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REVIEW

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Endothelial dysfunction and cardiovascular risk in non-alcoholic fatty liver disease – a systematic review and meta-analysis

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Abstract

Background Nonalcoholic fatty liver disease (NAFLD) is a prevalent metabolic disorder that has been associated with an increased risk of cardiovascular diseases. Endothelial dysfunction, characterized by impaired flow-mediated dilation (FMD) of the brachial artery, is a known predictor of cardiovascular risk. However, the relationship between NAFLD and endothelial dysfunction, as well as the impact of NAFLD on clinical cardiovascular events, remains unclear.

Objective The aim of this systematic literature review was to determine the association between endothelial dysfunction, as measured by FMD of the brachial artery, and NAFLD. Additionally, we aimed to investigate the relationship between NAFLD and clinical cardiovascular events (CVE).

Methods A systematic search was conducted in PubMed, Scopus, ScienceDirect, and Google Scholar for articles published between 2000 and July 2023. The reference lists of the included studies were also searched to retrieve possible additional studies. Original studies published in English focusing on adults with NAFLD and endothelial dysfunction are included. Editorials, commentaries, letters and studies focusing on pediatric populations and non-NAFLD liver diseases were excluded. The quality of included studies was appraised using the Newcastle–Ottawa scale. Meta-analyses were performed using Review Manager 5.4 software.

Results The initial search yielded a total of 1792 articles and ultimately only 20 studies met the criteria. A total 6396 NAFLD patients were studied. Meta-analysis showed that individuals diagnosed with NAFLD had significantly lower brachial FMD values compared to their respective control groups (standardized mean difference: -4.63, 95% confidence interval: -5.68 to -3.58, $p < 0.0001$). Furthermore, NAFLD patients exhibited a significantly higher risk of clinical cardiovascular events compared to controls (odds ratio: 2.61; 95% CI: 1.41–4.83, $p < 0.002$). Subgroup analysis of studies focusing on non-alcoholic steatohepatitis (NASH) versus pure steatosis demonstrated that individuals with NASH had even lower FMD values than those with pure steatosis (standardized mean difference: -3.84, 95% confidence interval: -7.56 to -0.13, $p = 0.03$, $I2 = 66\%$).

Limitations, bias and heterogeneity The review included studies published in English language, over last 23 years and specified database resulted in language bias and might have missed older pertinent studies from another important database. The overall heterogeneity is attributed to variations in study populations, outcome measurements, differences in methodological approaches among included studies, and diverse diagnostic criteria for NAFLD.

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Conclusion Individuals with NAFLD exhibited impaired brachial FMD, indicating compromised endothelial function. Furthermore, NAFLD patients had an elevated risk of clinical cardiovascular events.

Keywords NAFLD, NASH, MASLD, FMD, SLD, CVE, CVD

Research question and objective

Research Question

What is the relationship between endothelial dysfunction and the cardiovascular risk profile in individuals with nonalcoholic fatty liver disease (NAFLD)?

Objectives

To evaluate the association of endothelial dysfunction, assessed by flow-mediated dilation (FMD) of the brachial artery, with nonalcoholic fatty liver disease (NAFLD).

To investigate the relationship between NAFLD and clinical cardiovascular events (CVE).

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease in the West that affects approximately 20% of the total population in the United States, equivalent to approximately 30 million people [1–3]. It is characterized by the formation of fat in the liver without heavy alcohol consumption, infection or the use of drugs that cause adiposity. NAFLD covers a range of conditions from simple fatty liver steatosis to NASH with or without fibrosis [4]. Nonalcoholic steatohepatitis (NASH) is a progressive disease associated with increased mortality and confirmed by liver biopsy [3]. NAFLD is commonly associated with metabolic syndrome and exhibits strong associations with dyslipidemia, obesity, and insulin resistance [5]. The male gender, metabolic syndrome components (elevated body mass index, high triglyceride levels, high blood sugar levels, hypertension), and hyperuricemia are recognized as established risk factors contributing to the development of NAFLD [6].

Previously, NAFLD was typically diagnosed by excluding alcohol intake, viral hepatitis, or autoimmune liver diseases. However, it is important to acknowledge that the pathophysiology of NAFLD often coexists with the aforementioned factors, particularly in individuals residing in developed countries. Additionally, assessing alcohol consumption through questionnaires is subjective, and establishing safe limits for alcohol intake remains a topic of debate. Consequently, associating fatty liver disease with metabolic disturbances solely with alcohol intake may not be appropriate. Furthermore, it is crucial to emphasize that staging liver fibrosis, which carries significant prognostic implications, should take precedence over a binary classification of NASH or non-NASH. The management of NAFLD patients should prioritize addressing the underlying pathophysiology, considering the heterogeneity often observed. As a result, a new term, metabolic-associated fatty liver disease (MAFLD), has been introduced, reflecting these nuanced considerations in the diagnosis and treatment of the condition [7]. Despite an improved understanding and recognition of its significance, the screening and referral rates to hepatologists for suspected NAFLD remain low within primary care and non-hepatology specialties [8, 9]. Consequently, NAFLD tends to be underdiagnosed, leading to compromised long-term outcomes associated with both liver-related and extrahepatic manifestations. Notably, NAFLD is not only linked to heightened morbidity and mortality related to liver conditions but also demonstrates an increased risk of mortality from cardiovascular disease (CVD) and cancer [10, 11].

NAFLD and CVD share several common risk factors, including obesity, diabetes, dyslipidemia, and physical inactivity, indicating a shared pathogenesis [12]. Moreover, individuals with NAFLD have shown evidence of heightened atherosclerotic risk, including increased inflammation, endothelial dysfunction, and surrogate markers of accelerated atherosclerosis such as heightened carotid intimal medial thickness [13]. As CVD accounts for over 30% of deaths in the United States and represents the leading cause of mortality in NAFLD patients, it underscores the crucial importance of recognizing and addressing CVD in individuals with NAFLD [14]. In addition to the spectrum of NAFLD, which encompasses conditions ranging from simple steatosis to NASH, other classifications of the disease deserve attention. One such classification is steatotic liver disease (SLD), characterized by the presence of hepatic steatosis either in conjunction with metabolic dysfunction, known as MASLD, or in the absence of secondary causes. SLD emerges as a prominent contributor to advanced liver disease in the United States, presenting an elevated risk of mortality and burden of cardiovascular conditions [15–17]. Key factors linked to unfavorable outcomes include the extent of fibrosis and metabolic comorbidities like diabetes and obesity. Lifestyle intervention, focusing on essential elements such as achieving a 7% to 10% reduction in total body weight, adopting a high-quality diet, and engaging in regular physical activity, forms the cornerstone of therapy for SLD.

