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Prognostic value of FIB-4 and NFS for cardiovascular events in patients with and without NAFLD

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Abstract

Background The association between non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) is well studied. Liver fibrosis is the main histopathologic manifestations of NAFLD. However, whether concomitant NAFLD influence the association of non-invasive liver fibrosis scores with CVD remains unclear.

Methods We systematically searched PubMed, Cochrane Library, and Embase databases for cohort studies exploring the association between liver fibrosis score (LFS)and CVD events up to June 10, 2025. Random-effects model was used to pool results. CVD events were defined as cardiovascular mortality, myocardial infarction, and coronary heart disease.

Results Nineteen cohorts involving 1,481,875 adults were included with an average age of 54.8 years old, and 50.2% males. Fibrosis 4 score (FIB-4), nonalcoholic fatty liver disease fibrosis score (NFS) and APRI (Aspartate transaminase/platelet ratio index) were associated with increased risks of CVD events (FIB-4: odds ratio [OR] 1.77, 95% confidence interval [CI] 1.58–1.99, low certainty; NFS: OR 2.40, 95% CI 1.83–3.14, low certainty; APRI: OR 1.61, 95% CI 1.17–2.21, low certainty). Each one-unit increment in FIB-4, NFS scores was associated with CVD events (FIB-4: OR 1.21, 95% CI 1.12–1.31; NFS: OR 1.38, 95% CI: 1.17–1.62). A positive linear relationship was observed between FIB-4 (P-nonlinearity = 0.000), NFS (P-nonlinearity = 0.7145) and CVD events. Risk estimates for cardiovascular events were similar in patients with NAFLD (FIB-4: OR 1.87, 95% CI 1.53–2.28; NFS: OR 2.59, 95% CI 1.55–4.33) and without NAFLD (FIB-4: OR 1.74, 95% CI 1.51-2.00; NFS: OR 2.26, 95% CI 1.64–3.11) (P for difference: FIB-4 = 0.56; NFS = 0.66).

Conclusion FIB-4 and NFS were associated with an increased risk of CVD events in patients with and without NAFLD. FIB-4 and NFS risk estimates for cardiovascular events were not influenced by concomitant NAFLD.

Registration URL: http://www.crd.york.ac.uk/prospero/ PROSPERO (registration number: CRD42023421092).

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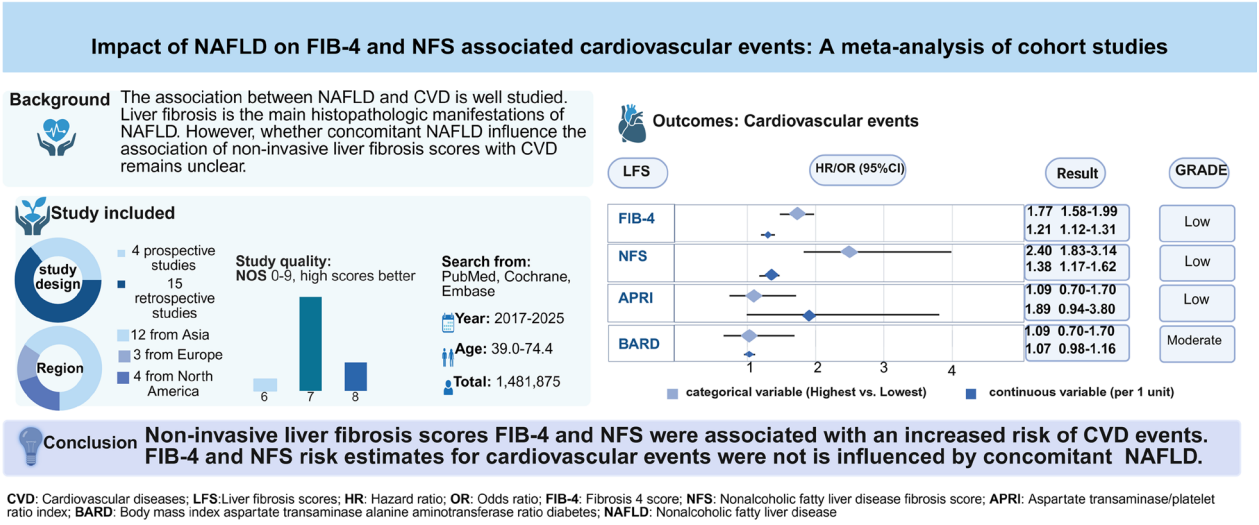
Keywords Nonalcoholic fatty liver disease, Cardiovascular disease, Cardiovascular mortality, Meta-analysis

Graphical Abstract



Clinical perspective

What is already known on this topic?

- Nonalcoholic fatty liver disease (NAFLD) as a predictor of cardiovascular events, especially during the fibrosis phase. Fibrosis 4 score (FIB-4) and nonalcoholic fatty liver disease fibrosis score (NFS) are widely used and validated for assessment of liver fibrosis.

What is new?

- The liver fibrosis score (LFS) score is associated with cardiovascular disease (CVD) in NAFLD and non-NAFLD populations, with similar risk magnitudes, suggesting that the relationship between LFS score and CVD is independent of NAFLD.

What is the clinical implication?

