants who underwent a health screening program	4.2	Ultrasound and positron emission tomography/computed tomography with F-18 fluoro-2-deoxyglucose (FDG)	Non-fatal CVD events (myocardial infarction, angina, coronary revascularization, and stroke)	NAFLD with high-hepatic FDG uptake was the only independent predictor for CVD events. Subgroup analysis performed in the NAFLD group showed that high-hepatic FDG uptake was an independent predictor of CVD events
Matteoni et al. (1999) [99]	Patient-based retrospective cohort, $n = 132$ patients with NAFLD	18	Histology	All-cause and cause-specific mortality	Increasing all-cause and liver-related mortality with the severity of NAFLD histology. CVD mortality was not significantly different across the histologic subtypes
Dam-Larsen et al. (2004) [100]	Patient-based retrospective cohort (Danish national registry of patients), $n = 109$ subjects with nonalcoholic simple steatosis	16.7	Histology	All-cause and cause-specific mortality	All-cause and cause-specific mortality did not significantly differ between patients with nonalcoholic simple steatosis and the matched general population

Table 4 continued

Authors (year) [Ref.]	Study characteristics	Years of follow-up	Diagnosis of NAFLD	Study outcomes	Main findings
Adams et al. (2005) [101]	Community-based retrospective cohort, $n = 420$ patients with NAFLD	7.6	Ultrasound/computed tomography and histology	All-cause and cause-specific mortality	Higher rates of all-cause, CVD and liver-related mortality in patients with NAFLD (especially in those with NASH or cirrhosis) than in the general population with CHD being the second cause of mortality
Ekstedt et al. (2006) [102]	Patient-based retrospective cohort, $n = 129$ consecutive patients with NAFLD and elevated serum liver enzymes (55 % NASH)	13.7	Histology	All-cause and cause-specific mortality	Increased rates of CVD and liver-related mortality in patients with NASH, but not in those with simple steatosis, compared with the reference population
Rafiq et al. (2009) [103]	Patient-based retrospective cohort, $n = 173$ patients with NAFLD (41.6 % NASH)	13	Histology	All-cause and cause-specific mortality	CHD was the first cause of mortality in this cohort. Liver-related mortality, but not all-cause or CVD mortality, was higher in NASH versus non-NASH. No comparison was provided with the general population
Söderberg et al. (2010) [104]	Patient-based retrospective cohort, $n = 118$ patients with NAFLD and elevated serum liver enzymes (43 % NASH)	24	Histology	All-cause and cause-specific mortality	Increased rates of all-cause, CVD and liver-related mortality in patients with NASH, but not in those with simple steatosis, compared with the matched general population
Ekstedt et al. (2015) [105]	Patient-based retrospective cohort, $n = 229$ patients with NAFLD and elevated serum liver enzymes (49 % NASH)	26.4	Histology	All-cause and cause-specific mortality	Increased rates of all-cause, CVD and liver-related mortality in patients with NAFLD. NAFLD activity score was not able to predict all-cause mortality, whereas fibrosis stage predicted all-cause, CVD and liver-related mortality
Angulo et al. (2015) [106]	Patient-based retrospective multinational cohort, $n = 619$ patients with NAFLD (28.9 % definitive NASH)	12.6	Histology	All-cause mortality and liver-related events	Increased rates of all-cause mortality and liver-related events in patients with NAFLD. CVD was the leading cause of mortality (38.3 %). Fibrosis stage, but no other histologic features of NASH, was independently associated with all-cause mortality and liver-related events. Use of statins was also independently associated with better clinical outcomes

BMI body mass index, *MetS* metabolic syndrome, *NASH* nonalcoholic steatohepatitis, *CVD* cardiovascular disease

to extra-hepatic complications in NAFLD and that NAFLD may interact with the MetS in the development of atherosclerosis in both diabetic and non-diabetic individuals [2, 111–114].

A consistent and ever-growing line of research has led to the idea that the liver, the intestine, and the heart constitute a closely interconnected network that cooperates in the regulation of lipid metabolism. The physiological orchestration of this network may play a role in maintaining the health of these three organs through complex and intertwined interactions between microRNAs, fatty acids, bile acids, gut microbiota, and hormones; conversely, the perturbation of this collaborative network leads to systemic chronic inflammation, dyslipidemia, and enhanced oxidative stress [115]. Changes in gut microbiota associated with a variety of other pathophysiological factors, including aging, lifestyle habits, medication use, and comorbidities [115], may also modulate the risk of developing the MetS [116–119], NAFLD/NASH [120–123], and CHD [124–127].