Significantly, recent findings from a systematic review and meta-analysis conducted by Montovani et al. [18] highlight that both NAFLD and NASH independently increase the risk of developing cardiovascular events, surpassing the influence of their established risk factors. Moreover, advanced NAFLD has been associated with an elevated likelihood of developing heart failure, resulting in increased hospitalization rates, as well as higher all-cause and cardiovascular mortality [19]. In addition to the shared risk factors, various pathophysiological mechanisms have been elucidated, linking NAFLD to the incidence of cardiovascular diseases. These mechanisms encompass vascular inflammation, the promotion of a prothrombotic state, dysregulated gut microbiota, and genetic or epigenetic modifications [20]. With that in mind, the present systematic literature review aims to investigate the intricate relationship between endothelial dysfunction, a key pathophysiological mechanism, and the cardiovascular risk profile in individuals diagnosed with NAFLD.

Methods

This review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) 2020 guidelines [21]. A thorough search was conducted in three databases, namely PubMed, Scopus, and ScienceDirect, to locate articles that were published in English and covered a broad range of topics. The articles included in the search spanned from 2000 to July 2023 and focused on the association between endothelial dysfunction, cardiovascular risk, and NAFLD. The reference lists of the included studies were also searched to retrieve possible additional studies. Among the three databases, PubMed was given priority as it contained internationally-indexed articles.

Primary search

In the PubMed search strategy, a combination of both free keyword searches and controlled MeSH terms was employed. The keyword search focused on analyzing the entire text to enhance the search strategy's sensitivity. The search strategies used for Scopus and ScienceDirect were slightly adjusted versions of the strategy used in PubMed. Table 1 below represents the selection of keywords considered for the search.

Secondary search

In addition to searching the three databases mentioned previously, a direct search was conducted using the Google Scholar database. To prioritize the presentation of the most relevant results in the initial pages, the search incorporated specific keywords associated with "Nonalcoholic fatty liver disease" (NAFLD, FMD, MASLD, SLD, and MetALD) to identify any relevant articles.

Eligibility criteria

All studies had to meet the following pre-defined inclusion criteria:

- Original studies
- Published in English
- Focus on studies involving adult individuals (18 years and above) diagnosed with nonalcoholic fatty liver disease (NAFLD).
- Include studies that assess endothelial dysfunction using reliable methods such as flow-mediated dilation (FMD) of the brachial artery, and endothelial biomarkers. Also, include studies reporting cardiovascular risk factors and outcomes.
- Include appropriate comparison groups, such as individuals without NAFLD or those with healthy livers, to facilitate comparisons of endothelial dysfunction and cardiovascular risk profile between NAFLD and control groups.

Table 1 Search strings

Database	Search field	Search string
PubMed	Title, abstract	("Endothelial dysfunction" OR "Vascular dysfunction" OR "endothelial impairment") AND ("Cardiovascular risk" OR "Cardiovascular profile" OR "cardiovascular complications" OR "cardiovascular disease") AND ("Nonalcoholic fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "NASH" OR "fatty liver" OR "MASLD" OR "SLD" OR "steatotic liver disease")
Scopus	Title, abstract, keywords	("Endothelial dysfunction" OR "Vascular dysfunction" OR "endothelial impairment") AND ("Cardiovascular risk" OR "Cardiovascular profile" OR "cardiovascular complications" OR "cardiovascular disease") AND ("Nonalcoholic fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "NASH" OR "fatty liver" OR "MASLD" OR "SLD" OR "steatotic liver disease")
ScienceDirect	All fields	("Endothelial dysfunction" OR "Vascular dysfunction") AND ("Cardiovascular risk" OR "Cardiovascular profile") AND ("Nonalcoholic fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "MASLD" OR "fatty liver")

No data range was used in any of the index databases

Following studies were excluded:

- Editorials, commentaries, letters, and conference abstracts.
- Studies involving pediatric populations.
- Studies focusing primarily on non-NAFLD liver diseases.
- Animal studies, and studies with insufficient data or irrelevant outcomes

Outcome assessed

Development of endothelial dysfunction indicated by impaired FMD of brachial artery and risk of CVD and CVE in patients with NAFLD.

Study selection and data extraction

The screening process for potentially eligible studies was conducted using Zotero software. The selection involved a thorough evaluation of titles, abstracts, and full texts to determine suitability. Following the selection of articles for inclusion, relevant data was extracted into a predefined data descriptor. The data descriptor included specific fields such as Author and Year of publication, Study design, Geographic Location, NAFLD Diagnosis, Cuff Inflation, Study group's population, and Control group's population.

Study quality assessment

The methodological quality of the included studies was appraised using the Newcastle–Ottawa scale for cohort studies [22]. Each criterion, evaluated on a 1 (met) or 0 (not met) basis, covered crucial aspects like group selection, cohort comparability, and outcome ascertainment. With a maximum possible score of 8 indicating high quality, we classified studies scoring 7–8 as high quality, 5–6 as medium, and below 5 as poor.

Statistical analysis

We conducted a meta-analysis to compare the brachial flow-mediated dilation (FMD) between individuals diagnosed with NAFLD and a control group. Effect sizes were combined using a random-effects model, and the results were reported as uncorrected standardized mean differences (SMD) with 95% confidence intervals (CI), utilizing Cohen's d as the effect size measure. To evaluate heterogeneity among studies, we calculated I^2, where values of 25%, 50%, and 75% indicated mild, moderate, and substantial heterogeneity, respectively. Statistical significance was determined by a p-value of less than 0.05. Odds ratios were calculated to measure the association between NAFLD and cardiovascular risks. The meta-analyses were performed using Review Manager 5.4 software, employing the random-effects model.

Results

Search results

The initial search yielded a total of 1792 articles, from which 19 duplicate articles were removed. Through the screening of titles and abstracts, 1713 articles were excluded based on the predetermined eligibility criteria, leaving 50 articles for full-text review. Among these, 30 articles were excluded for multiple reasons as outlined in the PRISMA flowchart below. Ultimately, 20 articles met the inclusion criteria and were included in this review paper. The study selection process is depicted in Fig. 1, presented below.

