Endocrine (2019) 66:467–476
https://doi.org/10.1007/s12020-019-02070-0

META-ANALYSIS

Check for updates

Association between nonalcoholic fatty liver disease and cardiac function and structure—a meta-analysis

Marta Borges-Canha[1,2] · João Sérgio Neves[1,2] · Diogo Libânio[3] · Madalena Von-Hafe[1] · Catarina Vale[1] · Miguel Araújo-Martins[1] · Ana Rita Leite[1] · Pedro Pimentel-Nunes[1,3] · Davide Carvalho[2,4] · Adelino Leite-Moreira[1]

Received: 2 May 2019 / Accepted: 21 August 2019 / Published online: 3 September 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Purpose Nonalcoholic fatty liver disease is increasingly recognized as the hepatic counterpart of metabolic syndrome. It is hypothesized that structural and functional cardiac changes may be associated with this metabolic disease. We aimed to gather the existing information on the association of nonalcoholic fatty liver disease with cardiac alterations, and to evaluate a possible correlation between them.

Methods Systematic review of Medline searching results for original articles studying NAFLD and cardiac parameters until August 2018. A meta-analysis was conducted to each parameter of cardiac structure and function selected, using Review Manager 5.3 software. This study was conducted according to preferred reporting items for systematic reviews and meta-analysis (PRISMA).

Results A total of 16 studies met the eligibility criteria and were included in the meta-analysis. There was a significant association between nonalcoholic fatty liver disease and (1) higher left ventricle mass and ratios between left ventricle mass and both height and body surface area; (2) higher LVEDD; (3) higher left atrium diameter and ratio between left atrial volume and body surface area; (4) higher posterior wall and septum thickness; (5) lower E/A wave ratio; (6) higher E/E' ratio; (7) longer deceleration time and (8) longer relaxation time.

Conclusion NAFLD associates with adverse structural alterations and cardiac dysfunction. Our results highlight the importance of identifying NAFLD in patients with metabolic dysfunction as this may represent an additional contributor to cardiovascular risk.

Keywords NAFLD · Fatty liver · Metabolic syndrome · Echocardiography · Meta-analysis

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic liver disease characterized by an extensive continuum of liver injury, varying from nonalcoholic fatty liver to non-alcoholic steatohepatitis, fibrosis and cirrhosis, which can ultimately give rise to hepatocellular carcinoma. It represents a growing clinical and socio-economic challenge, as it is one of the most common causes of chronic liver disease globally [1, 2].

NAFLD is commonly seen among patients with other metabolic disorders, such as obesity, dyslipidemia, and insulin resistance (IR) and diabetes. This entity increasingly recognized as the hepatic counterpart of metabolic syndrome [2, 3].

As it would be expected, these patients have a high cardiovascular risk, and cardiac-related death is one of the leading causes of their mortality. The range of cardiac complications and events that can be associated with

These authors contributed equally: Marta Borges-Canha, João S. Neves, Diogo Libânio

These authors contributed equally: Madalena Von-Hafe, Catarina Vale, Miguel Araújo-Martins, Ana Rita Leite, Pedro Pimentel-Nunes, Davide Carvalho, Adelino Leite-Moreira

Supplementary information The online version of this article (https://doi.org/10.1007/s12020-019-02070-0) contains supplementary material, which is available to authorized users.

✉ Marta Borges-Canha
marta.canha@gmail.com

1 Departamento de Cirurgia e Fisiologia, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

2 Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal

3 Serviço de Gastroenterologia, Instituto Português de Oncologia do Porto, Porto, Portugal

4 Instituto de Investigação e Inovação em Saúde (i3s), Faculdade de Medicina da Universidade do Porto, Porto, Portugal

NAFLD is broad and it is even hypothesized that structural and functional cardiac changes may be associated with this hepatic disease [4, 5]. These changes are easily evaluated by echocardiography, as it is a non-invasive, innocuous, and bedside technique [6].

Therefore, the aim of this study was to gather the existing information on the association of NAFLD with cardiac alterations, evaluated by echocardiography by a multitude of observational studies that have been done so far, and to hypothesize about possible correlation between them.

Methods

Search strategy

A search of PubMed and Medline databases was carried out for english-written original articles, studying NAFLD and cardiac parameters from inception until August 2018. This study was conducted according to PRISMA (http://www.prisma-statement.org/). The following query was used: ("non-alcoholic fatty liver disease" [MeSH Terms] OR ("nonalcoholic" [All Fields] AND "fatty" [All Fields] AND "liver" [All Fields] AND "disease"[All Fields]) OR "non-alcoholic fatty liver disease" [All Fields] OR "nafld" [All Fields]) AND (("heart failure" [MeSH Terms] OR ("heart" [All Fields] AND "failure" [All Fields]) OR "heart failure" [All Fields]) OR ("echocardiography" [MeSH Terms] OR "echocardiography" [All Fields])). A total amount of 138 articles were retrieved from the search.

Study selection

The following inclusion criteria were defined: (1) studies published in peer-reviewed journals until August 2018; (2) original studies (both cross-sectional and longitudinal studies where accepted); (3) studies conducted in adults aged 18 or older; and (4) studies relevant to the topic, presenting original data. About the last criterion, we included studies evaluating at least one of the following echocardiographic variables (1) left ventricle ejection fraction (LVEF); (2) relaxation time; (3) deceleration time; (4) peak E wave; (5) E/e' ratio; (6) peak A wave; (7) E/A ratio; (8) left ventricle mass (LVM); (9) left ventricle end-diastolic diameter or volume (LVEDD or LVEDV); (10) left ventricle end-systolic diameter or volume (LVESD or LVESV); (11) left atrial diameter or volume (LAD or LAV); (12) posterior wall thickness; and (13) septum thickness, in patients with NAFLD and controls. The definition of NAFLD both by non-invasive parameters and/or liver biopsy was accepted. We excluded (1) non-original studies; (2) studies conducted in children and adolescents; (3) studies that did not present at least one of the echocardiographic variables mentioned above, both in patients with NAFLD and controls.