- LFS may improve the prediction of cardiovascular events, independent of concomitant NAFLD.

Introduction

Epidemiological research has consistently linked nonalcoholic fatty liver disease (NAFLD) to an elevated incident cardiovascular disease (CVD), including coronary heart disease, heart failure, and atrial fibrillation [1]. A recent meta-analysis report found that regardless of sex, age, the presence of hypertension, type 2 diabetes mellitus, and other common cardiovascular metabolic risk factors, NAFLD is associated with the risk of heart failure [2, 3]. Hepatic fibrosis is the most common features of various chronic liver disorders and has been shown to be the strongest histologic predictor for disease-specific and overall mortality in patients with liver diseases [4–6]. Traditionally, liver biopsies have been the gold standard for assessing fibrosis severity. However, their limited availability necessitated the development of noninvasive scoring systems, such as liver fibrosis score (LFS) includes fibrosis 4 scores (FIB-4), NAFLD fibrosis score (NFS), based on routine clinical and laboratory variables. These scores offer advantages such as wide applicability, accessibility, affordability, and safety, as a measurement and real-time prognostic tool for liver fibrosis instead of liver biopsy [7].

Several articles have reported association between LFS and the incident myocardial infarction, heart failure, and major adverse cardiovascular events [8–14]. We also previously showed LFS were associated with adverse outcomes in patients with CVD [15]. Despite these advances, the systematic research between LFS and incident CVD remains limited. Hence, this study aims to systematically explore the relationship between LFS and the risk of CVD events.

Methods

Protocol and registration

The protocol of this study was registered in PROSPERO (International Prospective Register of Systematic Reviews-registration number-CRD42023421092). This meta-analysis was reported according to the PRISMA 2020 guidelines (Online Table S1).

Search strategy

We followed the population, intervention, comparison, outcome, and study design (PICOS) framework to combine keywords and MeSH terms/emtree terms for our search across electronic databases (PubMed, Cochrane Library, Embase) until June 10, 2025 (Online Table S2). We did not limit the search by language, titles, or abstracts to ensure a comprehensive review. Manual searches and Google Scholar were used to identify additional relevant studies, including grey literature (e.g. conference papers, theses/dissertation):

For exposure and comparison: 'FIB4' OR 'FIB-4' OR 'Fibrosis-4' OR 'NAFLD-FS' OR 'NAFLD fibrosis score' OR 'aspartate aminotransferase to platelet ratio index' OR 'APRI' OR 'BARD score' OR 'liver fibrosis'.

For outcome: 'cardiovascular disease' OR 'heart disease' OR 'cardiovascular mortality' OR 'cardiopathy' OR 'heart trouble' OR 'atrial fibrillation' OR 'coronary artery disease' OR 'coronary disease' OR 'coronary arteriosclerosis' OR 'myocardial infarction' OR 'heart attack' OR 'heart failure' OR 'heart decompensation' OR 'arrhythmia'.

Non-invasive liver fibrosis scoring systems play a crucial role in assessing chronic hepatic conditions, especially in patients with NAFLD. Predominantly utilized metrics include FIB-4, NFS, aspartate transaminase/platelet ratio index (APRI), and Body mass index aspartate transaminase alanine aminotransferase ratio Diabetes (BARD) scores, with FIB-4 and NFS being the most prevalent non-invasive screening tools for liver fibrosis. Additional scores like APRI and BARD were also considered [6].

Calculation of four liver fibrosis scoring systems:

$$\begin{aligned}\text{FIB}-4 \;=\; &\text{Age} \;\times\; \text{glutamic oxaloacetic transaminase (AST))} \\ &/\ (\text{platelet (PLT)} \;\times\; \sqrt{\text{glutamic pyruvic}} \\ &\text{transaminase (ALT))}\end{aligned}$$

$$\begin{aligned}\text{NFS} \;=\; &-1.675 \;+\; 0.037 \;\times\; \text{Age} \;+\; 0.094 \\ &\times\; \text{body mass index (BMI)} \left(\frac{\text{kg}}{\text{m2}}\right) \\ &+\; 1.13 \;\times\; \text{impaired fasting} \frac{\text{glocuse}}{\text{diabetes}} \\ &[\text{yes}=1, \text{no}=0] + 0.99 \times (\text{AST})/(\text{ALT}) \\ &- 0.013 \times \text{PLT}(10^9/\text{L}) - 0.66 \times \text{albumin(g/dl)}\end{aligned}$$

$$\begin{aligned}\text{APRI} \;=\; &[(\text{AST} \;/\; \text{upper limit of normal (ULN))} \;/\; \text{PLT}] \\ &\times\; 100\end{aligned}$$

$$\begin{aligned}\text{BARD} \;=\; &\text{BMI} \;\geq\; 28\ \text{kg/m2} \;=\; 1\ \text{point;}\ \ \text{AST/ALT ratio} \;\geq\; 0.8 \\ &=\; 2\ \text{points;}\ \ \text{and diabetes mellitus} \;=\; 1\ \text{point.}\end{aligned}$$

Study selection

Three investigators (L-L, Q-L, and YH-G) independently managed the literature search, selection, and data extraction using Endnote X9 software (Tomson Reuters, New York, New York, USA). The process involved initial screening through titles and abstracts, followed by full-text reviews to identify relevant studies. In cases of missing information, we reached out to the corresponding authors. Any disagreements were resolved by consulting a senior reviewer (X-L).