Quality appraisal

Out of the total articles assessed using the Newcastle–Ottawa Scale [22], 18 articles demonstrated high quality with scores ranging from 6 to 8. These articles met the criteria and provided robust evidence for the review. Conversely, one article was deemed to have poor quality, scoring 4. The results of the quality assessment are presented below in the Table 2.

Data extraction results (Table 3)

Included studies

This systematic review includes 20 studies; 3 prospective observational cohort studies, 4 prospective cohort studies, 6 cohort studies, 2 case–control studies, 4 cross-sectional studies, and 1 randomized controlled trial. Out of the 20 studies analyzed, a total of 6396 individuals were diagnosed with NAFLD, and 13386 control subjects were identified. The diagnosis of NAFLD was established using various methods, including liver ultrasound in 6 out of the 20 studies, liver biopsy in 6 out of 20 studies, and a combination of methods in 8 out of 20 studies. Among the 20 included studies, the majority were conducted in Europe (8 studies), followed by Asia (4 studies) and the Middle East (2 studies). One study was conducted in North America, while 5 studies did not specify their geographical location. Regarding the NAFLD groups, NASH presence was evaluated in 6 out of the 20 studies. In the majority of these studies (17/20), a noticeably higher occurrence of obesity indicators was observed in the NAFLD group when compared to the control group.

Association between NAFLD and clinical cardiovascular events (CVE)

El Azeem et al. [23] investigated the association between ultrasound-diagnosed NAFLD and the likelihood of developing cardiovascular and renal impairment events.

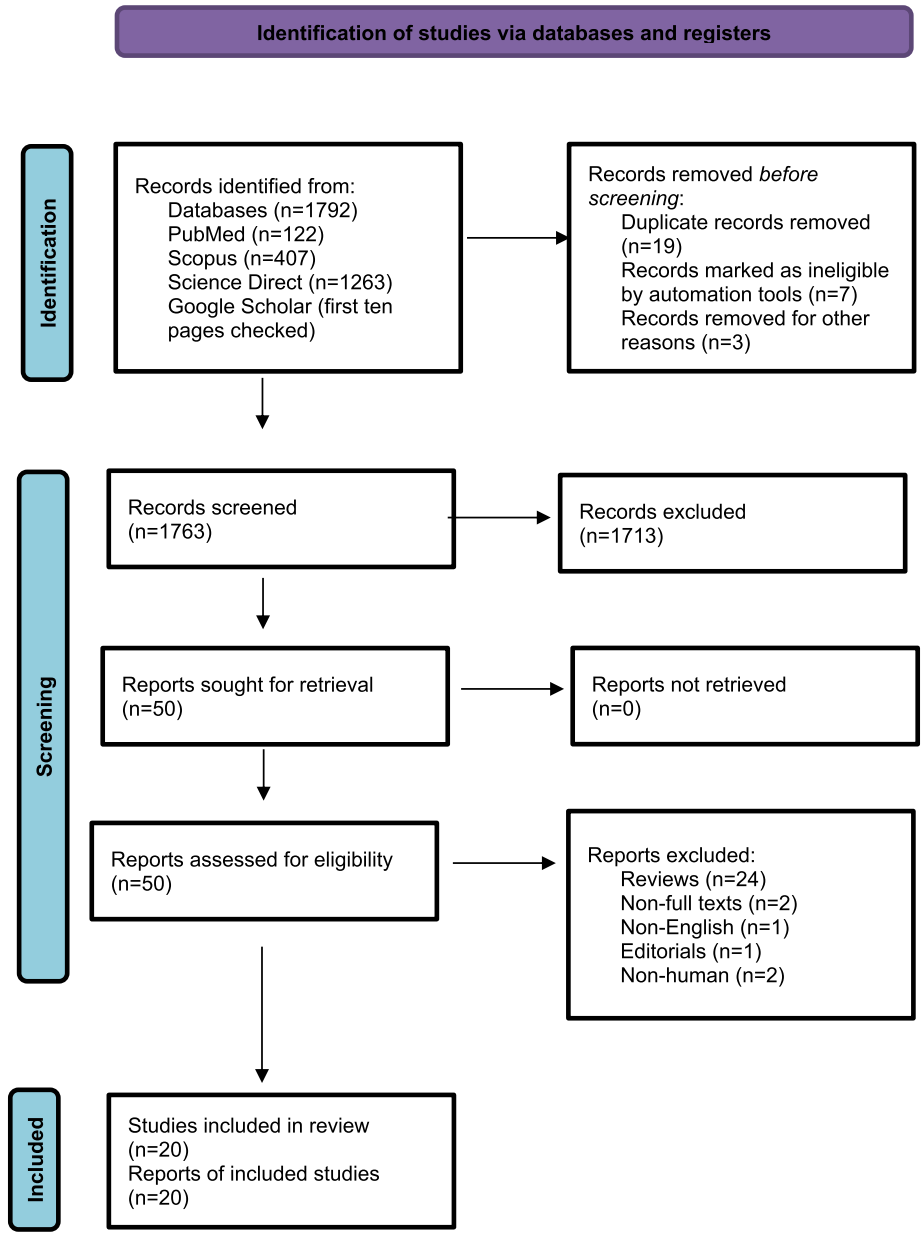

Fig. 1 PRISMA flowchart showing the study selection process

The authors concluded that the NAFLD group exhibited a significantly higher occurrence of cardiovascular accidents and renal impairment compared to the control group. Fracanzani et al. [39] aimed to assess the incidence of major cardiovascular events in patients with NAFLD and matched controls after a 10-year follow-up period. The authors concluded that there were thirty-five instances of major cardiovascular events observed, with a higher occurrence in subjects with NAFLD (17 out of 91, 19%) compared to controls (18 out of 182, 10%). The estimated cumulative risk was found to be significantly higher in the NAFLD group than in the control group. Another study by Hamaguchi et al. [40] investigated whether there is an elevated risk of cardiovascular disease associated with NAFLD. The authors noted that among 231 subjects with NAFLD at the beginning of the study, there was a higher occurrence of cardiovascular disease, including 5 cases of coronary heart disease, 6 cases of ischemic stroke, and 1 case of cerebral hemorrhage. In comparison, among 990 subjects without NAFLD, there were 3 cases of coronary heart disease, 6 cases of ischemic stroke, and 1 case of cerebral hemorrhage.