We have not limited the inclusion based on study size. When more than one article utilized the same database, only the one with the most comprehensive data was included.

Two of the authors independently applied these criteria firstly by reading the title and abstract. After this step, 56 studies were selected for full-text reading. On a second level of eligibility, 40 more studies were excluded and, in the end, 16 studies were selected (Table 1 [7–22]), analyzed and included in this study. Disagreements were solved by consensus. The selection process is shown in Fig. 1. Excluded articles are shown in Supplementary Table 1.

Data extraction and quality assessment

Data extraction was completed by the same two authors and was divided in the following sections:

(1) Article identification (title; authors; date of publication; study design; general description of the study).
(2) Article characterization (number of patients and controls; definition of NAFLD used; diagnostic procedures for NAFLD).
(3) Participants' characterization (age; gender; body mass index (BMI); blood pressure; tobacco use).
(4) Echocardiographic measures (LVEF; peak E wave; peak A wave; E/A ratio; LVM; left ventricle volume and diameter; left atrial diameter; posterior wall thickness; septum thickness; deceleration time; relaxation time).
(5) Biochemistry parameters (glycated hemoglobin; homeostatic model assessment for IR, HOMA-IR; aspartate and alanine transaminases; gamma-glutamyl transferase; albumin).

The Newcastle–Ottawa Quality Assessment Form for Cohort Studies was used to assess the quality and the risk of bias of the studies included. It evaluates nonrandomized studies on the study design (selection of the sample and comparability of the cohorts) and content (outcome). A "star system" is employed and the sum of the stars allows classifying the articles in three categories: good quality; fair quality and poor quality [23].

Statistical analysis

Proportions, means and standard deviations of each of the parameters analyzed were registered. Studies providing data allowing the calculation of odds ratios (for categorical variables) and mean differences (for continuous variables) were then included in meta-analysis, using a random-effects

Table 1 Characteristics of studies included in meta-analysis

Ref.	Study design and sample size	NAFLD diagnosis	Echocardiographic evaluation	Main results	NOS score (quality assessment)[23]
Chung et al. [10]	Cross-sectional study 3300 participants (1310 with NAFLD and 1990 without NAFLD)	Fatty liver on ultrasonography without secondary causes.	Systolic function Diastolic function Structural evaluation	NAFLD was associated with increased risk for LV diastolic dysfunction.	Good quality (4; 2; 3)
Simon et al. [19]	Longitudinal 65 participants (14 with NASH and 61 without NASH)	Hepatic biopsy	Systolic function Diastolic function Structural evaluation	NASH was associated with changes in myocardial structure and in load-dependent indices of LV diastolic function, suggestive of subclinical HF, in a bariatric cohort.	Good quality (4; 2; 3)
Jung et al. [14]	Cross-sectional 20821 participants (14641 with NAFLD and 1137 without NAFLD)	Fatty liver on ultrasonography	Systolic function Diastolic function Structural evaluation	NAFLD is significantly associated with LV functional and structural alteration.	Good quality (4; 2; 3)
Trovato et al. [21]	Cross-sectional 1451 participants (660 with NAFLD and 791 without NAFLD)	Fatty liver on ultrasonography	Systolic function Diastolic function Structural evaluation	The ratio LVM/m^2 is significantly greater in NAFLD, both in men and in women. EF is slightly smaller only in men with NAFLD; no significant difference was observed for the E/A ratio.	Good quality (4; 2; 3)
Metwaly et al. [17]	Cross-sectional 140 participants (60 with NAFLD and 20 without NAFLD)	Fatty liver on ultrasonography without secondary causes.	Systolic function Diastolic function Structural evaluation	Cardiac morphofunctional changes that occur in fatty liver disease patients alter their BNP levels.	Fair quality (2; 2; 3)
Mantovani et al. [16]	Cross-sectional 222 participants (158 with NAFLD and 64 without NAFLD)	Fatty liver on ultrasonography without secondary causes.	Systolic function Diastolic function Structural evaluation	NAFLD is independently associated with early left ventricular diastolic dysfunction in type 2 diabetic patients with preserved systolic function.	Good quality (4; 2; 3)
VanWagner et al. [22]	Cross-sectional 2713 participants (271 with NAFLD and 2442 without NAFLD)	Fatty liver on Computed Tomography	Systolic function Diastolic function Structural evaluation	NAFLD is independently associated with subclinical myocardial remodeling and dysfunction.	Good quality (4; 2; 3)
Bekler et al. [8]	Cross-sectional 54 participants (32 with NAFLD and 22 without NAFLD)	Fatty liver on ultrasonography	Systolic function Diastolic function Structural evaluation	Non-diabetic and normotensive NAFLD patients presented significant impairment in diastolic function, compared to the controls.	Fair quality (2; 2; 3)
Sunbul et al. [20]	Cross-sectional 135 participants (90 with NAFLD and 45 without NAFLD)	Hepatic biopsy	Systolic function	No differences were found between NAFLD patients and controls in ejection fraction.	Fair quality (2; 2; 3)
Baktir et al.	Cross-sectional 56 participants (28 with NASH and 28 without NASH)	Hepatic biopsy	Systolic function Diastolic function Structural evaluation	LV longitudinal and radial systolic functions may deteriorate in patients with NASH without an apparent decrease in the LVEF.	Fair quality (2; 2; 3)
Kim et al. [15]	Cross-sectional 1886 participants (180 with NAFLD and 1105 without NAFLD)	Fatty liver on Computed Tomography	Systolic function Diastolic function Structural evaluation	NAFLD associated with early alterations of cardiovascular system.	Good quality (4; 2; 3)
Bonapace et al. [9]	Cross-sectional 50 participants (32 with NAFLD and 18 without NAFLD)	Fatty liver on ultrasonography	Systolic function Diastolic function Structural evaluation	In patients with type 2 diabetes and NAFLD, even if the LV morphology and systolic function are preserved, early features of LV diastolic dysfunction may be detected.	Good quality (4; 2; 3)
Niaz et al. [18]	Cross-sectional 952 participants (129 with NAFLD and 823 without NAFLD)	Fatty liver on ultrasonography	–	13.5% of the individuals were found to have NAFLD among those selected for the study.	Good quality (4; 2; 3)
Fotbolcu et al. [12]	Cross-sectional 65 participants (35 with NAFLD and 30 without NAFLD)	Fatty liver on ultrasonography	Systolic function Diastolic function Structural evaluation	Patients with NAFLD presented impaired LV systolic and diastolic functions.	Fair quality (2; 2; 3)
Fallo et al. [11]	Cross-sectional 86 participants (48 with NAFLD and 38 without NAFLD)	Fatty liver on ultrasonography	Systolic function Diastolic function Structural evaluation	NAFLD associated with abnormalities of left ventricular diastolic function in a cohort of patients with essential hypertension.	Good quality (4; 2; 3)
Goland et al. [13]	Cross-sectional 63 participants (38 with NAFLD and 25 without NAFLD)	Hepatic biopsy	Systolic function Diastolic function Structural evaluation	Patients with NAFLD presented mildly altered LV geometry and early features of left ventricular diastolic dysfunction.	Fair quality (2; 2; 3)