Eligible studies met the following PICOS criteria:

(1) population: adult (age > 18 years); (2) intervention (exposure) and comparator: high liver fibrosis versus low liver fibrosis score; (3) outcomes: reporting the association between LFS and CVD events expressing as OR/RR/HR. CVD events were defined as cardiovascular mortality, myocardial infarction, heart failure, or coronary heart diseases [16], either individually or combined. (4) study design: retrospective or prospective cohort studies. Protocols, cross-sectional studies, meta-analyses, reviews, and animal studies were excluded.

Data extraction and quality assessment

Data extraction and quality assessment were conducted by three authors (L-L, Q-L, and YH-G) using established criteria, with discrepancies resolved by consensus. A senior author (X-L) verified the data. Study quality was assessed using the Newcastle Ottawa Scale, with scores above 6 indicating acceptable quality [17]. The Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) system was utilized for evidence quality levels and recommendations [18, 19].

Statistical analysis

For statistical analysis, the 95% confidence intervals (CIs) corresponding to ORs/RRs or HRs were utilized to determine the relationship between LFS and the risk of CVD. LFS was treated as a categorical variable, comparing the highest LFS levels to the lowest group. RRs/HRs were considered as equal to ORs [20, 21]. Inconsistencies across studies were assessed using the I2 statistics. The presence of true heterogeneity was evaluated using the Q test ($P < 0.10$ is considered indicative of heterogeneity) and Tau2 (τ2) [22]. The random-effects model was employed to pool the effect size [23]. We analyzed the publication bias for the results with more than 10 eligible articles by funnel plot, and Egger's test [24]. Pre-plan subgroup analysis based on NAFLD, mean age, sample size, follow-up, study design, region, and adjustments were conducted when included studies ≥ 10. A statistically significant effect was considered when the P value was less than 0.05. RevMan software, version 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Center Copenhagen, Denmark) was used for analyses.

Results

Figure 1 shows the database search procedure. We initially retrieved 2,953 articles from PubMed, Cochrane Library, and Embase. After removing 95 repetitions, we received 2,858 initial citations. By reviewing the titles and the abstract, we excluded 2,755 unrelated articles. A total of 103 articles were initially evaluated for eligibility. Out of these, 84 articles were subsequently excluded for the following reasons: (1) focused on other populations (8 articles), (2) focused on irrelevant exposure (6 articles), (3) without targeted outcomes (65 articles), (4) cross-sectional or case-control studies (4 articles), and (5) duplicated population (1 article) (Online Table S3). Finally, this meta-analysis included 19 cohort studies.

Study characteristics

The characteristics of the included studies are summarized in Table 1. We included 4 prospective cohorts, and 15 retrospective cohorts, involving 1,481,875 adults. The sample size varied from 477 to 413,860. The average age of participants ranged from 39.0 to 74.4 years, with male participation rates varying from 29.8 to 96.0%. Twelve studies from Asia [8, 11, 25–34], three from Europe [35–37], and four from North America [9, 10, 38, 39].

Nineteen articles reported FIB-4 (1,481,875 participants) [8–11, 25–39], 9 articles reported NFS (819,517 participants) [8, 10, 27, 28, 31, 33, 35, 37, 38], 5 articles reported APRI (449,260 participants) [10, 25, 28, 37, 38], and 3 articles reported BARD (12,828 participants) [25, 28, 35]. The follow-up period varied from 0.5 to 14.5