Table 2 Quality appraisal

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total
El Azeem et al. [23]	1	1	1	1	1	1	1	1	8
Al-hamoudi et al. [24]	1	1	1	1	1	1	1	1	8
Colak et al. [25]	1	1	1	1	1	1	0	0	6
Huseyin et al. [26]	1	1	1	1	1	1	1	0	7
Ibrahim et al. [27]	1	1	0	1	1	1	0	1	6
Jose et al. [28]	1	1	1	1	1	1	0	0	6
Long et al. [29]	1	0	1	0	1	1	0	0	4
Metin et al. [30]	1	1	1	1	1	1	1	0	7
Narayan et al. [31]	1	1	1	1	1	1	1	1	8
Ozturk et al. [32]	1	1	1	1	1	1	0	1	7
Sapmaz et al. [33]	1	1	1	1	1	1	0	0	6
Sayki et al. [34]	1	1	0	1	1	1	0	1	6
Senturk et al. [35]	1	1	1	1	1	1	1	1	8
Thakur et al. [36]	1	1	1	1	1	1	1	1	8
Villanova et al. [37]	1	1	1	1	1	1	1	1	8
Vlachopoulos et al. [38]	1	0	1	1	1	1	1	0	6
Fracanzani et al. [39]	1	1	1	1	1	1	1	1	8
Hamaguchi [40]	1	0	1	1	1	1	1	1	7
Stepanova & Younossi [41]	1	1	1	1	1	1	1	1	8

Item 1: Representativeness of the exposed cohort; Item 2: Selection of the non-exposed cohort; Item 3: Ascertainment of exposure; Item 4: Demonstration that outcome of interest was not present at start of study; Item 5: Comparability of cohorts on the basis of the design or analysis; Item 6: Assessment of outcome; Item 7: Was follow-up long enough for outcomes to occur; Item 8: Adequacy of follow up of cohorts

Stepanova, & Younossi, [41] explored the relationship between NAFLD, cardiovascular disease, and cardiovascular mortality. The author's findings indicated that NAFLD is independently associated with a higher risk of CVD. However, over a 14-year duration, NAFLD did not contribute to an increased risk of cardiovascular mortality. Ibrahim et al. [27] assessed the CVD risk in patients with NAFLD and examine the correlation between serum levels of selenoprotein P (SelP) and the risk of CVD in individuals with NAFLD. The authors found out that in young NAFLD patients without additional comorbidities, there is an increased risk of CVD. Long et al. [29] investigated the correlation between NAFLD and vascular function. Based on their analysis, the authors concluded that the association between NAFLD and various indicators of vascular function was primarily influenced by common cardiometabolic risk factors. However, the continued correlation observed in reduced peripheral arterial tonometry response, even after accounting for established risk factors, suggests that NAFLD could potentially contribute to microvascular dysfunction.

In the NAFLD group, there was a total of 1116 CVEs (36.2%), and in the non-NAFLD group, there was a total of 2807 CVEs (26.05%). NAFLD patients had a significantly higher risk of clinical CVE compared to controls (OR: 2.61; 95% CI: 1.41–4.83, $p < 0.002$) (Figs. 2 and 3). There was substantial heterogeneity observed among the included studies regarding the outcome of cardiovascular events (CVE), with an I-squared value of 91%.

Association of endothelial dysfunction risk and NAFLD

Al-Hamoudi et al. [24] Assessed endothelial function in patients with confirmed NAFLD through the evaluation of brachial artery flow-mediated dilatation (FMD). The author noted that the control group exhibited a higher mean FMD compared to the NAFLD group. Colak et al. [25] assessed the endothelial functions in individuals diagnosed with NAFLD. The authors reported that NAFLD is linked to endothelial dysfunction and is observed to occur earlier in patients with atherosclerosis compared to control subjects. A study by Huseyin et al. [26] examined the presence of endothelial dysfunction in patients with NASH and investigated whether serum levels of liver enzymes could indicate the severity of this endothelial dysfunction. The authors reached the conclusion that individuals diagnosed with NASH exhibited impaired FMD and increased carotid artery intima-media thickness (CIMT) in comparison to healthy control subjects. A cohort study by Jose et al. [28] examined the differences in flow-mediated dilatation between individuals with NAFLD and those without any liver abnormalities. The authors reported that individuals with fatty livers demonstrated a lower level of flow-mediated vasodilation compared to those with a healthy liver. Metin et al. [30]

Table 3 Study descriptor table

Author and Year of publication	Study design	Geographic location	NAFLD diagnosis	Cuff inflation	Study group		Control group	
					Population	N	Population	N
El Azeem et al. [23]	Prospective observational cohort study	Middle East	Liver function test	NA	NAFLD	747	Healthy	268
Al-hamoudi et al. [24]	Prospective cohort study	Middle East	Liver biopsy	200 mmHg	NAFLD + NASH	89	NA	50
Colak et al. [25]	Observational case–control study	NA	Liver biopsy	200 mmHg	NAFLD + NASH	51	Healthy	21
Huseyin et al. [26]	Cohort study	Europe	Liver biopsy	50 mmHg above SBP	NASH	50	Healthy, age- and sex-matched	30
(Ibrahim et al. [27]	Observational cohort study	Europe	Biochemical, radiological, and histological criteria	50 mmHg above SBP	NAFLD + NASH	93	Healthy and age- and sex-matched	37
Jose et al. [28]	Comparative cohort study	Asia	Liver ultrasound	250 mmHg	NAFLD	25	NA	25
Long et al. [29]	Cross-sectional study	NA	Multi-detector abdominal CT	NA	NAFLD	350	NA	1934
Metin et al. [30]	Cohort study	NA	Liver ultrasound	250 mmHg	NAFLD	117	NA	44
Narayan et al. [31]	Case–control study	Asia	Liver ultrasound	250 mmHg	NAFLD	126	HBV	31
Ozturk et al. [32]	Cross-sectional study	Europe	Liver biopsy	200 mmHg	NAFLD + NASH	61	Healthy	41
Sapmaz et al. [33]	Cross-sectional study	Europe	Liver ultrasound	50 mmHg above SBP	NAFLD	176	NA	90
Sayki et al. [34]	Prospective longitudinal cohort study	NA	Biochemical, radiological, and histological criteria	250 mmHg	NAFLD	100	Healthy, age- and sex-matched	45
Senturk et al. [35]	Comparative cohort study	Europe	Liver biopsy	NA	NAFLD + NASH	32	Healthy	16
Thakur et al. [36]	Cross-sectional study	Asia	Liver ultrasound	250 mmHg	NAFLD	40	Healthy and age- and sex-matched	40
Villanova et al. [37]	Cohort study	Europe	Biochemical and radiological criteria	250 mmHg	NAFLD	52	Age- and sex-matched without metabolic diseases	28
Vlachopoulos et al. [38]	Cohort study	Europe	Liver biopsy	NA	NAFLD	23	Age-, gender-, BMI-, and CVRF-matched	28
Fracanzani et al. [39]	Longitudinal cohort study	Europe	Assessment of fatty liver by ultrasonography, liver histology, and carotid atherosclerosis	200 mmHg	NAFLD	91	Negative for hepatitis B and C and had normal liver function tests	182
Hamaguchi [40]	Prospective observational study	Asia	Abdominal ultrasonography	NA	NAFLD	1647	Healthy	1335
Stepanova & Younossi [41]	Prospective cohort study	North America	Liver ultrasound	NA	NAFLD	2492	Healthy	9121
Pugh et al. [42]	Randomized controlled trial	NA	Magnetic resonance spectroscopy	220 mmHg	NAFLD	34	Obese	20