The NOS score represents the sum of stars in three domains- selection (maximum of 4 stars), comparability (maximum of 2 stars) and outcome/exposure (maximum of 3 stars). Here we present the conversion of the star system in Good/Fair/Poor quality and below the classification, the number of stars per domain (selection; comparability; outcome/exposure)

NAFLD nonalcoholic fatty liver disease, *NOS* Newcastle–Ottawa Scale, *LV* left ventricle, *LVM* left ventricular mass, *EF* ejection fraction, *NASH* nonalcoholic steatohepatitis

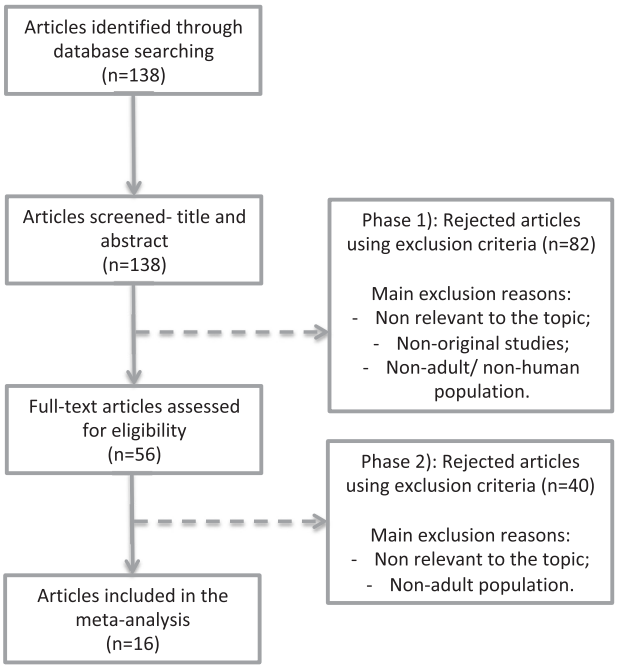

Fig. 1 Fluxogram for the selection of the studies

model, using Review Manager 5.3 software. Heterogeneity was evaluated with the I^2: values between 0 and 25% were considered as insignificant heterogeneity; 26–50% low heterogeneity; 51–75% moderate heterogeneity, and ≥75% high heterogeneity [24]. Subgroup, sensitivity, and stratified analyses were performed as a mean to assess bias or confounding; these data are presented as supplementary data (Supplementary Tables 2–6). We used the funnel plots of the main outcomes evaluated in order to address the presence of bias across the studies, namely publication bias.

Results

Characterization of the sample

As previously mentioned, 16 articles were included in this meta-analysis. The great majority ($n = 15$) are cross-sectional studies and only one is longitudinal. NAFLD was defined by non-invasive methods (as ultrasonography and abdominal-CT) in twelve of the papers, and by invasive techniques (namely hepatic biopsy) in four of them. All the studies evaluated one or more echocardiographic parameter mentioned in the section above. The majority of the studies ($n = 10$) are considered of *Good Quality*, by the Newcastle–Ottawa Scale. The remaining six are considered of *Fair Quality*.

Table 2 shows clinical and analytical characteristics of the population included in this meta-analysis. NAFLD population was shown to have a significantly higher BMI, higher diabetes prevalence (as well as higher glucose levels, glycated hemoglobin and HOMA-IR) and higher blood pressure (both systolic and diastolic), compared with controls (all statistically significant). NAFLD patients, as expected, also presented higher levels of both transaminases and gamma–glutamyl transferase. No differences were found concerning gender, age, or albumin level.

NAFLD and systolic cardiac function

Fourteen studies evaluated systolic cardiac function by LVEF. There were no statistically significant differences in this parameter between NAFLD patients and controls (MD −0.30; $p = 0.33$; I^2 70% Fig. 2).

NAFLD and diastolic cardiac function

Thirteen papers evaluated diastolic function, using various parameters.

In Fig. 3 we show the forest plots concerning NAFLD and diastolic cardiac function parameters. Actually, we found significant differences regarding peak A wave (MD 3.55; $p < 0.01$; I^2 95%), E/e' (MD 1.05; $p < 0.01$; I^2 93%) and E/A ratios (MD −0.15; $p < 0.01$; I^2 94%), and deceleration (MD 13.04; $p < 0.01$; I^2 89%) and relaxation (MD 10.00; $p < 0.01$; I^2 84%) times.