The link between intestinal dysbiosis, expanded adipose tissue, and NAFLD, and the signals passing between these three organs are schematically shown in Fig. 2. This figure also illustrates the putative role of the liver in NAFLD, which can subsequently affect the heart and the vascular system and thus predispose to CHD and other cardiac complications.

The putative biological mechanisms linking NAFLD, expanded/inflamed adipose tissue, and intestinal dysbiosis with cardiovascular and cardiac complications are complex. Both expanded/inflamed adipose tissue and altered intestinal microbiota are potentially able to influence the development of, and progression of NAFLD, via production of non-esterified fatty acids, pro-inflammatory cytokines (e.g., tumor necrosis factor alpha and interleukin-6), short-chain fatty acids (e.g., butyrate, propionate, and acetate), incretins (e.g., glucagon-like peptide 1), thrombospondin-1, and decreased production of adiponectin levels. As NAFLD develops and liver fat and inflammation progress (NASH), a variety of changes occur in liver structure and function, resulting in the production of atherogenic lipids and lipoproteins, pro-inflammatory factors, and vasoactive and thrombogenic molecules. These NAFLD-induced changes have the potential to adversely influence the risk of CHD, cardiac, and arrhythmic complications. Hepatic production of lipids, atherogenic lipoproteins, pro-inflammatory cytokines, and vasoactive and thrombogenic molecules all may increase risk of CHD and myocardial infarction. Myocardial steatosis, lipotoxicity, enhanced oxidative stress, impaired energy homeostasis, and increased epicardial/pericardial fat may exert local adverse effects that result in functional and structural derangements of the myocardium. With myocardial remodeling, there is also an increased risk of heart failure and cardiac arrhythmias.

By preventing the cell injury due to impaired energetic metabolism, over-production of reactive oxygen species, mitochondrial DNA mutations, and deregulated apoptotic and autophagic pathways, the integrity of mitochondria is a key requirement for the physiological functions of the liver, heart, and vessel cells. Several lines of evidence now support a role for mitochondrial dysfunction as a pathogenic feature shared by CHD and NAFLD/NASH, which may both be regarded as maladaptive processes resulting from a "subcellular organelle stress" [128–134]. Angiotensin II, a mediator of cardiohepatic cell damage and a potential target of treatment [107], may also be responsible for mitochondrial dysfunction, which occurs through a protein kinase C-dependent pathway endothelial cell NADPH oxidase activation and an increased peroxynitrite formation. Mitochondrial dysfunction, resulting from increased angiotensin II activity, may adversely affect endothelial singlet oxygen and nitric oxide production, which may cause circulatory endothelial dysfunction [135].

Presently, it is unclear whether individual molecular changes play specific roles in the pathophysiology of NAFLD-related cardiac abnormalities or whether such cardiac abnormalities may collectively result from the entire spectrum of hormonal, metabolic, and cytokine derangements observed among patients with NAFLD. For example, hypertension and atherogenic dyslipidemia are two ideal candidates that may account for the accelerated atherogenesis observed in NAFLD. Lonardo et al. [136] have reported that NAFLD may accelerate arterial aging by approximately 10 years. Among the individual MetS components, hypertension appears to be the component least associated with NAFLD [3]; however, a recent meta-analysis based on paired liver biopsies in NAFLD patients taken at least 1-year apart has found that hypertension strongly predicts the development of hepatic fibrosis both in patients with simple steatosis and in those with NASH at baseline [137]. As previously noted, although some studies have suggested that NASH is a stronger risk factor for CVD than simple steatosis [102, 104], the current evidence is insufficient to support this conclusion [81, 82]. In contrast, the idea that "the more the (liver) fat the higher the CVD risk" is gaining ever-growing interest owing to the availability of imaging methods enabling an accurate and reproducible quantification of the liver fat content [138]. Non-high-density lipoprotein cholesterol (non-HDL) levels play an important role in the link between NAFLD and CHD risk. Non-HDL hypercholesterolemia is very common in NAFLD and tends to be specifically associated with NASH, suggesting that individuals with this lipid abnormality should undergo liver biopsy for staging of their liver

