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The Association of Nonalcoholic Fatty Liver Disease with Subclinical Atherosclerosis: A Systematic Review

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ABSTRACT

Introduction: Nonalcoholic Fatty Liver Disease (NAFLD) has emerged as a global public health issue, increasingly recognized for its strong association with cardiovascular disease (CVD), the leading cause of mortality in this patient population. This systematic review aims to comprehensively evaluate and synthesize the evidence linking NAFLD to a wide array of markers for subclinical atherosclerosis, the earliest detectable stage of CVD.

Methods: A systematic search of PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library databases was conducted for observational studies investigating the association between NAFLD and subclinical atherosclerosis. The review adhered to the Preferred Reporting Items for Systematic Reviews

(PRISMA) guidelines. Included studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS).

Results: Synthesis of data from 17 selected high-quality observational studies, encompassing tens of thousands of participants, revealed a consistent and statistically significant association between NAFLD and multiple indices of subclinical atherosclerosis. Specifically, NAFLD was linked to increased carotid intima-media thickness (CIMT), a higher prevalence of carotid plaques, elevated coronary artery calcification (CAC) scores, and accelerated CAC progression. Furthermore, NAFLD was associated with significant functional vascular impairments, including endothelial dysfunction (manifested as reduced flow-mediated dilation) and increased arterial stiffness (measured by pulse wave velocity). These associations frequently persisted after adjustment for traditional metabolic risk factors.

Discussion: The findings support the biological plausibility of NAFLD as an active contributor to atherogenesis, not merely a passive bystander. Shared pathophysiological mechanisms, including systemic inflammation, insulin resistance, and atherogenic dyslipidemia, likely drive this liver-vessel axis. The presence of NAFLD may serve as a clinical risk enhancer, identifying individuals with a heightened burden of subclinical vascular disease who might be missed by conventional risk scoring.

Conclusion: NAFLD is a robust indicator for the presence of multi-site subclinical atherosclerosis. These findings underscore the importance of cardiovascular surveillance and aggressive risk

and Meta-Analyses

factor management in individuals diagnosed with NAFLD to mitigate the long-term risk of cardiovascular events.

Keywords: Nonalcoholic Fatty Liver Disease; Subclinical Atherosclerosis; Carotid Intima-Media Thickness; Coronary Artery Calcification; Endothelial Dysfunction; Arterial Stiffness.

INTRODUCTION

Background: The Growing Epidemic of NAFLD and its Systemic Impact

Nonalcoholic fatty liver disease (NAFLD) is defined by the excessive accumulation of fat (steatosis) in more than 5% of hepatocytes, occurring in the absence of significant alcohol consumption, viral hepatitis, or other specific causes of liver disease (Ludwig et al., 1980; Fracanzani et al., 2016). It has become the most common chronic liver condition globally, representing a significant public health challenge. The prevalence of NAFLD is estimated to affect approximately 25-30% of the world's adult population, with rates escalating to between 40% and 70% in high-risk groups such as individuals with obesity or type 2 diabetes mellitus (T2DM) (Mahfood Haddad et al., 2016).

NAFLD encompasses a spectrum of conditions, ranging from simple steatosis (nonalcoholic fatty liver, or NAFL), which is often considered benign, to nonalcoholic steatohepatitis (NASH). NASH is a more aggressive form of the disease characterized by hepatic inflammation and cellular injury, which can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma. Reflecting its deep-rooted connection to metabolic derangements, a recent international expert consensus has proposed renaming NAFLD to metabolic (dysfunction)-associated fatty liver disease (MAFLD). This new terminology utilizes positive diagnostic criteria—requiring evidence of hepatic steatosis plus either overweight/obesity, T2DM, or other evidence of metabolic dysregulation—thereby moving away from a diagnosis of exclusion and placing metabolic health at the core of the disease's identity. This conceptual shift underscores the systemic nature of the disease and reinforces the biological rationale for investigating its link to extrahepatic complications like atherosclerosis (Targher et al., 2010). While this review acknowledges the importance of the MAFLD paradigm, it will primarily use the term NAFLD to maintain consistency with the terminology used in the vast majority of the cited literature.

The Cardiovascular Burden in NAFLD

While the hepatic consequences of NAFLD are significant, the primary driver of mortality in this patient population is not liver failure but cardiovascular disease (CVD) (Targher et al., 2010). A large body of evidence from prospective and retrospective studies has established NAFLD as an independent risk factor for both fatal and non-fatal cardiovascular events (Mahfood Haddad et al., 2016). Individuals with NAFLD are estimated to have a 57% to 69% increased risk of CVD, an association that persists even after accounting for shared traditional risk factors such as obesity, hypertension, dyslipidemia, and T2DM. This highlights a critical need to identify and manage cardiovascular risk at its earliest, preclinical stage in the burgeoning NAFLD population. Subclinical atherosclerosis, the silent and asymptomatic phase of vascular disease, represents the ideal target for early detection and intervention (Mahfood Haddad et al., 2016).