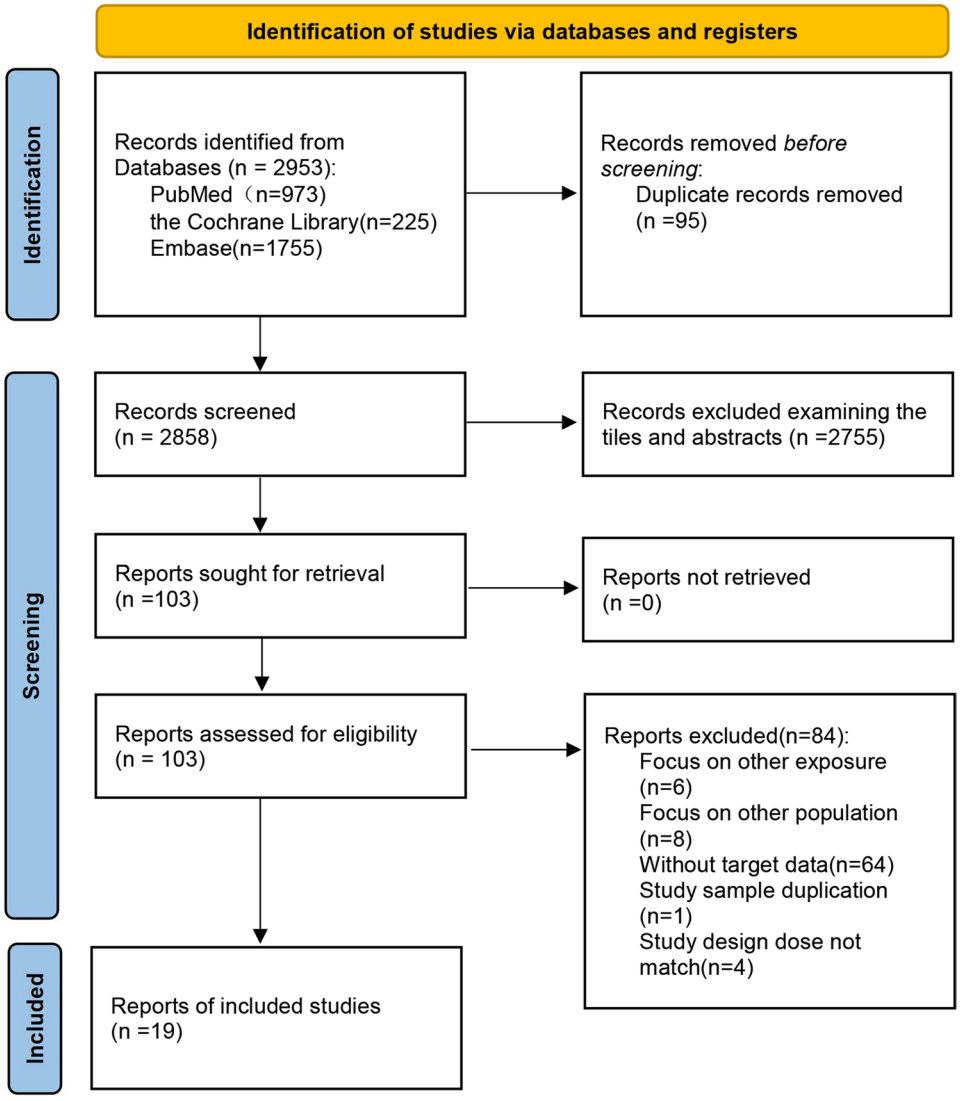


Fig. 1 Flow chart of the study selection process in prognostic value of FIB-4 and NFS for cardiovascular events in patients with and without NAFLD

Table 1 Characteristics of included studies in prognostic value of FIB-4 and NFS for cardiovascular events in patients with and without NAFLD

Author, year, country	Study design, data source	Study population	Follow-up time (year), sample sizes	Drug therapy (%)	Mean age(years), male%	Endpoint	Liver fibrosis score	HR or OR 95%CIs	Adjustments
Akuta, 2021, Japan [26]	Retrospective cohort study, Hepatology, Toranomon Hospital and Okinaka Memorial Institute for Medical Research	Patients with histopathologically-confirmed NAFLD	5.9, 477	\	53.0, 59.1	CVD (heart failure, coronary artery disease, hypertension, orthostatic hypotension, shock, heart valve disease, endocarditis, arrhythmia, disorders of the peripheral vascular system, diseases of the aorta and its branches, and stroke)	FIB-4<2.67 FIB-4≥2.67	Ref (HR) 2.73 1.21-6.14	BMI, previous or current malignancies, CKD, comorbid hypertension, PNPLA3 genotype
Anstee, 2024, United Kingdom [36]	Retrospective cohort study, CPRD GOLD	Adults with obesity (BMI ≥30 kg/m2)and/or type 2 diabetes	10.0, 44,481	Anti-hypertensive (31.0), metformin (19.0), Lipid-lowering medication (34.0)	58.8, 46.0	CVD (heart failure and stroke)	FIB-4<2 2≤FIB-4≤2.67 FIB-4≥2.67	Ref (HR) 1.01 0.95-1.07 1.34 1.21-1.48	Age and sex
Baek, 2024, Korea [32]	Retrospective cohort study, the Korean Cancer Prevention Study-II	Adults	10.6, 104,399	\	39.0, 52.7	CVD	No-FIB-4 FIB-4<1.3 FIB-4≥1.3 No-FIB-4 FIB-4<1.3 FIB-4≥1.3 No-FIB-4 FIB-4<1.3 FIB-4≥1.3 No-FIB-4 FIB-4<1.3 FIB-4≥1.3 No-FIB-4 FIB-4<1.3 FIB-4≥1.3	Ref (HR) 2.07 (1.83-2.32) 2.27 (1.87-2.76) Ref (HR) 1.67 (1.45-1.90) 1.67 (1.30-2.10) Ref (HR) 1.67 (1.41-2.00) 2.56 (1.99-3.30) Ref (HR) 1.63 (0.96-2.80) 0.78 (0.19-3.10) Ref (HR) 1.83 1.57-2.05 2.06 1.60-2.66	Age, sex, smoking status, exercise status, eGFR

Table 1 (continued)