SBP Systolic blood pressure, *NAFLD* Nonalcoholic fatty liver disease, *NASH* Nonalcoholic steatohepatitis, *HBV* Hepatitis B virus, *CVRF* Cardiovascular risk factors

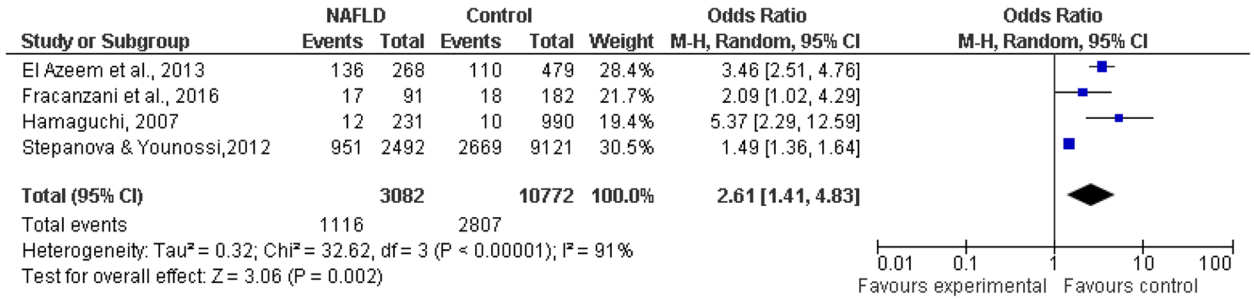

Fig. 2 OR results for cardiovascular risk

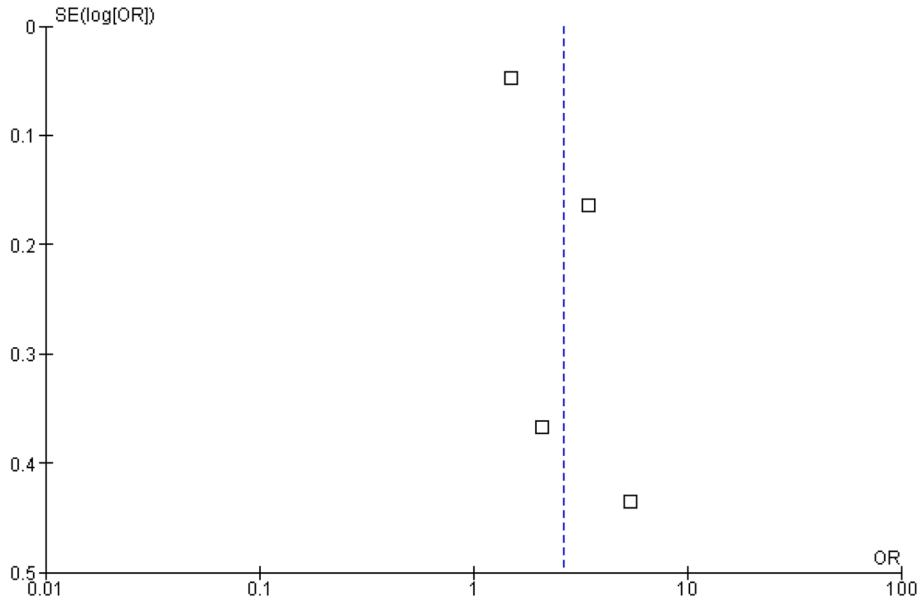

Fig. 3 Funnel plot

assessed the presence of early markers of atherosclerosis in individuals diagnosed with NAFLD. The authors found that NAFLD is linked to diminished FMD compared to the healthy control group. This indicator is considered early signs of atherosclerosis. Narayan et al. [31] examined cardiovascular risk factors, specifically percentage FMD and CIMT, in individuals diagnosed with NAFLD. The authors concluded that patients with NAFLD exhibited significantly elevated markers of endothelial dysfunction compared to the control group. Ozturk et al. [32] investigated the correlation between NAFLD and subclinical atherosclerosis in adult male patients. The authors' conclusion stated that the presence of NAFLD in adult male patients independently contributes to a heightened risk of endothelial dysfunction and atherosclerosis. A randomized controlled study by Pugh et al. [42] investigated the link between liver fat, visceral adipose tissue (VAT), and endothelial dysfunction in obese patients diagnosed with NAFLD. The authors discovered that the presence of endothelial dysfunction in NAFLD cannot be solely attributed to excessive VAT, but they also observed that exercise training can effectively reverse this dysfunction. Sapmaz et al. [33] determined, in a prospective manner, whether steatosis or fibrosis score plays a more significant role in the development of endothelial dysfunction in patients with NAFLD. Based on their findings, the authors concluded that there is an association between endothelial dysfunction and steatosis in patients diagnosed with NAFLD. Sayki et al. [34] assessed the endothelial function and cardiovascular risk profile in individuals with NAFLD and investigated whether there is an association between these parameters and metabolic syndrome (MS). The author's findings revealed that patients with NAFLD have an elevated risk of cardiovascular events. Furthermore, the association with MS further increases this risk. Senturk et al. [35] examined the dilation of the brachial artery in patients with NAFLD, specifically evaluating endothelial-dependent dilatation