Pathophysiological Mechanisms Linking NAFLD and Atherosclerosis

The strong association between NAFLD and atherosclerosis is underpinned by a complex interplay of shared pathophysiological mechanisms, positioning the liver not as a passive bystander but as an active contributor to the atherogenic process (Targher et al., 2010). Key drivers of this liver-vessel axis include insulin resistance, systemic inflammation, and atherogenic dyslipidemia. Central to the pathogenesis of both NAFLD and T2DM, insulin resistance promotes hepatic fat accumulation and concurrently contributes to endothelial dysfunction and vascular inflammation. The steatotic and inflamed liver in NAFLD/NASH also becomes a source of pro-inflammatory cytokines and acute-phase reactants, creating a chronic, low-grade systemic inflammatory state that promotes the formation and destabilization of atherosclerotic plaques. Finally, NAFLD is characteristically associated with a pro-atherogenic lipid profile, featuring hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, and a predominance of small, dense, and highly atherogenic low-density lipoprotein (LDL) particles (Targher et al., 2010).

Rationale, Objectives, and Hypothesis

Research Gap: While numerous studies have investigated the link between NAFLD and individual markers of subclinical atherosclerosis, there is a need for a comprehensive systematic review that synthesizes the evidence across a broad spectrum of these markers. Such a review can provide a holistic understanding of the extent and nature of early vascular damage in the NAFLD population (Targher et al., 2010).

Objectives: The primary objective of this systematic review is to synthesize and critically evaluate the evidence from observational studies on the association between NAFLD and a comprehensive panel of subclinical atherosclerosis markers. These markers include structural indicators (carotid intima-media thickness, carotid plaque, coronary artery calcification), functional indicators (flow-mediated dilation, pulse wave velocity), and other emerging markers of cardiovascular risk.

Hypothesis: It is hypothesized that the presence and severity of NAFLD are significantly and independently associated with evidence of subclinical atherosclerosis across multiple vascular beds and functional domains.

Novelty: The novelty of this review lies in its exhaustive scope, synthesizing data from at least 17 distinct studies to examine over 15 different outcome measures. This approach aims to construct a detailed and compelling picture of NAFLD's impact on the entire spectrum of early atherogenesis, from initial endothelial dysfunction to established structural plaque formation and calcification.

METHODS

Protocol and Reporting

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to ensure methodological transparency and rigor.

Search Strategy

A comprehensive and systematic literature search was performed across three major electronic databases: PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library. The search was conducted to identify all relevant studies published up to October 2024, with no restrictions on language or publication date. The search strategy combined Medical Subject Headings (MeSH) and free-text words related to the exposure (NAFLD) and the outcomes of interest (subclinical atherosclerosis).

Eligibility Criteria

Studies were selected for inclusion based on the following predefined criteria:

Inclusion Criteria:

1. **Study Design:** Observational studies, including cross-sectional, case-control, and cohort designs.
2. **Population:** Adult human participants (>18 years of age).
3. **Exposure:** A clear diagnosis of NAFLD based on established imaging techniques (ultrasonography, computed tomography, or magnetic resonance imaging) or liver biopsy.
4. **Comparator:** A control group of participants without NAFLD.
5. **Outcomes:** Reporting of at least one quantifiable measure of subclinical atherosclerosis, such as CIMT, presence of carotid plaque, CAC score, FMD, or PWV.
6. **Data Availability:** Provision of effect estimates (e.g., Odds Ratio, Hazard Ratio, Mean Difference) with 95% confidence intervals (CIs) or sufficient raw data to allow for their calculation.

Exclusion Criteria:

1. Studies conducted exclusively in pediatric or adolescent populations.
2. Studies lacking a non-NAFLD comparator group.

3. Non-original research articles, such as case reports, editorials, letters to the editor, and review articles.
4. Studies that focused solely on clinical cardiovascular events (e.g., myocardial infarction, stroke) without reporting on subclinical markers.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Adults	Adult Population	Patients (with NAFLD)	Human Participants
Intervention (I)	Nonalcoholic Fatty Liver Disease (NAFLD)	Hepatic Steatosis	Metabolic (dysfunction)-associated fatty liver disease (MAFLD)	Nonalcoholic Steatohepatitis (NASH)
Comparison (C)	Without NAFLD	Control Group	Non-NAFLD (comparator group)	Healthy Controls
Outcome (O)	Subclinical Atherosclerosis	Carotid Intima-Media Thickness (CIMT)	Coronary Artery Calcification (CAC)	Endothelial Dysfunction

The Boolean MeSH keywords inputted on databases for this research are: *("Adults" OR "Adult Population" OR "Patients" OR "Human Participants") AND ("Nonalcoholic Fatty Liver Disease (NAFLD)" OR "Hepatic Steatosis" OR "Metabolic (dysfunction)-associated fatty liver disease (MAFLD)" OR "Nonalcoholic Steatohepatitis (NASH)") AND ("Without NAFLD" OR*

"Control Group" OR "Non-NAFLD" OR "Healthy Controls") AND ("Subclinical Atherosclerosis" OR "Carotid Intima-Media Thickness (CIMT)" OR "Coronary Artery Calcification (CAC)" OR "Endothelial Dysfunction")

Study Selection and Data Extraction

Two independent reviewers screened the titles and abstracts of all retrieved records to identify potentially relevant studies. The full texts of these selected articles were then assessed for final eligibility against the inclusion criteria. Any disagreements between the reviewers during the screening or eligibility assessment were resolved through discussion and consensus, with arbitration by a third reviewer if necessary. A standardized data extraction form was used to collect relevant information from each included study, including author, year, study design, sample size, population characteristics, NAFLD diagnostic method, atherosclerosis markers, and primary outcomes.