Author, year, country	Study design, data source	Study population	Follow-up time (year), sample sizes	Drug therapy (%)	Mean age(years), male%	Endpoint	Liver fibrosis score	HR or OR 95%CIs	Adjustments
Barbosa, 2022, USA [39]	Retrospective cohort study, the TriNetX database	Patients with NAFLD, NASH, or a specific RISK profile for NAFLD/nonalcoholic steatohepatitis	3.0, 67,273	Glucagon-like peptide-1 receptor agonist (3.0), diumglucose cotransporter-2 inhibitor (1.8), dipeptidyl peptidase-4 inhibitor (4.7), peroxisome proliferator-activated receptor agonist (1.5), statin (50.9)	62.0, 49.6	MACE (myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, and coronary revascularization, including coronary artery bypass graft or percutaneous coronary intervention, according to ICD codes)	FIB-4<1.3 1.3≤FIB-4≤2.66 FIB-4≥2.67	Ref (HR) 1.25 1.16-1.35 1.80 1.61-2.02	Diagnostic group, gender, race/ethnicity, type 2 diabetes, hypertension, hyperglycemia, high LDL cholesterol, low HDL, high triglycerides, and previous CVD
Chew, 2022, USA [10]	Retrospective cohort study, NAHNES 1999-2018	Patients with NAFLD	NR, 12,380	\	52.7, 48.9	CVD mortality	FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4≥2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS≥0.676 APRI≤2 APRI>2	Ref (SHR) 1.08 0.89-1.31 1.42 1.04-1.94 Ref (SHR) 0.89 0.65-1.23 1.32 0.76-2.27 Ref (SHR) 2.02 0.17-23.89	Not provided
Choi, 2022, Korea [28]	Prospective cohort study, Dong-gu district of Gwangju Metropolitan City	Adults without history of liver diseases	10.3, 7,702	\	65.4, 33.7	CVD mortality	FIB-4<1.3 FIB-4≥1.3 NFS<-1.455 NFS≥-1.455 APRI<0.5 APRI≥0.5 0≤BARD≤1 2≤BARD≤4	Ref (HR) 2.60 1.30-5.20 Ref (HR) 3.60 1.80-6.90 Ref (HR) 0.44 0.10-1.90 Ref (HR) 0.50 0.10-1.50	Sex, age, log-waist circumference, smoking (current), alcohol intake, regular walking, hypertension, diabetes, log-SBP, log-hbA1c, log-total cholesterol, log-triglyceride, log-HDL, and log-GGT. Age was not considered in models with NFS and FIB-4 and diabetes mellitus was not considered in models with NFS and BARD

Table 1 (continued)

Author, year, country	Study design, data source	Study population	Follow-up time (year), sample sizes	Drug therapy (%)	Mean age(years), male%	Endpoint	Liver fibrosis score	HR or OR 95%CIs	Adjustments
Higashiura, 2020, Japan [11]	Retrospective cohort study, Keijinkai Maruyama Clinic of Sapporo	Adults without angina pectoris, myocardial infarction or treatment with percutaneous coronary intervention and/or coronary artery bypass grafting	6.5, 13,448	\	48.0, 65.2	CVD (angina pectoris, myocardial infarction or treatment with percutaneous coronary intervention and/or coronary artery bypass grafting)	FIB-4 per 1 SD	1.21 1.03-1.41	Age, sex, presence of fatty liver, current smoking habit, alcohol drinking habit, eGFR, family history of ischaemic heart disease and diagnosis of hypertension, diabetes mellitus and dyslipidaemia
Huang, 2025, China [33]	Retrospective cohort study, the NHANES Survey and UK Biobank	Participants with NAFLD	UK Biobank 13.5, 234,725 NHANES 8.5, 19,143	\	UK Biobank 56.2, 40.6 NHANES 59.4, 45.1	Myocardial infarction (UK Biobank) CVD mortality (UK Biobank) (NHANES) UK Biobank (all)	FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS≥0.676 FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS≥0.676 FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS≥0.676 FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS≥0.676	Ref (HR) 0.93 0.85-1.02 0.94 0.72-1.22 Ref (HR) 0.96 0.88-1.06 0.95 0.76-1.19 Ref (HR) 1.08 0.96-1.23 1.70 1.30-2.22 Ref (HR) 1.29 1.13-1.46 2.46 2.02-3.00 Ref (HR) 1.21 0.93-1.58 2.04.32-3.14 Ref (HR) 1.20 0.91-1.58 2.33 1.70-3.19 Ref (HR) 1.00 0.86-1.16 1.26 0.7-2.26 Ref (HR) 1.11 0.84-1.47 1.53 0.60-3.89	UK Biobank: age, gender, ethnicity/race, educational level, Townsend deprivation index, smoking status, alcohol drinking, BMI, and history of diabetes, eGFR and systolic blood pressure. US NHANES: age, gender, ethnicity/race, educational level, ratio of family income to poverty, smoking status, alcohol drinking, BMI, and history of diabetes., eGFR and systolic blood pressure
Hwang, 2017, Korean [29]	Prospective cohort study, a Kangbuk Samsung Hospital Total Healthcare Center	Adults without other known liver diseases	5.7, 318,224	\	39.3, 51.9	CVD mortality	FIB-4<1.3(men) FIB-4≥1.3(men) FIB-4≥1.3(women) FIB-4<1.3(women) FIB-4<1.3(all) FIB-4≥1.3(all)	Ref (HR) 3.05 1.84-5.08 Ref (HR) 1.44 0.58-3.58 Ref (HR) 2.55 1.64-3.98	Age, BMI, smoking status (current), daily alcohol consumption, and physical activity