NAFLD and cardiac structure

In Fig. 4 (and 4a in appendices) we show the forest plots concerning NAFLD and systolic cardiac function parameters. We found significant differences regarding LVM (and the ratios between LVM and both height and body surface area) (respectively MD 47.22, $p < 0.01$, I^2 92%; MD 3.82, $p < 0.01$, I^2 91% and MD 7.39, $p < 0.01$, I^2 86%); LVEDD (MD 1.32, $p < 0.01$, I^2 38%); left atrium diameter (and the ratio between left atrium volume and body surface area) (respectively MD 2.19, $p < 0.01$, I^2 95% and MD 1.52, $p = 0.04$, I^2 32%); and septum and posterior wall thickness (respectively MD 1.06, $p < 0.01$, I^2 94% and MD 1.14, $p < 0.01$, I^2 96%).

Table 3 summarizes the results of the echocardiographic evaluation included in this meta-analysis.

Evaluation of publication bias, assessment of bias, and confounding

Visual inspection of funnel plots does not suggest the existence of publication bias (Supplementary Fig. 5a).

As a mean to assess bias and confounding, subgroup, sensitivity, and stratified analyses were performed (Supplementary Tables 2–6). In these analyses, the associations found did not change expressively.

Table 2 Clinical and analytical characteristics of the population included

	NAFLD (*n*)	Controls (*n*)	OR NAFLD*/mean difference#	I^2	Number of papers	*p* value
Age, years	17583	7735	3,34 [−4.83, 11.52]*	100%	14	0.42
Female sex, %	3552	21314	0.76 [0.47, 1.23]#	94%	13	0.26
Body mass index, kg/m^2	17523	7735	3.33 [2.36, 4.29]#	98%	13	**<0.01**
Diabetes mellitus, %	2962	20251	4.01 [2.19, 7.35]*	94%	6	**<0.01**
Hypertension, %	3058	20427	2.11 [1.40, 3.17]*	92%	8	**<0.01**
Systolic blood pressure, mmHg	17325	6659	4.30 [1.47, 7.14]#	95%	12	**<0.01**
Diastolic blood pressure, mmHg	17325	6659	3.11 [0.99, 5.23]#	96%	12	**<0.01**
HbA1c, %	3644	20584	1.32 [1.07, 1.63]#	66%	9	**<0.01**
Glucose, mg/dL	17343	6630	10.02 [6.98, 13.05]#	93%	12	**<0.01**
HOMA-IR, mg/dL	16993	6456	1.89 [1.53, 2.25]#	96%	7	**<0.01**
ALT, IU/L	16988	4195	17.21 [9.00, 25.41]#	100%	12	**<0.01**
AST, IU/L	16956	4177	6.74 [3.19, 10.30]#	99%	11	**<0.01**
GGT, IU/L	15447	2037	15.57 [5.91, 25.24]#	95%	6	**<0.01**
Albumin, g/dL	734	862	−0.23 [−0.61, 0.15]#	95%	3	0.23

OR odds ratio, I^2 heterogeneity, *HbA1c* glycated hemoglobin, *HOMA-IR* homeostatic model assessment for insulin resistance, *AST* aspartate transaminase, *ALT* alanine transaminase, *GGT* Gamma–Glutamyl transferase

Bold values indicate *p* value < 0.01

*Indicates OR NAFLD

#Indicates mean difference

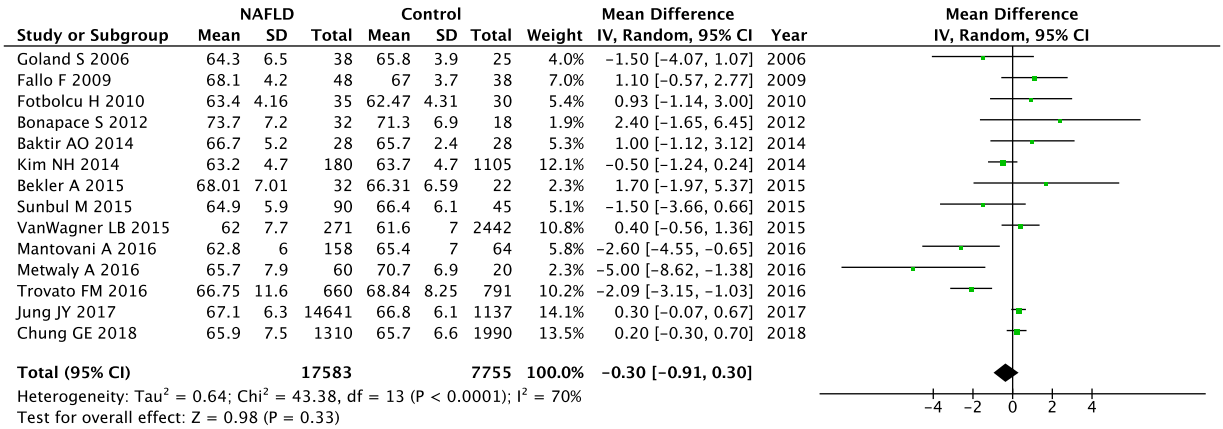

Fig. 2 Forest plot of left ventricle ejection fraction in NAFLD patients versus controls

Discussion and conclusion

NAFLD is a growing clinical and socio-economic challenge. The range of cardiac complications and events that can be associated with NAFLD is broad. It is hypothesized that structural and functional cardiac changes may be associated with this hepatic disease.

In this meta-analysis we aimed to uncover a possible association of NAFLD and cardiac echocardiographic alterations. The analysis shows a clear association between the presence of NAFLD and adverse cardiac changes. Cardiac diastolic function and structure seem to be particularly affected.