Quality and Risk of Bias Assessment

The methodological quality and risk of bias of each included observational study were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). The NOS is a validated tool designed for non-randomized studies and evaluates quality across three key domains: Selection (up to 4 stars), Comparability (up to 2 stars), and Outcome (up to 3 stars). Studies were awarded a star for each quality item met, with a maximum possible score of nine stars. Based on the total score, studies were categorized as high quality (7–9 stars), fair quality (4–6 stars), or low quality (0–3 stars). The results of this quality assessment are summarized in Table 2.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Adults" OR "Adult Population" OR "Patients" OR "Human Participants") AND ("Nonalcoholic Fatty Liver Disease (NAFLD)" OR "Hepatic Steatosis" OR "Metabolic (dysfunction)-associated fatty liver disease (MAFLD)" OR "Nonalcoholic Steatohepatitis (NASH)") AND "Without NAFLD" OR "Control Group" OR "Non-NAFLD" OR "Healthy Controls" AND ("Subclinical Atherosclerosis" OR "Carotid Intima-Media Thickness (CIMT)" OR "Coronary Artery Calcification (CAC)" OR "Endothelial Dysfunction")*	127
Semantic Scholar	*("Adults" OR "Adult Population" OR "Patients" OR "Human Participants") AND ("Nonalcoholic Fatty Liver Disease (NAFLD)" OR "Hepatic Steatosis" OR "Metabolic (dysfunction)-associated fatty liver disease (MAFLD)" OR "Nonalcoholic Steatohepatitis (NASH)") AND ("Without NAFLD" OR "Control Group" OR "Non-NAFLD" OR "Healthy Controls") AND ("Subclinical Atherosclerosis" OR "Carotid Intima-Media Thickness (CIMT)" OR "Coronary Artery Calcification (CAC)" OR "Endothelial Dysfunction")*	250
Springer	*("Adults" OR "Adult Population" OR "Patients" OR "Human Participants") AND ("Nonalcoholic Fatty Liver Disease (NAFLD)" OR "Hepatic Steatosis" OR "Metabolic (dysfunction)-associated fatty liver disease (MAFLD)" OR "Nonalcoholic Steatohepatitis (NASH)") AND ("Without NAFLD" OR "Control Group" OR "Non-NAFLD" OR "Healthy Controls") AND ("Subclinical Atherosclerosis" OR "Carotid Intima-Media Thickness (CIMT)" OR "Coronary Artery Calcification (CAC)" OR "Endothelial Dysfunction")*	935
Google Scholar	*("Adults" OR "Adult Population" OR "Patients" OR "Human Participants") AND ("Nonalcoholic Fatty Liver Disease (NAFLD)" OR "Hepatic Steatosis" OR "Metabolic (dysfunction)-associated fatty liver disease (MAFLD)" OR "Nonalcoholic Steatohepatitis (NASH)") AND ("Without NAFLD" OR "Control Group" OR "Non-NAFLD" OR "Healthy Controls") AND ("Subclinical Atherosclerosis" OR "Carotid Intima-Media Thickness (CIMT)" OR "Coronary Artery Calcification (CAC)" OR "Endothelial Dysfunction")*	7,320
Wiley Online Library	*("Adults" OR "Adult Population" OR "Patients" OR "Human Participants") AND ("Nonalcoholic Fatty Liver Disease (NAFLD)" OR "Hepatic Steatosis" OR "Metabolic (dysfunction)-associated fatty liver disease (MAFLD)" OR "Nonalcoholic Steatohepatitis (NASH)") AND ("Without NAFLD" OR "Control Group" OR "Non-NAFLD" OR "Healthy Controls") AND ("Subclinical Atherosclerosis" OR "Carotid Intima-Media Thickness (CIMT)" OR "Coronary Artery Calcification (CAC)" OR "Endothelial Dysfunction")*	17