(EDD) and endothelial-independent dilatation (EID). The authors discovered that patients diagnosed with NASH exhibited notably more severe endothelial dysfunction in comparison to patients with simple steatosis as well as individuals in good health. Thakur et al. [36] investigated the connection between subclinical atherosclerosis, endothelial dysfunction, and NAFLD in individuals of Asian Indian descent. Based on their analysis, the authors concluded that among Asian Indians, NAFLD is significantly linked to subclinical atherosclerosis and endothelial dysfunction, regardless of obesity and metabolic syndrome. According to Villanova et al. [37] report, there was a moderate increase in the 10-year probability of cardiovascular events among individuals with NAFLD, particularly in those diagnosed with NASH. A cohort study by Vlachopoulos et al. [38] explored the associations between NAFLD and functional changes in arteries as well as early signs of atherosclerosis. Based on their findings, the authors concluded that NAFLD is linked to both arterial stiffness and endothelial dysfunction.

According to the findings from our meta-analysis, individuals diagnosed with NAFLD exhibited significantly lower brachial FMD compared to their respective control groups (standardized mean difference: -4.63, 95% confidence interval: -5.68 to -3.58, $p<0.0001$) (Figs. 4 and 5). However, there was notable heterogeneity observed among the included studies (I-squared = 92%).

We analyzed studies involving participants who were diagnosed with either histologically confirmed NASH or pure steatosis (Figs. 6 and 7). According to these findings, individuals diagnosed with non-alcoholic steatohepatitis (NASH) exhibited significantly lower FMD values in comparison to those with pure steatosis (standardized mean difference: -3.84, 95% confidence interval -7.56 to -0.13, $p=0.03$, I2 = 66%).

Discussion

NAFLD has become an important public health problem with its increasing prevalence worldwide. NAFLD encompasses a range of liver disorders characterized by excessive accumulation of fat in the liver in the absence of significant alcohol consumption. It is now clear that NAFLD is not just a liver-centered disease, but a multifactorial disease with multiple effects on the liver. Notably, increasing evidence suggests that NAFLD is closely associated with cardiovascular complications, making it a topic of great interest in the field of cardiovascular research. In this systematic literature review, we sought to evaluate the association of endothelial dysfunction, assessed by FMD of the brachial artery, with NAFLD. Additionally, we aim to examine the relationship between NAFLD and clinical cardiovascular events. By synthesizing and analyzing the available evidence, we sought to further our understanding of the interplay between NAFLD, endothelial dysfunction, and cardiovascular risk.

The results from this systematic literature review show a consistent association between NAFLD and endothelial dysfunction. Several studies have reported significantly elevated markers of endothelial dysfunction, impaired FMD and increased CIMT in individuals with NAFLD compared to control subjects [Al-Hamoudi et al., [24]; Colak et al., [25]; Huseyin et al., [26]; Jose et al., [28]; Metin et al., [30]; Narayan et al., [31]; Dogru et al., [43]; Fan et al., [44]] Some of these studies reveal that patients

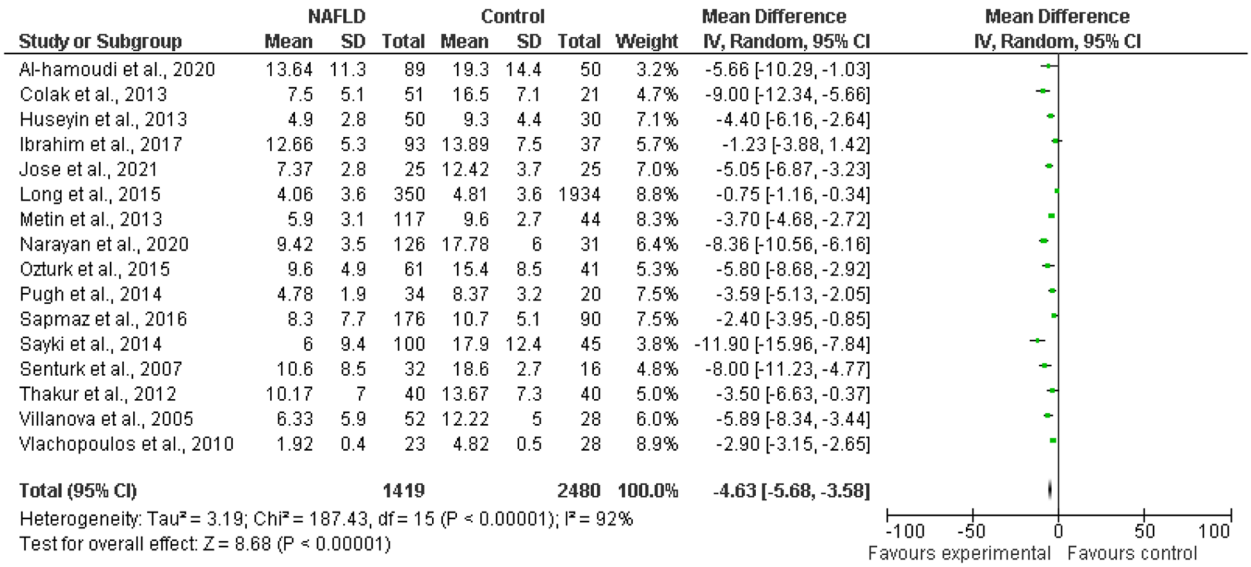

Fig. 4 Forest plot displaying the meta-analysis of FMD difference between individuals with NAFLD and controls