Systolic function is satisfactorily characterized by ejection fraction [6]. Regarding this parameter, we found no significant difference between NAFLD and non-NAFLD populations. The lack of differences may either be due to a true lack of difference between NAFLD and non-NAFLD populations or to the different methodologies used in the papers included in this meta-analysis. For example, some authors included diabetic and/or hypertensive patients, while others excluded them. However, even making

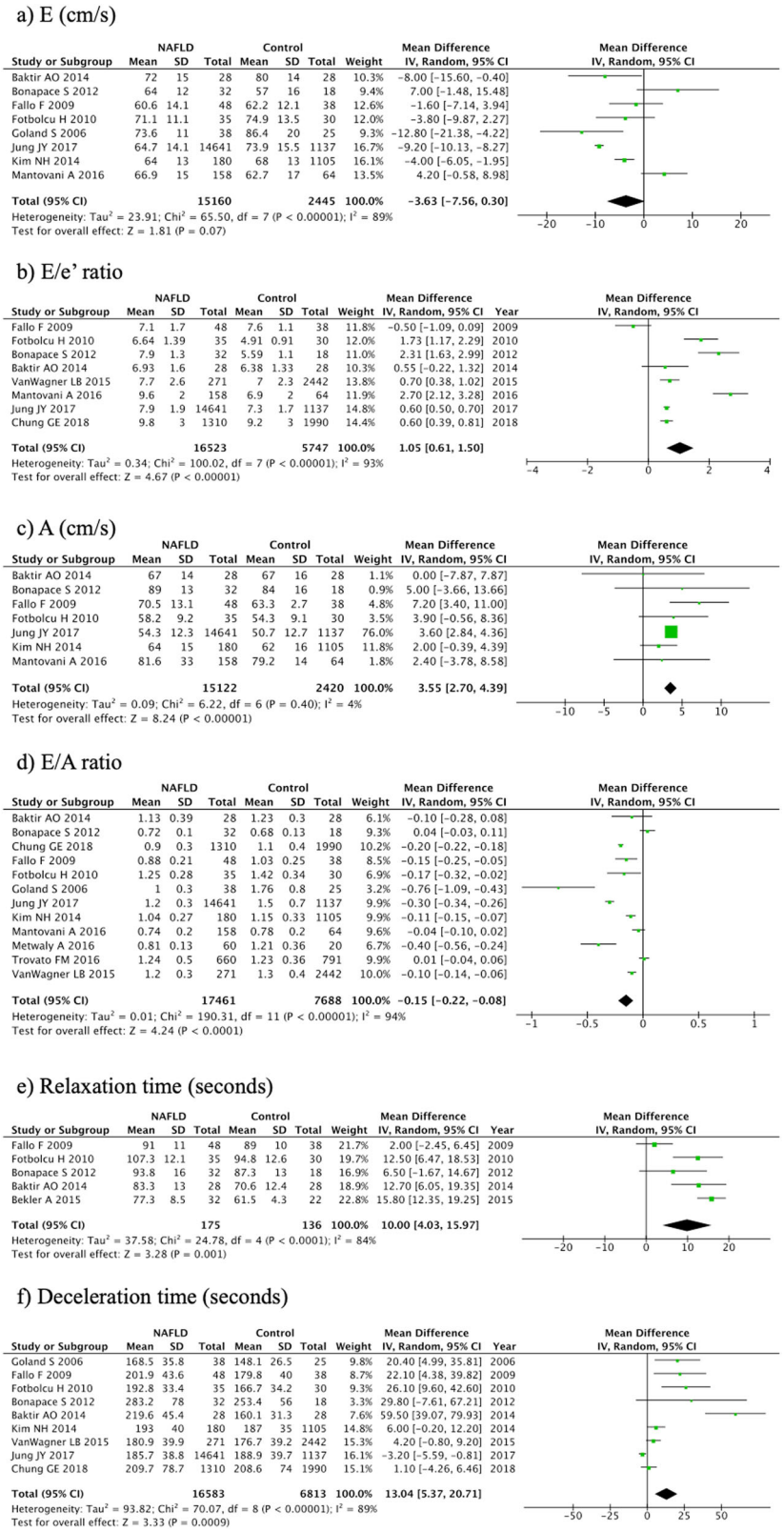

Fig. 3 Forest plots concerning diastolic cardiac function parameters in NAFLD versus controls: **a** Peak E velocity (cm/s); **b** E/e' ratio; **c** Peak A velocity (cm/s); **d** E/A ratio; **e** Isovolumic relaxation time (seconds); **f** Deceleration time (seconds)

subgroup analysis a statistically significant difference was not found.

On the other hand, **diastolic function** can be evaluated by the E/A ratio (used as an estimate of the relaxation