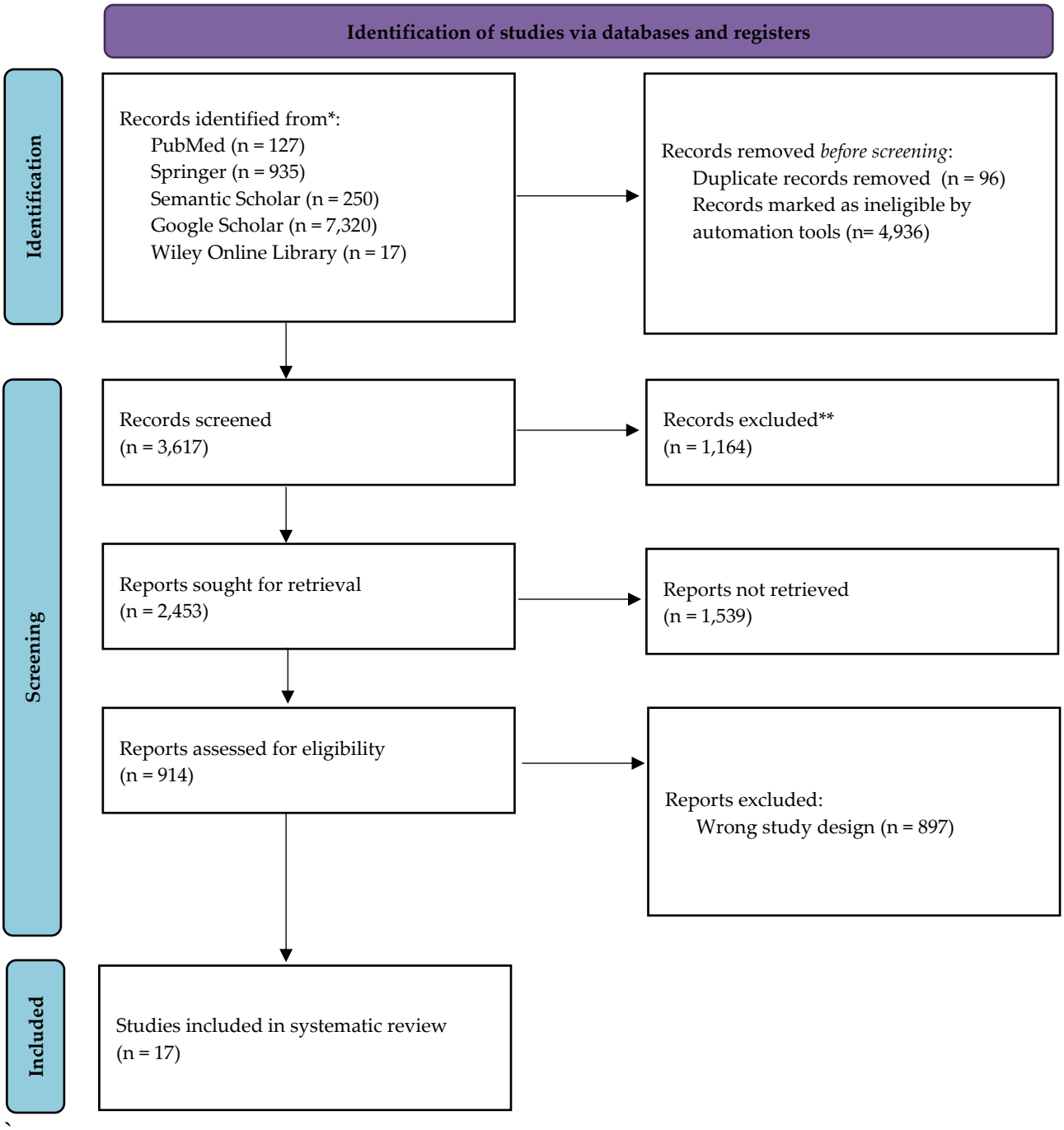

Figure 1. Article search flowchart

RESULTS

Study Characteristics

Ultimately, 17 observational studies met all inclusion criteria and were included in this systematic review. The included studies were published between 2005 and 2019 and were conducted across various countries in Europe, Asia, and North America, reflecting the global interest in this topic. The total number of participants across all studies was 42,308, including 11,546 patients with NAFLD and 30,762 controls. The diagnosis of NAFLD was primarily made using ultrasonography. Detailed characteristics of each included study are presented in Table 1.

Table 1. Characteristics of Included Studies

First Author (Year)	Country	Study Design	Participants (NAFLD/Control)	Mean Age (years)	% Male	NAFLD Diagnostic Method	Subclinical Atherosclerosis Marker(s)
Brea A et al. (2005)	Spain	Case-Control	40 / 40	53.2 / 51.6	50.0	Ultrasound	CIMT, Carotid Plaque
Volzke H et al. (2005)	Germany	Cross-Sectional	1262 / 2960	~54	~50	Ultrasound	CIMT, Carotid Plaque

Villanova N et al. (2005)	Italy	Case-Control	52 / 28	44.0 / 44.0	80.8	Ultrasound, Biopsy	FMD
Targher G et al. (2007)	Italy	Case-Control	125 / 250	48.0 / 48.0	66.4	Ultrasound	CIMT, Carotid Plaque
Fracanzani AL et al. (2008)	Italy	Case-Control	123 / 252	48.0 / 48.0	66.0	Ultrasound, Biopsy	CIMT, Carotid Plaque
Lee YJ et al. (2010)	USA	Cross-Sectional	350 / 1934	52.0	48.6	CT Scan	cf-PWV, FMD
Kim D et al. (2012)	Korea	Cross-Sectional	1617 / 2406	56.9	60.7	Ultrasound	CAC

Colak Y et al. (2012)	Turkey	Cross-Sectional	84 / 65	~40	100	Ultrasound	CIMT, FMD, EAT
Kozakova M et al. (2012)	Europe	Cohort	138 / 1121	50.8	49.0	Fatty Liver Index	CIMT, Carotid Plaque
Kim BJ et al. (2013)	Korea	Cross-Sectional	208 / 1168	48.0	69.7	Ultrasound	ba-PWV
Lankarani KB et al. (2013)	Iran	Case-Control	290 / 290	46.1 / 44.9	47.6	Ultrasound	CIMT
Sunbul M et al. (2014)	Turkey	Cross-Sectional	102 / 102	51.1 / 50.4	47.1	Ultrasound	ba-PWV
VanWagner LB et	USA	Cross-Section	232 / 2192	50.1	42.7	CT Scan	CAC, AAC

al. (2014)		al					
Ozturk K et al. (2015)	Turkey	Case-Control	113 / 57	31.7 / 30.1	100	Biopsy	CIMT
Sinn DH et al. (2016)	Korea	Cohort	2043 / 2688	45.9	82.5	Ultrasound	CAC Progression
Al-Hamami A et al. (2017)	China	Cross-Sectional	5792 / 7198	70.8	59.2	Ultrasound	Carotid Plaque
Vita T et al. (2019)	USA	Retrospective	125 / 761	62.0	28.8	CT Scan	CMD (CFR)

Abbreviations: AAC, Abdominal Aortic Calcification; ba-PWV, Brachial-Ankle Pulse Wave Velocity; CAC, Coronary Artery Calcification; cf-PWV, Carotid-Femoral Pulse Wave Velocity; CIMT, Carotid Intima-Media Thickness; CMD, Coronary Microvascular Dysfunction; CT,

Computed Tomography; EAT, Epicardial Adipose Tissue; FMD, Flow-Mediated Dilation.