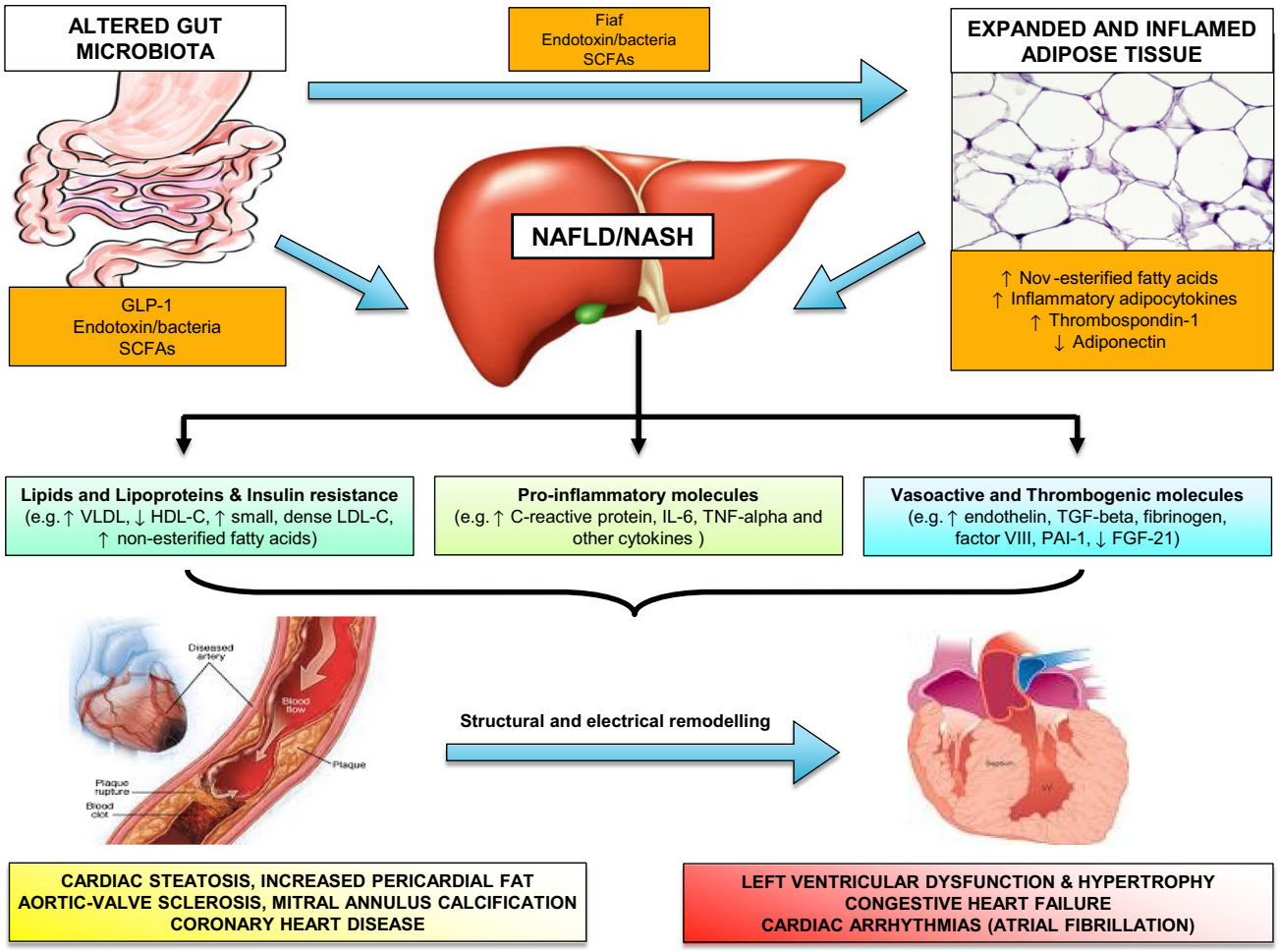

Fig. 2 Putative biological mechanisms linking NAFLD, expanded, and inflamed adipose tissue and altered gut microbiota with cardiovascular and cardiac complications. *Fiaf* fasting-induced adipose factor (also referred to as angiopoietin-like protein 4), *HDL-C* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein, *PAI-1* plasminogen activator inhibitor-1, *TGF* transforming growth factor

disease [3]. Consistently with this link, growing evidence has suggested that statin treatment, in addition to reducing CVD events and mortality, might also exert beneficial effects on either NAFLD histology or some of its hepatic complications, such as advanced fibrosis, portal hypertension, and hepatocellular carcinoma [107, 139–143]. Experimental studies have suggested that the lysosomal cholesterol accumulation may contribute to the progression toward those states of "sterile" inflammation [144], which are closely related to CHD and NASH, and may, therefore, represent potential targets for treatment [145].