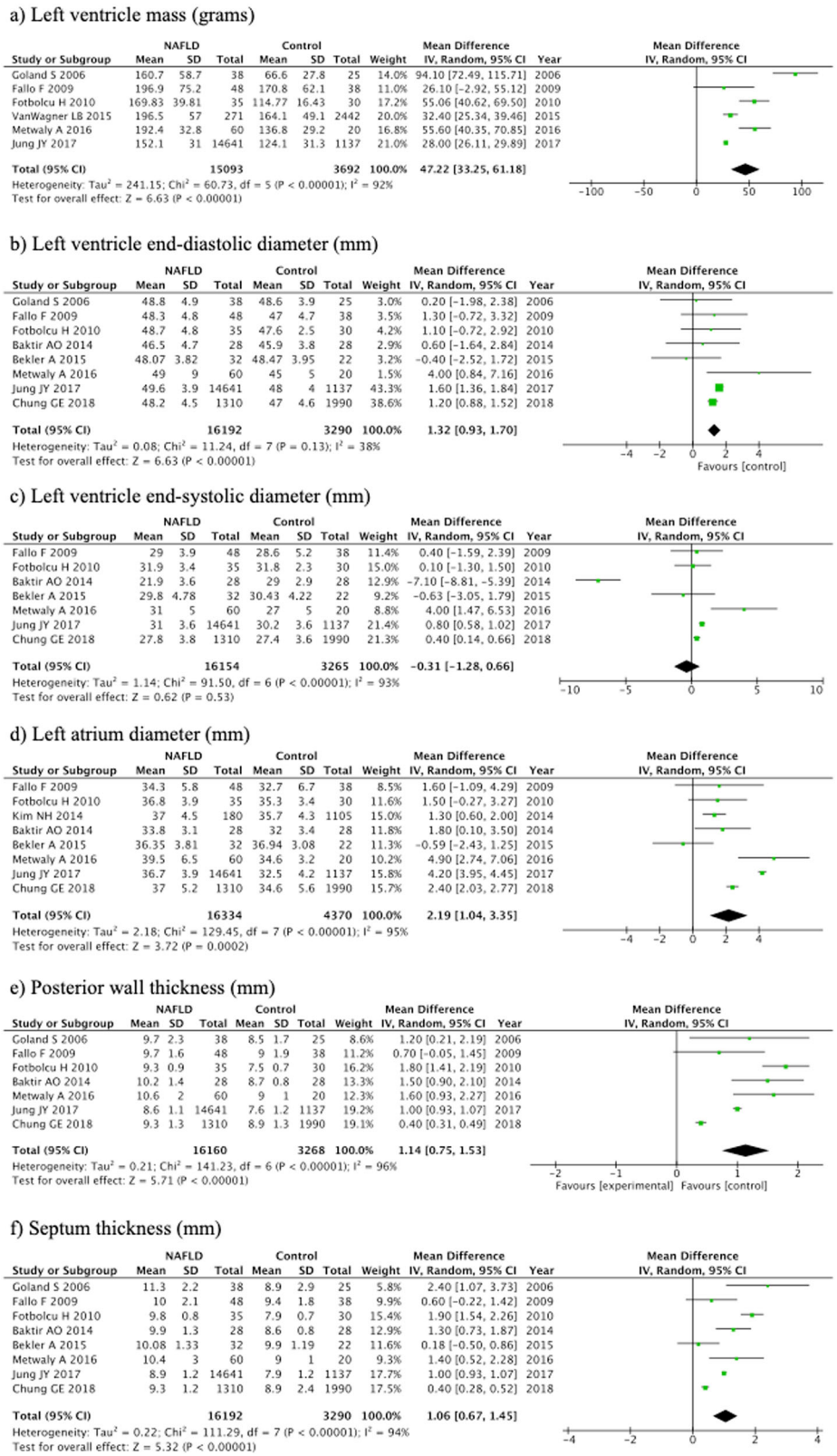

Fig. 4 Forest plots concerning cardiac structure parameters in NAFLD *vs* controls: **a** Left ventricle mass (LVM; grams); **b** Left ventricle end-diastolic diameter (mm); **c** Left ventricle end-systolic diameter (mm); **d** Left atrium diameter (mm); **e** Posterior wall thickness (mm); **f** Interventricular septum thickness (mm)

pattern of the ventricle) and E/e' ratio (that estimates left ventricular filling pressures), amongst other parameters [6]. We detected significant differences concerning both ratios, as well as relaxation and deceleration times. This suggests that patients with NAFLD are prone to have diastolic dysfunction, comparing with controls. In agreement with our

Table 3 Results of the echocardiographic evaluation included in the meta-analysis

	Mean difference, 95% CI	I^2	Heterogeneity	p value
Systolic cardiac function				
LVEF, %	−0.30 [−0.91, 0.30]	70%	Moderate	0.33
Diastolic cardiac function				
E, cm/s	−3.63 [−7.56, 0.30]	89%	High	0.07
E/e'	1.05 [0.61, 1.50]	93%	High	**<0.01**
A, cm/s	3.55 [2.70, 4.39]	4%	Insignificant	**<0.01**
E/A	−0.15 [−0.22, −0.08]	94%	High	**<0.01**
Relaxation time, s	10.00 [4.03, 15.97]	84%	High	**<0.01**
Deceleration time, s	13.04 [5.37, 20.71]	89%	High	**<0.01**
Cardiac structure				
LVM, g	47.22 [33.25, 61.18]	92%	High	**<0.01**
LVM/height, $g/m^{2.7d}$	3.82 [1.61, 6.03]	91%	High	**<0.01**
LVM/BSA, g/m^2	7.39 [2.22, 12.56]	86%	High	**<0.01**
LVEDD, mm	1.32 [0.93, 1.70]	38%	Low	**<0.01**
LVEDV, mL	2.23 [−2.09, 6.55]	49%	Low	0.31
LVESD, mm	−0.31 [−1.28, 0.66]	93%	High	0.53
LVESV, mL	1.13 [−1.01, 3.28]	27%	Low	0.30
LAD, mm	2.19 [1.04, 3.35]	95%	High	**<0.01**
LAV/BSA, mL/m^2	1.52 [0.05, 3.00]	32%	Low	**0.04**
Posterior wall thickness, mm	1.14 [0.75, 1.53]	96%	High	**<0.01**
Septum thickness, mm	1.06 [0.67, 1.45]	94%	High	**<0.01**

I^2 evaluates the heterogeneity. Values between 0 and 25% mean insignificant heterogeneity; 26–50% low heterogeneity; 51–75% moderate heterogeneity; ≥75% high heterogeneity

LVEF left ventricle ejection fraction, *LVM* left ventricle mass, *BSA* body surface area, *LVEDD* left ventricle end-diastolic diameter, *LVEDV* left ventricle end-diastolic volume, *LVESD* left ventricle end-systolic diameter, *LVESV* left ventricle end systolic volume, *LAD* left atrial diameter, *LAV* left atrial volume

Bold values indicates p value <0.01

results, a recent meta-analysis has shown an approximately twofold increased odds of having diastolic cardiac dysfunction among patients with NAFLD (comparing to individuals without NAFLD) [5]. In this paper, the authors evaluated diastolic cardiac dysfunction only a as a global classification. We must highlight that our meta-analysis is the only current study that individually evaluated the parameters of diastolic function. Also, in 2015 similar conclusions were reached by Bonci et al. [25]. These authors described both adult and pediatric studies on the theme. The results on adults studies also lead to conclude that NAFLD patients have lower E/A and higher E/e' ratios, comparing with non-NAFLD individuals.