Risk of Bias Assessment

The methodological quality of the included studies was generally high. As shown in Table 2, all 17 studies scored 6 or higher on the 9-star NOS, with 12 studies rated as "Good" quality (7-9 stars) and 5 as "Fair" quality (4-6 stars). Most studies demonstrated adequate selection of cases and controls and utilized reliable methods for outcome assessment (Wells et al., 2000). The primary area of potential bias was in the comparability domain, where some studies did not fully adjust for all relevant confounding variables.

Table 2. Newcastle-Ottawa Scale (NOS) for Risk of Bias Assessment

Study (Author, Year)	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)	Quality Rating
Brea A et al. (2005)	4	2	3	9	Good
Volzke H et al. (2005)	3	2	3	8	Good
Villanova N et al. (2005)	4	1	3	8	Good

Targher G et al. (2007)	4	2	3	9	Good
Fracanzani AL et al. (2008)	4	2	3	9	Good
Lee YJ et al. (2010)	3	2	3	8	Good
Kim D et al. (2012)	3	2	3	8	Good
Colak Y et al. (2012)	3	1	2	6	Fair
Kozakova M et al. (2012)	3	2	3	8	Good
Kim BJ et al. (2013)	3	1	2	6	Fair
Lankarani	4	2	3	9	Good

KB et al. (2013)					
Sunbul M et al. (2014)	3	1	2	6	Fair
VanWagner LB et al. (2014)	3	2	3	8	Good
Ozturk K et al. (2015)	4	1	2	7	Good
Sinn DH et al. (2016)	4	2	3	9	Good
Al-Hamami A et al. (2017)	3	1	2	6	Fair
Vita T et al. (2019)	3	1	2	6	Fair

Overview of Findings

The included studies consistently demonstrated a significant association between NAFLD and a wide range of subclinical atherosclerosis markers. As summarized in Table 3, NAFLD was linked to both structural and functional vascular abnormalities across multiple arterial beds. This widespread impact suggests a systemic effect of NAFLD on the cardiovascular system, extending beyond its role as a simple marker of metabolic dysfunction.

Table 3. Overview of Significant Associations Between NAFLD and Subclinical Atherosclerosis Markers by Study

Study (Author, Year)	CIMT	Carotid Plaque	CAC	CAC Progression	FMD	PWV	EAT	CMD	AAC
Brea A et al. (2005)	Yes	Yes	No	No	No	No	No	No	No
Volzke H et al. (2005)	Yes	Yes	No	No	No	No	No	No	No
Villanova N et al. (2005)	No	No	No	No	Yes	No	No	No	No

Targher G et al. (2007)	Yes	Yes	No	No	No	No	No	No	No
Fracanzani AL et al. (2008)	Yes	Yes	No	No	No	No	No	No	No
Lee YJ et al. (2010)	No	No	No	No	Yes	Yes	No	No	No
Kim D et al. (2012)	No	No	Yes	No	No	No	No	No	No
Colak Y et al. (2012)	Yes	No	No	No	Yes	No	Yes	No	No
Kozakova M et al.	Yes	Yes	No	No	No	No	No	No	No

(2012)									
Kim BJ et al. (2013)	No	No	No	No	No	Yes	No	No	No
Lankarani KB et al. (2013)	Yes	No	No	No	No	No	No	No	No
Sunbul M et al. (2014)	No	No	No	No	No	Yes	No	No	No
VanWagner LB et al. (2014)	No	No	Yes	No	No	No	No	No	Yes
Ozturk K et al. (2015)	Yes*	No	No	No	No	No	No	No	No

Sinn DH et al. (2016)	No	No	No	Yes	No	No	No	No	No
Al-Hamami A et al. (2017)	No	Yes	No	No	No	No	No	No	No
Vita T et al. (2019)	No	No	No	No	No	No	No	Yes	No

*Yes indicates a statistically significant association was found. No indicates the marker was not assessed or no significant association was found. *Association was significant in unadjusted analysis but not after adjustment for metabolic factors.

Association of NAFLD with Structural Atherosclerosis

Carotid Intima-Media Thickness (CIMT)

A majority of the studies investigating CIMT found that individuals with NAFLD had significantly greater carotid artery wall thickness, a well-established marker of early structural atherosclerosis (Table 4). Several studies reported a mean difference of 0.14 mm to 0.32 mm in CIMT between NAFLD and control groups, a clinically meaningful difference (Brea et al., 2005; Targher et al., 2007; Colak et al., 2012). Furthermore, Lankarani et al. (2013) found that after adjusting for multiple confounding variables, NAFLD was associated with a nearly twofold

increased odds of having a thickened CIMT. However, the study by Ozturk et al. (2015) noted that this association disappeared after adjusting for metabolic factors, highlighting the complex interplay between NAFLD, metabolic syndrome, and vascular disease.