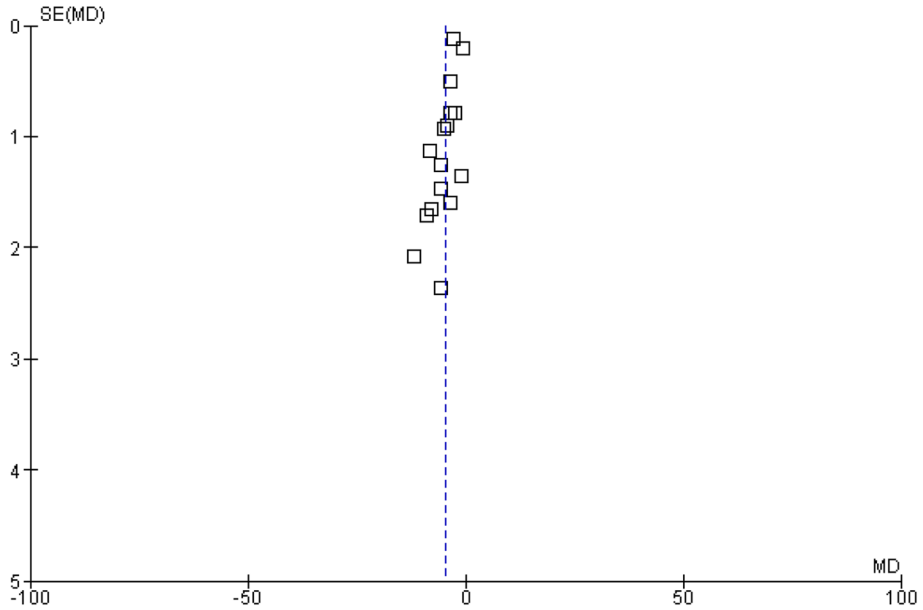

Fig. 5 Funnel plot

Study or Subgroup	NASH Mean	NASH SD	NASH Total	Pure steatosis Mean	Pure steatosis SD	Pure steatosis Total	Weight	Mean Difference IV, Random, 95% CI
Ozturk et al., 2015	9.2	4.3	39	10.2	5.8	22	32.0%	-1.00 [-3.77, 1.77]
Ibrahim et al., 2017	12.66	5.3	11	13.89	7.5	18	24.1%	-1.23 [-5.90, 3.44]
Colak et al., 2013	7.5	5.1	43	16.5	7.1	8	22.3%	-9.00 [-14.15, -3.85]
Al-hamoudi et al., 2020	13.64	11.3	42	19.3	14.4	47	21.6%	-5.66 [-11.01, -0.31]
Total (95% CI)			**135**			**95**	**100.0%**	**-3.84 [-7.56, -0.13]**

Heterogeneity: Tau² = 9.20; Chi² = 8.70, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 2.03 (P = 0.04)

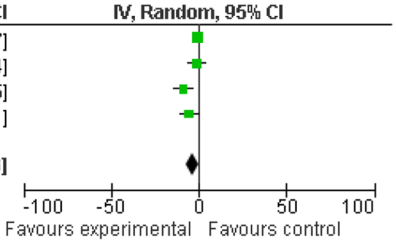

Fig. 6 FMD difference between individuals with NASH and pure steatosis

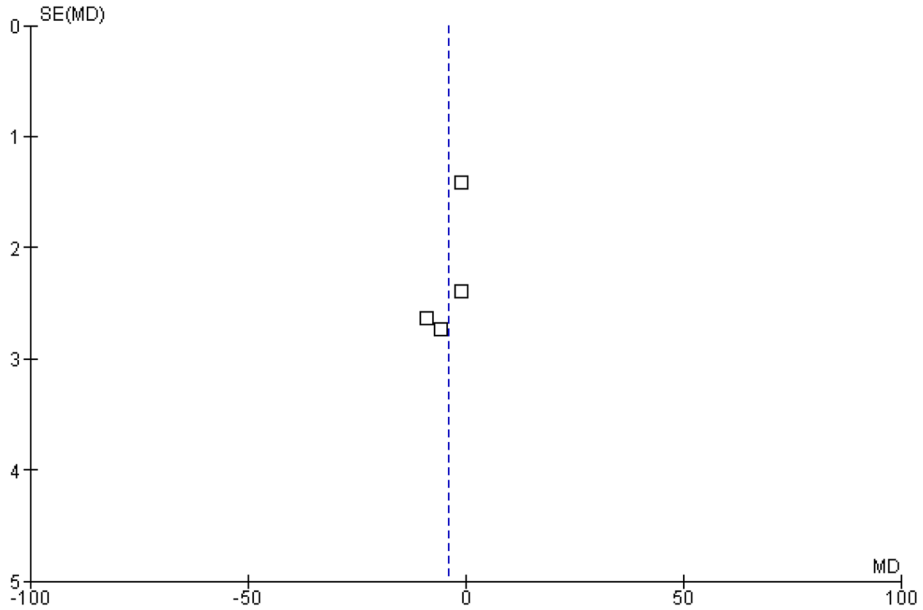

Fig. 7 Funnel plot

with NAFLD exhibit lower levels of flow-mediated vasodilation compared to individuals with a healthy liver. This further supports the notion that NAFLD is associated with endothelial dysfunction and impaired vascular function, suggesting the presence of early signs of atherosclerosis. Furthermore, it was observed that NAFLD independently contributes to a heightened risk of endothelial dysfunction and atherosclerosis, irrespective of the presence of metabolic syndrome (Ozturk et al., [32]). These findings underscore the need to consider NAFLD as an independent risk factor for cardiovascular disease.

Interestingly, excessive visceral adipose tissue (VAT), though associated with endothelial dysfunction, was not found to be the sole contributor of endothelial dysfunction in obese NAFLD patients (Pugh et al., [42]). Exercise training was identified as a potential intervention that can effectively reverse endothelial dysfunction in NAFLD. This suggests that lifestyle modifications, such as regular physical activity, may have a positive impact on vascular function in patients with NAFLD. Steatosis was found to be significantly associated with endothelial dysfunction in NAFLD patients (Sapmaz et al., [33]). Additionally, patients diagnosed with NASH were found to exhibit more severe endothelial dysfunction compared to those with simple steatosis and individuals in good health (Senturk et al., [35]). These findings highlight the potential impact of disease progression on endothelial function in NAFLD. A study among individuals of Asian Indian descent (Thakur et al., [36]) also identified a significant association between NAFLD and subclinical atherosclerosis, as well as endothelial dysfunction. This association remained significant even after controlling for obesity and metabolic syndrome, suggesting that NAFLD itself contributes to cardiovascular risk in this population. Furthermore, the findings from Villanova et al. [37] revealed a moderate increase in the 10-year probability cardiovascular events among individuals with NAFLD, particularly those diagnosed with NASH. Fracanzani et al. [39] reported a higher incidence of major cardiovascular events in subjects with NAFLD compared to controls during a 10-year follow-up period. The cumulative risk of cardiovascular events was significantly higher in the NAFLD group. Stepanova and Younossi [41] found that NAFLD was independently associated with a higher risk of cardiovascular disease but did not contribute to an increased risk of cardiovascular mortality over a 14-year duration. Ibrahim et al. [27] found an increased risk of CVD, particularly in young NAFLD patients without additional comorbidities. Long et al. [29] concluded that while the association between NAFLD and vascular function was primarily influenced by common cardiometabolic risk factors, there was evidence of reduced peripheral arterial tonometry response, suggesting a potential contribution of NAFLD to microvascular dysfunction.