Finally, we also focused on **structural parameters**. LVM is consistently higher in NAFLD patients (as well as LVM/height and LVM/BSA ratios), and these results are partially in conflict to the ones described by Bonci et al., which show a significant decrease in LVM/BSA ratio, in NAFLD patients [25]. Furthermore, LVEDD and LAD are also consistently greater in these patients. We also assessed posterior wall and septum thicknesses that, once more, were higher in the NAFLD group.

There are many possible explanations to the association of NAFLD with cardiac alterations. Firstly, we must emphasize that NAFLD is strongly associated with cardiovascular risk factors. These alter cardiac function and structure per se, thus confounding the results. Despite this, it is biologically plausible that NAFLD can independently be responsible for them. A recent review reinforces NAFLD as a multisystem disease that affects the heart and vessels, possibly through low-grade systemic inflammation [26, 27]. In NAFLD, systemic inflammation arises from interactions between environmental factors (namely diet), gastrointestinal microbiota, host's genetics, and adipose tissue (explicitly visceral adipose tissue), among others. One possible explanation relies on the role of pro-inflammatory cytokines that can induce cardiac remodeling, dysfunction of calcium homeostasis, and cardiac arrhythmias [26]. Other possible explanation relies on IR, common among NAFLD patients [28, 29]. IR states present with decreased glucose contribution to heart's energy supply, proportionally increasing fatty acid oxidation. This may have deleterious consequences on cardiomyocytes and participate in cardiac dysfunction [29]. Notwithstanding, dyslipidemia is also a

possible contributor to the referred association. NAFLD is characterized by high levels of triglyceride, dense low-density lipoprotein cholesterol and very low-density lipoprotein, and by low levels of high-density lipoprotein cholesterol. This profile has paramount effects in cardiomyocytes metabolism and function [27, 29]. We believe that, given the complexity of the topic, all of these hypotheses may be accurate and contribute partially to the cardiovascular dysfunction in NAFLD patients.

We must acknowledge some limitations of this analysis. Despite the through process of literature review and fulfilling the PRISMA checklist, high heterogeneity was found in several parameters. It can be due to the different methodologies used and the different populations included. Besides, the severity of liver disease was not considered in most of the studies (possible due to the invasiveness of liver biopsy). Finally, we could not establish whether NAFLD is independently associated to the cardiac changes or if this association is confounded by the cardiovascular risk factors. The reported analyses relied on the mean differences between NAFLD patients and controls without adjustment for potential confounders.

In summary, the presence of NAFLD was associated with adverse structural alterations and cardiac dysfunction (mainly diastolic). Our results therefore highlight the importance of identifying NAFLD in patients with metabolic dysfunction as this may represent an additional contributor to the cardiovascular risk. Furthermore, patients with NAFLD must be thoroughly evaluated regarding cardiovascular risk. More studies are needed to understand the mechanisms of cardiac dysfunction in patients with NAFLD.

Funding This work was supported by the project DOCnet (NORTE-01-0145-FEDER-000003), supported by Norte Portugal Regional Operational Program (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF), and the project NETDIAMOND (POCI-01-0145-FEDER-016385), supported by European Structural and Investment Funds, Lisbon's Regional Operational Program 2020 and national funds from the Portuguese Foundation for Science and Technology.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. M. Borges Canha, J.P. Portela-Cidade, G. Conceicao, C. Sousa-Mendes, S. Leite, D. Fontoura et al. Characterization of liver changes in ZSF1 rats, an animal model of metabolic syndrome. Rev. Esp. Enferm. Dig. **109**(7), 491–497 (2017). https://doi.org/10.17235/reed.2017.4575/2016.
2. Z.M. Younossi, A.B. Koenig, D. Abdelatif, Y. Fazel, L. Henry, M. Wymer, Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology **64**(1), 73–84 (2016). https://doi.org/10.1002/hep.28431.
3. N. Chalasani, Z. Younossi, J.E. Lavine, A.M. Diehl, E.M. Brunt, K. Cusi et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology **142**(7), 1592–1609 (2012). https://doi.org/10.1053/j.gastro.2012.04.001.
4. M. Ekstedt, H. Hagstrom, P. Nasr, M. Fredrikson, P. Stal, S. Kechagias et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology **61**(5), 1547–1554 (2015). https://doi.org/10.1002/hep.27368.
5. K. Wijarnpreecha, S. Lou, P. Panjawatanan, W. Cheungpasitporn, S. Pungpapong, F.J. Lukens et al. Association between diastolic cardiac dysfunction and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Dig. Liver Dis. **50**(11), 1166–1175 (2018). https://doi.org/10.1016/j.dld.2018.09.004.
6. S.H. Wan, M.W. Vogel, H.H. Chen, Pre-clinical diastolic dysfunction. J. Am. Coll. Cardiol. **63**(5), 407–416 (2014). https://doi.org/10.1016/j.jacc.2013.10.063.
7. A.O. Baktir, B. Sarli, R.E. Altekin, A. Karaman, H. Arinc, H. Saglam et al. Non alcoholic steatohepatitis is associated with subclinical impairment in left ventricular function measured by speckle tracking echocardiography. Anatol. J. Cardiol. **15**(2), 137–142 (2015). https://doi.org/10.5152/akd.2014.5212.
8. A. Bekler, E. Gazi, G. Erbag, E. Binnetoglu, A. Barutcu, H. Sen et al. Right ventricular function and its relationship with grade of hepatosteatosis in non-alcoholic fatty liver disease. Cardiovasc J. Afr. **26** (3), 109–113 (2015). https://doi.org/10.5830/CVJA-2014-068.
9. S. Bonapace, G. Perseghin, G. Molon, G. Canali, L. Bertolini, G. Zoppini et al. Nonalcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes. Diabetes Care. **35**(2), 389–395 (2012). https://doi.org/10.2337/dc11-1820.
10. G.E. Chung, J.H. Lee, H. Lee, M.K. Kim, J.Y. Yim, S.Y. Choi et al. Nonalcoholic fatty liver disease and advanced fibrosis are associated with left ventricular diastolic dysfunction. Atherosclerosis **272**, 137–144 (2018). https://doi.org/10.1016/j.atherosclerosis.2018.03.027.
11. F. Fallo, A. Dalla Pozza, N. Sonino, M. Lupia, F. Tona, G. Federspil et al. Non-alcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in essential hypertension. Nutr. Metab. Cardiovasc. Dis. **19**(9), 646–653 (2009). https://doi.org/10.1016/j.numecd.2008.12.007.
12. H. Fotbolcu, T. Yakar, D. Duman, T. Karaahmet, K. Tigen, C. Cevik et al. Impairment of the left ventricular systolic and diastolic function in patients with non-alcoholic fatty liver disease. Cardiol. J. **17**(5), 457–463 (2010). Epub 2010/09/25.
13. S. Goland, S. Shimoni, T. Zornitzki, H. Knobler, O. Azoulai, G. Lutaty et al. Cardiac abnormalities as a new manifestation of non-alcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. J. Clin. Gastroenterol. **40**(10), 949–955 (2006). https://doi.org/10.1097/01.mcg.0000225668.53673.e6.
14. J.Y. Jung, S.K. Park, J.H. Ryoo, C.M. Oh, J.G. Kang, J.H. Lee et al. Effect of non-alcoholic fatty liver disease on left ventricular diastolic function and geometry in the Korean general population. Hepatol. Res. **47**(6), 522–532 (2017). https://doi.org/10.1111/hepr.12770.
15. N.H. Kim, J. Park, S.H. Kim, Y.H. Kim, D.H. Kim, G.Y. Cho et al. Non-alcoholic fatty liver disease, metabolic syndrome and subclinical cardiovascular changes in the general population. Heart **100**(12), 938–943 (2014). https://doi.org/10.1136/heartjnl-2013-305099.