Table 4. Association Between NAFLD and Carotid Intima-Media Thickness (CIMT)

Study (Author, Year)	NAFLD Group Mean CIMT (mm)	Control Group Mean CIMT (mm)	Adjusted Effect Estimate (OR)	95% CI	p-value
Brea A et al. (2005)	0.70 \pm 0.20	0.54 \pm 0.13	-	-	<0.0001
Targher G et al. (2007)	1.14 \pm 0.20	0.82 \pm 0.12	-	-	<0.001
Colak Y et al. (2012)	0.65 \pm 0.09	0.51 \pm 0.08	-	-	<0.001
Lankarani KB et al. (2013)	-	-	1.91	1.17–3.10	0.009

Carotid Plaques

Beyond diffuse wall thickening, NAFLD was also strongly associated with the presence of focal, established carotid plaques (Table 5). The prevalence of plaques was consistently higher in NAFLD cohorts, with some studies reporting a twofold to threefold increase in odds (Brea et al., 2005). A large cross-sectional study by Al-Hamami et al. (2017) involving over 12,000 participants confirmed this, finding that NAFLD was associated with an 89% increased odds of having carotid plaque, an association that remained robust after extensive statistical adjustment.

Table 5. Association Between NAFLD and Carotid Plaque Prevalence

Study (Author, Year)	NAFLD Group Plaque Prevalence	Control Group Plaque Prevalence	Adjusted Effect Estimate (OR)	95% CI	p-value
Brea A et al. (2005)	50.0%	25.0%	2.9	1.1-7.6	0.021
Volzke H et al. (2005)	76.8%	66.6%	-	-	<0.001
Al-Hamami A et al. (2017)	22.4%	16.3%	1.89	1.59–2.24	<0.001

Coronary Artery Calcification (CAC)

The link between NAFLD and atherosclerosis extends to the coronary arteries, the primary site of ischemic heart disease (Table 6). Multiple large studies demonstrated that NAFLD is independently associated with both the presence and severity of CAC (Kim et al., 2012; VanWagner et al., 2014). Perhaps most compellingly, a large longitudinal study by Sinn et al. (2016) showed that NAFLD was a significant predictor of CAC *progression* over a nearly four-year follow-up period. This finding provides strong evidence that NAFLD is involved in the active, dynamic process of coronary atherosclerosis development, rather than being a static marker of risk.

Table 6. Association Between NAFLD and Coronary Artery Calcification (CAC)

Study (Author, Year)	Outcome	Adjusted Effect Estimate	95% CI	p-value
Kim D et al. (2012)	Increased CAC Score	OR: 1.28	1.04–1.59	0.023
VanWagner LB et al. (2014)	Presence of CAC (CAC > 0)	OR: 1.33	1.001–1.82	<0.05
Sinn DH et al. (2016)	CAC Progression Rate	Rate Ratio: 1.04	1.02–1.05	<0.001

Association of NAFLD with Functional Vascular Impairment

Endothelial Dysfunction (Flow-Mediated Dilation - FMD)

Endothelial dysfunction is a critical initiating event in atherogenesis, and the included studies consistently showed that patients with NAFLD exhibit impaired endothelial function (Table 7). As measured by FMD of the brachial artery, NAFLD patients had a significantly reduced vasodilatory response compared to controls (Villanova et al., 2005; Colak et al., 2012). Notably, Villanova et al. (2005) also found that endothelial dysfunction was more severe in patients with NASH compared to those with simple steatosis, suggesting a dose-response relationship between the severity of liver inflammation and the degree of vascular impairment.

Table 7. Association Between NAFLD and Endothelial Dysfunction (Flow-Mediated Dilation)

Study (Author, Year)	NAFLD Group (Mean FMD %)	Control Group (Mean FMD %)	Mean Difference (%)	p-value
Villanova N et al. (2005)	6.33 \pm 5.93	12.22 \pm 5.05	-5.89	<0.0001
Colak Y et al. (2012)	10.1 \pm 3.1	15.2 \pm 2.8	-5.10	<0.001
Lee YJ et al. (2010)	-	-	r = -0.05 (correlation)	0.02

Arterial Stiffness (Pulse Wave Velocity - PWV)

Arterial stiffness, a powerful independent predictor of future cardiovascular events, was also found to be significantly increased in patients with NAFLD (Table 8). Studies using both carotid-femoral PWV (cf-PWV) and brachial-ankle PWV (ba-PWV) reported higher values in NAFLD cohorts (Lee et al., 2010; Kim et al., 2013; Sunbul et al., 2014). Kim et al. (2013) found that after adjusting for confounders, NAFLD remained an independent predictor of higher ba-PWV, reinforcing the link between the liver disease and adverse changes in vascular mechanics.