Table 1 (continued)

Author, year, country	Study design, data source	Study population	Follow-up time (year), sample sizes	Drug therapy (%)	Mean age(years), male%	Endpoint	Liver fibrosis score	HR or OR 95%CIs	Adjustments
Hydes, 2024, United Kingdom [37]	Retrospective cohort study, United Kingdom Biobank data	Middle-aged and older adults	10.7, 413,860	\	\, \	Hospitalization or death from heart failure	FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4≥2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS≥0.676 APRI<1 APRI≥1	Ref (HR) 1.17 1.12-1.23 1.69 1.55-1.84 Ref (HR) 1.30 1.24-1.37 1.59 1.47-1.78 Ref (HR) 1.85 1.56-2.19	Age, sex, deprivation, ethnicity, alcohol (continuous), smoking (never, previous, current), diabetes, waist circumference, hypertension, dyslipidemia baseline acute coronary syndrome, valve disease, cardiomyopathy
Kaku,2020, USA [9]	Retrospective cohort study, Veterans Aging Cohort	Patients with human immunodeficiency virus	12.0, 92,647	Cocaine (0.2)	49.0, 96.0	Heart failure	FIB-4<1.45 1.45≤FIB-4≤3.25 FIB-4≥3.25	Ref (HR) 1.10 1.00-1.20 1.30 1.20-1.60	Age and race/ethnicity and all covariates
Kim, 2013, USA [38]	Retrospective cohort study, NHANES (1988–1994)	Adults with hepatic steatosis	14.5, 11,154	\	43.0, 47.5	CVD mortality (congestive heart failure mortality, stroke mortality, or myocardial infarction mortality)	FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS>0.676 APRI≤0.5 0.5<APRI<1.5 APRI≥1.5	Ref (HR) 1.75 1.26-2.43 2.68 1.44-4.99 Ref (HR) 2.16 1.41–3.29 3.46 1.91–6.25 Ref 0.97 0.40-2.34 2.53 1.33-4.83	Age, sex, race-ethnicity, education, income, diabetes, hypertension, history of cardiovascular disease, lipid-lowering medication, smoking status (ongoing smoking or smoked at least 100 cigarettes in the preceding 5 years), waist circumference, alcohol consumption, caffeine consumption, total cholesterol, high-density lipoprotein-cholesterol, transferrin saturation, and C-reactive protein.
Sasaki, 2025, Japan [34]	Retrospective cohort study, Glucose Metabolism and Cardiovascular Diseases database	Adults	9.3, 8,689	Antihypertensive medication (23.0), antihyperlipidaemic Medication (24.0), antihyperuricaemic Medication (4.0)	69.7, 51.0	CVD mortality	FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67	Ref (HR) 1.39 1.10-1.76 2.34 1.78-3.06	Age, sex, BMI, smoking habit (current smokers were defined as those who currently had a smoking habit, regardless of the number of cigarettes smoked per day), drinking habit, hyperglycaemia, hypertension, hyperlipidaemia, hyperuricaemia, renal dysfunction, CVD history and plasma volume status.

Table 1 (continued)

Author, year, country	Study design, data source	Study population	Follow-up time (year), sample sizes	Drug therapy (%)	Mean age(years), male%	Endpoint	Liver fibrosis score	HR or OR 95%CIs	Adjustments
Shibata, 2024, Japan [31]	Retrospective cohort study, Ogaki Municipal Hospital	Patients with NAFLD	6.6, 4,071	\	61, 54.1	MACE (cardiac death, nonfatal myocardial infarction, and revascularization due to coronary artery disease)	FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67 NFS<-1.455 -1.455≤NFS≤0.676 NFS>0.676	Ref (HR) 1.86 1.33-2.61 3.33 2.02-5.48 Ref (HR) 1.94 1.39-2.70 3.49 2.00-6.11	Sex, BMI, past history of hypertension, diabetes mellitus, dyslipidemia, prior percutaneous coronary intervention, prior coronary artery bypass graft, smoking, CKD, the level of albumin, gamma-glutamyl transpeptidase, total-bilirubin, and ultrasonography fatty liver scores Sex, past history of hypertension, dyslipidemia, prior percutaneous coronary intervention, prior coronary artery bypass graft, smoking, CKD, the level of, gamma-glutamyl transpeptidase, total-bilirubin, and ultrasonography fatty liver scores
Sinn, 2020, Korea [8]	Retrospective cohort study, a health screening exam at the Samsung Medical Center Health Promotion Center in Seoul	Adults without history of CVD, liver disease, or cancer	6.9, 111,492	Lipid-lowering medication (2.6), aspirin (5.8), antithrombotic medication (0.4)	52.0, 51.2	Myocardial infarction	No FIB-4 FIB-4 <1.3 FIB-4≥1.3 No NAFLD NFS <-1.455 NFS≥-1.455	Ref (HR) 1.51 1.06–2.14 1.54 0.96–2.47 Ref (HR) 1.70 1.22–2.36 1.88 1.24–2.87	Baseline sex, and year of visit, baseline smoking (never, former, current, and missing), alcohol (none and moderate), and BMI, systolic blood pressure, fasting glucose, LDL cholesterol, use of antihypertensive medications, use of antidiabetic medications, use of lipid-lowering medications, use of aspirin, and antithrombotic medications
Tada, 2017, Japan [27]	Retrospective cohort study, Ogaki Municipal Hospital in Between January 2006 and December 2015	Patients with NAFLD	7.1, 4,073	\	61.0, 54.1	Cerebrovascular and cardiovascular diseases	FIB-4<1.3 FIB-4≥1.3 NFS≤-1.455 -1.455<NFS<0.676 NFS≥0.676	Ref (HR) 1.96 1.06-3.63 Ref (HR) 2.27 1.14-4.50 8.48 3.56-20.22	NR
Vincentis, 2019, Italy [35]	Prospective cohort study, InCHIANTI study	General popualtion	7.975, 962	\	74.4,44.5	CVD mortality	FIB-4<2 2≤FIB-4≤2.67 FIB-4>2.67 NFS<0.12 0.12≤NFS≤0.676 NFS>0.676 0≤BARD≤1 2≤BARD≤3 BARD>3	Ref (HR) 1.76 1.17-2.64 2.22 1.36-3.60 Ref (HR) 2.90 1.80-4.66 2.42 1.61-3.64 Ref (HR) 0.97 0.38-2.46 1.23 0.45-3.38	Age, sex, BMI, arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, total cholesterol, Charlson comorbidity index, physical activity, alcohol consumption, smoke (pack-years), IL-6 and TNF-alpha. Age was not considered in models with NFS and FIB-4 and diabetes mellitus and body mass index were not considered in models with NFS and BARD, because already included in the liver scores, themselves