16. A. Mantovani, M. Pernigo, C. Bergamini, S. Bonapace, P. Lipari, I. Pichiri et al. Nonalcoholic fatty liver disease is independently associated with early left ventricular diastolic dysfunction in patients with type 2 diabetes. PLoS ONE **10**(8), e0135329 (2015). https://doi.org/10.1371/journal.pone.0135329.
17. A. Metwaly, A.A. Khalik, F.M. Nasr, A.I. Sabry, M.F. Gouda, M. Hassan, Brain natriuretic peptide in liver cirrhosis and fatty liver: correlation with cardiac performance. Electron Physician **8**(2), 1984–1993 (2016). https://doi.org/10.19082/1984.
18. A. Niaz, Z. Ali, S. Nayyar, N. Fatima, Prevalence of NAFLD in healthy and young male individuals. ISRN Gastroenterol. **2011**, 363546 (2011). https://doi.org/10.5402/2011/363546.
19. T.G. Simon, D.G. Bamira, R.T. Chung, R.B. Weiner, K.E. Corey, Nonalcoholic steatohepatitis is associated with cardiac remodeling and dysfunction. Obesity **25**(8), 1313–1316 (2017). https://doi.org/10.1002/oby.21879.
20. M. Sunbul, T. Kivrak, E. Durmus, H. Akin, Y. Aydin, R. Ergelen et al. Nonalcoholic steatohepatitis score is an independent predictor of right ventricular dysfunction in patients with nonalcoholic fatty liver disease. Cardiovasc Ther. **33**(5), 294–299 (2015). https://doi.org/10.1111/1755-5922.12145.
21. F.M. Trovato, G.F. Martines, D. Catalano, G. Musumeci, C. Pirri, G.M. Trovato, Echocardiography and NAFLD (non-alcoholic fatty liver disease). Int J. Cardiol. **221**, 275–279 (2016). https://doi.org/10.1016/j.ijcard.2016.06.180.
22. L.B. VanWagner, J.E. Wilcox, L.A. Colangelo, D.M. Lloyd-Jones, J.J. Carr, J.A. Lima et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: a population-based study. Hepatology **62**(3), 773–783 (2015). https://doi.org/10.1002/hep.27869.
23. G. Wells, B. Shea, D. O'Connell, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in metaanalyses; 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2 Nov 2015.
24. J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses. BMJ **327**(7414), 557–560 (2003). https://doi.org/10.1136/bmj.327.7414.557.
25. E. Bonci, C. Chiesa, P. Versacci, C. Anania, L. Silvestri, L. Pacifico, Association of nonalcoholic fatty liver disease with subclinical cardiovascular changes: a systematic review and meta-analysis. Biomed. Res Int. **2015**, 213737 (2015). https://doi.org/10.1155/2015/213737.
26. Q.M. Anstee, A. Mantovani, H. Tilg, G. Targher, Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nat. Rev. Gastroenterol. Hepatol. **15**(7), 425–439 (2018). https://doi.org/10.1038/s41575-018-0010-0.
27. E. Bugianesi, Nonalcoholic fatty liver disease (NAFLD) and cardiac lipotoxicity: another piece of the puzzle. Hepatology **47**(1), 2–4 (2008). https://doi.org/10.1002/hep.22105.
28. L.S. Bhatia, N.P. Curzen, P.C. Calder, C.D. Byrne, Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur. Heart J. **33**(10), 1190–1200 (2012). https://doi.org/10.1093/eurheartj/ehr453.
29. E.D. Abel, K.M. O'Shea, R. Ramasamy, Insulin resistance: metabolic mechanisms and consequences in the heart. Arterioscler. Thromb. Vasc. Biol. **32**(9), 2068–2076 (2012). https://doi.org/10.1161/ATVBAHA.111.241984.