Table 8. Association Between NAFLD and Arterial Stiffness (Pulse Wave Velocity)

Study (Author, Year)	PWV Type	NAFLD Group (Mean PWV)	Control Group (Mean PWV)	Adjusted Effect Estimate (β)	p-value
Lee YJ et al. (2010)	cf-PWV (m/s)	8.0 \pm 1.9	7.4 \pm 1.6	-	<0.0001
Kim BJ et al. (2013)	ba-PWV (cm/s)	1400 \pm 210	1290 \pm 150	45.3	0.008
Sunbul M et al. (2014)	ba-PWV (cm/s)	1428 \pm 239	1291 \pm 175	-	<0.001

Association of NAFLD with Other Markers of Cardiovascular Risk

The systemic impact of NAFLD was further demonstrated by its association with other emerging markers of cardiovascular risk, as detailed in Table 9. These findings show that the disease's influence extends to ectopic fat deposition around the heart (EAT), the function of the coronary microvasculature (CMD), and calcification of the aorta (AAC). The study by Vita et al. (2019) is particularly noteworthy, as it links NAFLD directly to impaired coronary microvascular function, a condition that can cause ischemia and adverse cardiac events even in the absence of obstructive coronary artery disease.

Table 9. Association Between NAFLD and Other Markers of Cardiovascular Risk

Study (Author, Year)	Marker	NAFLD Group	Control Group	Adjusted Effect Estimate (OR)	p-value
Colak Y et al. (2012)	EAT Thickness (mm)	6.4 \pm 1.1	4.5 \pm 0.9	-	<0.001
VanWagner LB et al. (2014)	AAC Prevalence	65.1%	49.9%	1.74	<0.001
Vita T et al. (2019)	CMD Prevalence	64.8%	43.4%	-	<0.001

	Mean CFR	1.9 \pm 1.1	2.2 \pm 0.7	-	<0.001

DISCUSSION

Summary of Principal Findings

This systematic review synthesizes evidence from 17 observational studies and confirms a robust and consistent association between NAFLD and a wide spectrum of subclinical atherosclerosis markers. The findings demonstrate that individuals with NAFLD exhibit greater structural vascular damage, including increased carotid wall thickness, a higher burden of carotid plaque, and more prevalent and progressive coronary artery calcification (Brea et al., 2005; Kim et al., 2012; Sinn et al., 2016). Concurrently, NAFLD is associated with significant functional vascular impairments, such as endothelial dysfunction and increased arterial stiffness (Villanova et al., 2005; Sunbul et al., 2014). These associations span multiple vascular beds—from the carotid and coronary arteries to the aorta—and are frequently observed to be independent of traditional cardiovascular risk factors. This comprehensive body of evidence strongly supports the notion that NAFLD is not merely a marker of an unhealthy metabolic profile but is intrinsically linked to the early and progressive stages of atherosclerotic vascular disease (Targher et al., 2010).

The Atherosclerotic Cascade in NAFLD: From Functional to Structural Damage

The consistency of the findings across different markers and study populations lends strong support to the biological plausibility of a causal link between NAFLD and atherosclerosis. The results of this review can be framed within the natural history of atherosclerosis, beginning with functional changes and progressing to structural damage. The observed reduction in FMD in NAFLD patients (Villanova et al., 2005; Colak et al., 2012) reflects endothelial dysfunction, the well-established initial step in atherogenesis. This impairment is likely driven by the systemic milieu of inflammation, oxidative stress, and insulin resistance propagated by the diseased liver

(Targher et al., 2010). This early functional damage is followed by increased arterial stiffness, evidenced by higher PWV (Sunbul et al., 2014; Kim et al., 2013), which reflects a loss of vascular compliance. Over time, these functional deficits culminate in the structural changes of increased CIMT and the formation of carotid plaques and coronary calcification, as consistently reported in the included studies (Brea et al., 2005; Targher et al., 2007; Kim et al., 2012; Sinn et al., 2016).

A Graded Relationship: The Impact of Liver Disease Severity

A particularly compelling finding from this review is the apparent dose-response relationship between the severity of liver disease and the extent of vascular damage. For instance, Villanova et al. (2005) demonstrated that endothelial dysfunction was significantly worse in patients with NASH (the inflammatory form of NAFLD) than in those with simple steatosis. Similarly, Targher et al. (2007) found in their study of biopsy-proven NAFLD that carotid IMT was strongly associated not just with the presence of NAFLD, but with the histological severity of steatosis, necroinflammation, and fibrosis. This graded association argues against the possibility that NAFLD is a simple epiphenomenon. Instead, it suggests that as the liver disease progresses and becomes more metabolically active and inflamed, it exerts a proportionally greater pro-atherogenic effect on the entire cardiovascular system.

NAFLD as a Systemic Disease: Evidence from Multiple Vascular Beds

The findings of this review underscore that NAFLD is a systemic condition with far-reaching extrahepatic consequences. The association with atherosclerosis is not confined to a single vascular territory. Evidence of damage was found in the carotid arteries (Brea et al., 2005; Volzke et al., 2005), the coronary arteries (Kim et al., 2012; Sinn et al., 2016), and the abdominal aorta (VanWagner et al., 2014). Furthermore, the link extends to the microvasculature, as shown by the increased prevalence of coronary microvascular dysfunction (Vita et al., 2019), and to ectopic fat deposition around the heart itself, evidenced by increased epicardial adipose tissue (Colak et al., 2012). This multi-site impact reinforces the concept of a "liver-vessel axis" where the diseased liver

actively promotes widespread vascular pathology.