Hamaguchi et al. [40], Targher et al. [45] and Kasper et al. [46] reported a higher occurrence of cardiovascular accidents and major cardiovascular events including strokes, in individuals with NAFLD compared to control subjects. El Azeem et al. [23] and Lonardo et al. [47], reported a higher occurrence of cardiovascular accidents and renal impairment in individuals with NAFLD compared to the control group. Overall, these findings highlight the significant association between NAFLD and cardiovascular events. NAFLD, and NASH particularly appears to independently increase the risk of cardiovascular disease, including major cardiovascular events, coronary heart disease, stroke, and renal impairment. Understanding and managing the cardiovascular risks associated with NAFLD are crucial for preventive strategies and optimal patient care.

Our systematic literature review consistently demonstrated an association between endothelial dysfunction, NAFLD, and an increased cardiovascular risk profile. The main findings from the reviewed studies indicate that individuals with NAFLD exhibit impaired endothelial function, as evidenced by reduced FMD and increased CIMT. These indicators suggest early signs of atherosclerosis and are associated with a heightened risk of cardiovascular events. The observed link between endothelial dysfunction and NAFLD highlights the need for comprehensive cardiovascular risk management in patients diagnosed with NAFLD. While the exact mechanisms underlying this association require further investigation, it is important to recognize the role of NAFLD as a potential contributor to endothelial dysfunction and subsequent cardiovascular complications. Reinforcing the association between endothelial dysfunction, NAFLD, and the cardiovascular risk profile, is crucial for enhancing clinical awareness and improving patient outcomes. The noted high heterogeneity warrants a detailed exploration of potential sources contributing to this variability. Several factors may account for the observed heterogeneity, including variations in study populations, differences in methodological approaches among included studies, and diverse diagnostic criteria for NAFLD. Furthermore, variations in outcome measurements, study designs, and patient characteristics may contribute to the overall heterogeneity.

Healthcare providers should prioritize comprehensive cardiovascular risk assessment and management strategies in individuals with NAFLD, including lifestyle modifications, such as exercise training, weight loss, and optimal metabolic control.

However, further research is warranted to address several aspects. Future studies should explore the temporal relationship between NAFLD and endothelial dysfunction through longitudinal designs, assessing whether endothelial dysfunction precedes or develops concomitantly with NAFLD. Additionally, standardized methodologies for assessing endothelial dysfunction in NAFLD should be established, considering confounding factors and utilizing comprehensive markers of vascular function. Continued research efforts in this field will enable a better understanding of the underlying mechanisms, identify novel therapeutic targets, and develop targeted interventions to mitigate the cardiovascular risk associated with NAFLD.

Nonetheless, it is crucial to acknowledge and address potential biases and limitations in our search strategy. First, the inclusion of only studies published in English may introduce language bias, as relevant non-English publications might have been overlooked. Additionally, the choice of specific databases, while comprehensive, may have inherent limitations, as different databases vary in terms of coverage and indexing. This could potentially result in the exclusion of pertinent studies that may have been indexed differently or housed in less conventional databases. Moreover, the decision to impose a date range restriction warrants consideration, as it may lead to the exclusion of older studies that could contribute valuable insights.

By integrating the findings from these studies into clinical practice, we can improve patient care, optimize cardiovascular risk management, and ultimately reduce the burden of cardiovascular disease in individuals with NAFLD.

Conclusion

Our systematic literature review provides compelling evidence for the association between endothelial dysfunction, as assessed by FMD of the brachial artery, and NAFLD. Our meta-analysis revealed that individuals diagnosed with NAFLD exhibited significantly lower FMD values compared to their respective control groups. Moreover, when we specifically analyzed studies involving participants with NASH or pure steatosis, we found that individuals with NASH had even lower FMD values compared to those with pure steatosis. These findings highlight the detrimental impact of NAFLD, particularly NASH, on endothelial function. Furthermore, our review also sheds light on the clinical implications of NAFLD. We observed that patients with NAFLD had a significantly higher risk of clinical CVE when compared to controls. This suggests that NAFLD may serve as a potential risk factor for the development of cardiovascular diseases.

Taken together, our findings emphasize the importance of assessing endothelial function in individuals with NAFLD, as it may serve as a valuable biomarker for cardiovascular risk assessment. Additionally, identifying NASH within the NAFLD spectrum appears to be particularly relevant, as it is associated with further impairment of endothelial function. These results have implications for clinical practice, highlighting the need for comprehensive cardiovascular risk management in individuals diagnosed with NAFLD, particularly those with NASH.

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
FMD	Flow-mediated dilation
CVE	Cardiovascular events
NASH	Non-alcoholic steatohepatitis
MASLD	Metabolic-associated steatotic liver disease
SLD	Steatotic liver disease
CVD	Cardiovascular diseases
MAFLD/MetALD	Metabolic-associated fatty liver disease
EDD	Endothelial-dependent dilatation
SMD	Standardized mean differences
CI	Confidence intervals
SBP	Systolic blood pressure
CVRF	Cardiovascular risk factors
SeIP	Selenoprotein P
CIMT	Carotid artery intima-media thickness
VAT	Visceral adipose tissue
MS	Metabolic syndrome
EID	Endothelial-independent dilatation

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Authors' contributions
RA raised the research question and approached other authors related to concerned specialties. RA also interpreted & analyzed cardiovascular findings. All authors did online data search, collected the relevant studies and analyzed the results. PP helped in interpretation of various histopathological findings in the disease spectrum. PV interpreted the liver disease severity & its impact. TN contributed in writing and drafting the manuscript. All authors read and approved the final manuscript.

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Competing interests
All the authors declare that they have no competing interests.

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