Table 1 (continued)

Author, year, country	Study design, data source	Study population	Follow-up time (year), sample sizes	Drug therapy (%)	Mean age(years), male%	Endpoint	Liver fibrosis score	HR or OR 95%CIs	Adjustments
Xiong, 2023, China [25]	Prospective cohort study, Northeast China Rural Cardiovascular Health Study	Hypertensive participants	4.66, 4,164	Diuretics (1.0), angiotensin converting enzyme inhibitors (4.1), calcium channel blocker (4.6), beta-blockers (1.5), angiotensin receptor blocker (0.4), traditional Chinese medicine (15.9)	56.2, 49.8	Stroke or coronary heart disease	FIB-4<1.3 1.3≤FIB-4≤2.67 FIB-4>2.67 APRI≤0.5 APRI>0.5 Per 1 SD increment 0≤BARD≤2 3≤BARD≤4 Per 1 SD increment	Ref (HR) 1.88 1.44-2.45 2.98 1.99-4.46 Ref (HR) 1.63 1.14-2.32 1.30 1.05-1.65 Ref (HR) 1.20 1.03-1.66 1.21 1.05-1.41	Age, sex, smoking, drinking, diabetes, LDL-C, TG, TCH, mean waist circumference, blood pressure, FPG, antihypertensive medication
Yochai, 2020, Israel [30]	Retrospective cohort study, Clalit Health Services	Adults without CVD as well as strongly related diseases*	10.0, 8,511	Statin (19.2), aspirin (9.1)	61.8, 29.8	Fatal or non-fatal myocardial infarction or stroke	FIB-4≤1.3 1.3<FIB-4<2.66 FIB-4≥2.67	Ref (HR) 1.08 0.97-1.19 1.63 1.29-2.06	Social security waiver status (as a proxy for socioeconomic status), immigration (not born in Israel) and chronic renal failure, statin and aspirin use, and cardiovascular risk

HR Hazard Ratio, *OR* Odds ratio, *CI* Confidence interval, *FIB-4* Fibrosis 4 score, *NAFLD* Non-alcoholic fatty liver disease, *NFS* NAFLD fibrosis score, *APRI* Aspartate aminotransferase to platelet ratio index, *BARD* Diabetes mellitus score, *CVD* Cardiovascular disease, *BMI* Body mass index, *CKD* Chronic kidney disease, *NR* No report, *PNPLA3* Recombinant Patatin Like Phospholipase Domain Containing Protein 3, *USA* United States of America, *SBP* Systolic blood pressure, *HbA1c* Glycated hemoglobin, *HDL* High-density lipoprotein, *GGT* Gamma-glutamyl transpeptidase, *KITT* Rate constant for plasma glucose disappearance, *MAFLD* Metabolic Associated Fatty Liver Disease, *IL-6* Interleukin-6, *TNF* Tumor necrosis factor, *DM* Diabetes mellitus; *LDL-C* Low-density lipoprotein cholesterol, *TG* Triglyceride, *TCH* Plasma total Cholesterol, *FPG* Fasting blood glucose, *FRS* Framingham risk score, *NHANES* National Health and Nutrition Examination Survey

*Dialysis, diabetes, peripheral vascular disease, kidney transplant, cardiomyopathy, congestive heart failure, carotid artery occlusion and low-density lipoprotein >189

years. The definition of cardiovascular events of each cohort is shown in Online Table S4.

The quality of the studies was deemed acceptable, as all of them achieved ≥ 6 points in Newcastle-Ottawa Scale scores (Online Table S5).