The Role of Shared vs. Independent Pathophysiological Mechanisms

The question of whether NAFLD's effect is independent of or mediated by traditional risk factors is nuanced. Many studies included in this review found that the association with atherosclerosis persisted after statistical adjustment for metabolic syndrome, diabetes, and obesity (Lankarani et al., 2013; Al-Hamami et al., 2017). This points to an independent contribution from the liver itself, likely through the secretion of specific hepatokines, pro-inflammatory mediators, and pro-coagulant factors that are not captured by standard risk factor measurements (Targher et al., 2010). However, other studies noted that the association was attenuated after adjusting for measures of visceral adiposity or blood pressure (VanWagner et al., 2014; Lee et al., 2010). This does not contradict the former finding but rather paints a more complete picture. NAFLD is part of a complex metabolic web; its association with atherosclerosis is partly explained by shared upstream drivers like visceral obesity and insulin resistance. Yet, the persistence of a significant association after adjustment in most high-quality studies suggests the diseased liver adds a "value-added" risk, acting as both a mediator for traditional risk factors and an independent, organ-specific driver of vascular disease.

Clinical and Public Health Implications

The robust evidence linking NAFLD to subclinical atherosclerosis has profound clinical and public health implications. The incidental finding of hepatic steatosis on an abdominal ultrasound, a common occurrence in clinical practice, should no longer be dismissed as a benign condition. Instead, it should be recognized as a potent marker of heightened cardiovascular risk, prompting a more aggressive and comprehensive assessment of a patient's cardiovascular health (Targher et al., 2010). Based on these findings, NAFLD should be considered a "risk-enhancing" factor in cardiovascular risk stratification. For a patient with NAFLD, their calculated 10-year risk score may underestimate their true risk. The presence of NAFLD, particularly with elevated liver enzymes or

non-invasive markers suggesting fibrosis or NASH, justifies more intensive management of traditional risk factors like hypertension, dyslipidemia, and glucose intolerance. Furthermore, these findings raise the question of whether targeted screening for subclinical atherosclerosis—for example, with carotid ultrasound or a CAC scan—is warranted in selected NAFLD patients to refine risk stratification and guide preventive therapies (Kim et al., 2012).

Strengths and Limitations

The primary strength of this systematic review is its comprehensive scope, synthesizing evidence across a wide range of structural and functional markers of subclinical atherosclerosis from a large number of studies. The adherence to PRISMA guidelines and the use of the Newcastle-Ottawa Scale for quality assessment add to the methodological rigor (Wells et al., 2000). However, several limitations must be acknowledged. The foremost limitation is the observational design of all included studies. While these studies can demonstrate strong associations, they cannot definitively establish causality. Second, there was significant heterogeneity among the studies in terms of population characteristics, methods for diagnosing NAFLD, and techniques used to measure atherosclerosis markers. This heterogeneity can limit the generalizability of the findings. Finally, the potential for publication bias cannot be completely ruled out.

Future Research Directions

To address the limitations of the current evidence, future research should focus on several key areas. Large-scale, long-term prospective cohort studies are crucial to definitively establish the temporal sequence of events and confirm that NAFLD precedes and predicts the development of subclinical atherosclerosis (Sinn et al., 2016). Ultimately, the most compelling evidence will come from intervention studies. Randomized controlled trials are needed to determine whether treating NAFLD, through lifestyle modifications or emerging pharmacotherapies, can lead to a measurable regression or slowing of the progression of subclinical atherosclerosis. Such studies would provide definitive proof of a causal link and establish a new therapeutic paradigm for cardiovascular risk

reduction in this population.

CONCLUSION AND RECOMMENDATIONS

Conclusion

The evidence synthesized in this systematic review provides a clear and consistent conclusion: Nonalcoholic Fatty Liver Disease is strongly and significantly associated with the presence of subclinical atherosclerosis across multiple vascular territories and functional domains. This relationship extends from the earliest stages of endothelial dysfunction and arterial stiffening to the development of structural changes, including carotid plaque and coronary artery calcification (Targher et al., 2010). The association frequently transcends shared metabolic risk factors, positioning NAFLD not as a passive marker of an unhealthy lifestyle, but as a key player in the pathogenesis of early vascular disease.

Recommendations

Based on the comprehensive evidence presented, the following recommendations are proposed:

For Clinical Practice:

1. **Elevate the Significance of NAFLD:** Clinicians should recognize the diagnosis of NAFLD, even when discovered incidentally, as a significant indicator of increased cardiovascular risk.
2. **Initiate Aggressive Risk Factor Management:** The presence of NAFLD should trigger a comprehensive cardiovascular risk assessment and more aggressive management of all modifiable risk factors, including hypertension, dyslipidemia, hyperglycemia, and obesity.
3. **Consider Screening for Subclinical Atherosclerosis:** In patients with NAFLD, particularly those with additional risk factors or evidence of advanced liver disease, clinicians should consider screening for subclinical atherosclerosis (e.g., CAC scoring or carotid ultrasound) to further refine risk stratification and guide preventive strategies.

For Future Research:

1. **Conduct Longitudinal and Intervention Studies:** Priority should be given to long-term prospective studies to confirm causality and randomized controlled trials to evaluate whether effective treatment of NAFLD translates into a reduction in the progression of atherosclerosis and, ultimately, a decrease in cardiovascular events.
2. **Elucidate Mechanistic Pathways:** Further research should focus on identifying the specific molecular mediators that link the diseased liver to the vessel wall, providing potential novel targets for therapy.

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