Increased epicardial fat accumulation is an emerging cardiovascular risk factor that is closely associated with abdominal obesity and advanced hepatic fibrosis [21, 146] and might be, at least in part, implicated in the development of CVD outcomes among patients with NAFLD. Interestingly, increased epicardial and pericardial fat is associated with increased rates of AF [147] and CHD [148, 149], owing to their anatomical location very close to the heart to which they can locally deliver pro-inflammatory and pro-coagulant factors [150, 151].

How could NAFLD mechanistically predispose individuals to the development and progression of heart valve calcification? Dyslipidemia does not seem to play a major role in the development and progression of AVS, and treatment with statins has not been shown to be effective in preventing the progression of AVS [152–155]. In contrast, abdominal overweight/obesity and hypertension are two risk factors that are shared by AVS and NAFLD [152, 155–157]. Moreover, fetuin-A, a liver-secreted protein, inhibits heart valve calcification [158] and is inversely associated with hepatic and vascular fibrosis in NAFLD [159], thus suggesting that the more severe forms of NAFLD might, at least in part, contribute to the development and progression of AVS or MAC via decreased fetuin-A levels.

It is well established that LV hypertrophy in hypertensive patients is associated with an increased risk of supraventricular/atrial and ventricular arrhythmias [160].

Interestingly, LV hypertrophy has been found to be associated with NAFLD, independently of hypertension and other established risk factors, in both type 2 diabetic patients [12] and non-diabetic adults with NAFLD [13]. Moreover, certain evidence based on surrogate indices of NAFLD severity has also suggested that advanced NAFLD is associated with (mild) LV hypertrophy in both adults and children [27, 161]. The concurrent arrhythmogenic role of cardiac autonomic dysfunction, a common finding in NAFLD patients [162, 163], is also potentially treatable by improving body composition and body fat distribution [164] and by increasing levels of resistance exercise [165].

In summary, derangements spanning subtle subcellular changes through systemic hemodynamic, metabolic, hemostatic, hormonal, and cytokine abnormalities, as well as deregulation in multiple organ systems, may contribute to the development and progression of CHD/cardiac diseases in patients with NAFLD. A better understanding of the multiple pathophysiological and molecular pathways that link NAFLD to CHD/cardiac diseases might aid in the discovery of novel therapeutic treatments in the near future.

Conclusions

In the past decade, compelling evidence has substantiated a strong link between NAFLD and the risk of CHD and other cardiac (functional, structural, and arrhythmic) complications in individuals with or without coexisting MetS features. In particular, NAFLD is now increasingly recognized as a risk factor for CHD, with major vascular events representing the primary cause of mortality and morbidity among patients with NAFLD.

Collectively, these findings suggest that patients with NAFLD may benefit from more careful surveillance and early treatment interventions to decrease the risk of vascular and cardiac complications. However, there is still uncertainty regarding the prognostic role of NAFLD in risk stratification for CHD. Additional large follow-up studies are needed to establish whether adding NAFLD to the currently available risk scoring systems will improve CHD/CVD risk prediction. Moreover, the key question of whether the prognostic value of NAFLD in the development and progression of CHD/cardiac diseases is restricted to NASH or is also associated with simple steatosis remains unresolved. Finally, more research is needed to gain mechanistic insights into the pathophysiology linking NAFLD with CHD/cardiac diseases and to better elucidate whether NAFLD associated with specific genetic traits (e.g., PNPLA3-related NAFLD) carries the same cardiovascular risk as NAFLD associated with the MetS [166].

Key Messages

- Strong evidence indicates that NAFLD is associated with an increased risk of cardiovascular disease, independently of multiple cardiometabolic risk factors.
- Convincing evidence substantiates a link between NAFLD and functional and structural myocardial abnormalities in both adults and children with, or without, coexisting features of metabolic syndrome.
- Clinicians who manage patients with NAFLD should not focus only on liver disease but should also recognize the increased risk of cardiovascular, cardiac, and arrhythmic complications and undertake early, aggressive risk factor modification.

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Compliance with ethical standards

Conflict of interest None.

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