Association between FIB-4 and CVD events

Eighteen studies with 1,468,427 individuals reported the association between FIB-4 as a categorical variable and CVD events [8–10, 25–39]. The results showed that the higher FIB-4 levels were associated with CVD events (highest vs. lowest, OR: 1.77, 95% confidence interval [CI] 1.58–1.99, I2 = 76%, τ2 = 0.03, Fig. 2A). When the FIB-4 was analyzed as a continuous variable [8, 9, 11, 25, 28–30, 32, 33, 35, 37] (1,329,277 individuals), each unit of the FIB-4 increased the risk of CVD events by 21% (OR: 1.21, 95% CI 1.12–1.31, I2 = 81%, τ2 = 0.01, Fig. 2B). A positive linear association was found (1,329,277 individuals) (P-nonlinearity = 0.000) [8–10, 25–33, 35–39] (Online Figure S1 A).

NAFLD subgroup analyses showed no significant difference in the association between the FIB-4 and CVD events (with NAFLD, FIB-4: OR 1.87, 95% CI 1.53–2.28; without NAFLD, FIB-4: OR 1.74, 95% CI 1.51-2.00, P for difference = 0.56, Fig. 2C).

Association between NFS and incidence of CVD events

Nine studies (819,517 individuals) reported the association between NFS as a categorical variable [8, 10, 27, 28, 31, 33, 35, 37, 38], showing that the relationship between participants with the highest NFS was 2.40 times as associated with CVD events (highest vs. lowest, OR: 2.40, 95% CI: 1.83–3.14, I2 = 76%, τ2 = 0.12; Fig. 3A). When the NFS was treated as a continuous variable [8, 27, 28, 33, 35, 38] (807,182 individuals), each unit of the NFS increased the risk of CVD events by 38% (OR:1.38, 95% CI: 1.17–1.62, I2 = 84%, τ2 = 0.03, Fig. 3B).

NAFLD subgroup analyses showed no significant difference in the association between the NFS and CVD events (with NAFLD, OR 2.59, 95% CI 1.55–4.33; without NAFLD, OR 2.26, 95% CI 1.64– 3.11, P for difference = 0.66, Fig. 3C).

Association between APRI and BARD with the incidence of CVD events

Five cohorts (449,260 participants) showed the association between APRI and CVD events was statistically significant [10, 25, 28, 37, 38] (highest vs. lowest OR: 1.61, 95% CI: 1.17–2.21, I2 = 62%, τ2 = 0.06; each 1 unit increase, OR: 2.20, 95% CI: 1.23–3.93, I2 = 38%, τ2 = 0.12, Fig. 4A-B).

A non-significant association was found for BARD [25, 28, 35], (highest vs. lowest, HR: 1.09, 95% CI: 0.70–1.70, I2 = 26%, τ2 = 0.06; each 1 unit increase, OR:1.07, 95% CI: 0.98–1.16, I2 = 0%, τ2 = 0.00, Online Figure S2A-B).

Meta-regression, sensitivity analysis, publication bias, and GRADE assessment

A multivariate meta-regression analysis was performed on following variables, including mean age, sex, BMI, smoking, region, and study period. No significant sources of heterogeneity were found in the FIB-4 and NFS group (Online Table S6). Sensitivity analysis by leaving one out (Online Figure S3-5) and random effect model was consistent with the main results. GRADE assessment showed low certainty evidence for FIB-4 and BARD, and moderate certainty for APRI (Online Table S7).

Funnel plots, and Egger's test ($P = 0.014$) indicated low evidence of publication bias (Online Figure S5).

Subgroup analyses

Subgroup analyses showed no significant difference according to mean age, sample size, follow-up, study design, region, and adjustment for age, BMI, smoking, high-density lipoprotein, glycated hemoglobin and hypertension in the association between the FIB-4 and CVD events (Online Table S8). The association was stronger in groups with sample size adjustments (OR: 2.30 versus 1.56, $P = 0.001$), sex adjustments (OR: 1.94 versus 1.43, $P = 0.003$), suggesting a subgroup difference in sample size and the adjustment for sex.

Subgroup analyses showed no significant difference according to mean age, follow-up, study design, region, and adjustment for age, sex, BMI, smoking, diabetes, glycated hemoglobin and hypertension for the association between the NFS and CVD events (Online Table S9). The association was stronger in groups with sample size adjustments (OR: 3.60 versus 1.90, $P = 0.01$), suggesting a subgroup difference in sample size.

Discussion

Major finding

This meta-analysis revealed that higher FIB-4 and NFS scores are associated with an increased risk of CVD events, regardless of NAFLD at baseline. An exposure-effect analysis indicated a linear relationship between NFS and CVD events, with each increase in FIB-4 or NFS raising the risk by 21% and 38%, respectively. Furthermore, we firstly showed FIB-4 and NFS risk estimates for cardiovascular events were similar in patients with NAFLD and without NAFLD.

Comparison with previous studies

Although the FIB-4 score and NFS are known for their effectiveness in ruling out patients without liver fibrosis [40–42] and assessing liver-related risk, comprehensive reviews of their association with CVD events are limited. Yi et al. found that FIB-4 and NFS may be useful in identifying those who are at higher risk of CVD among patients with NAFLD [43]. Our research, compiling data

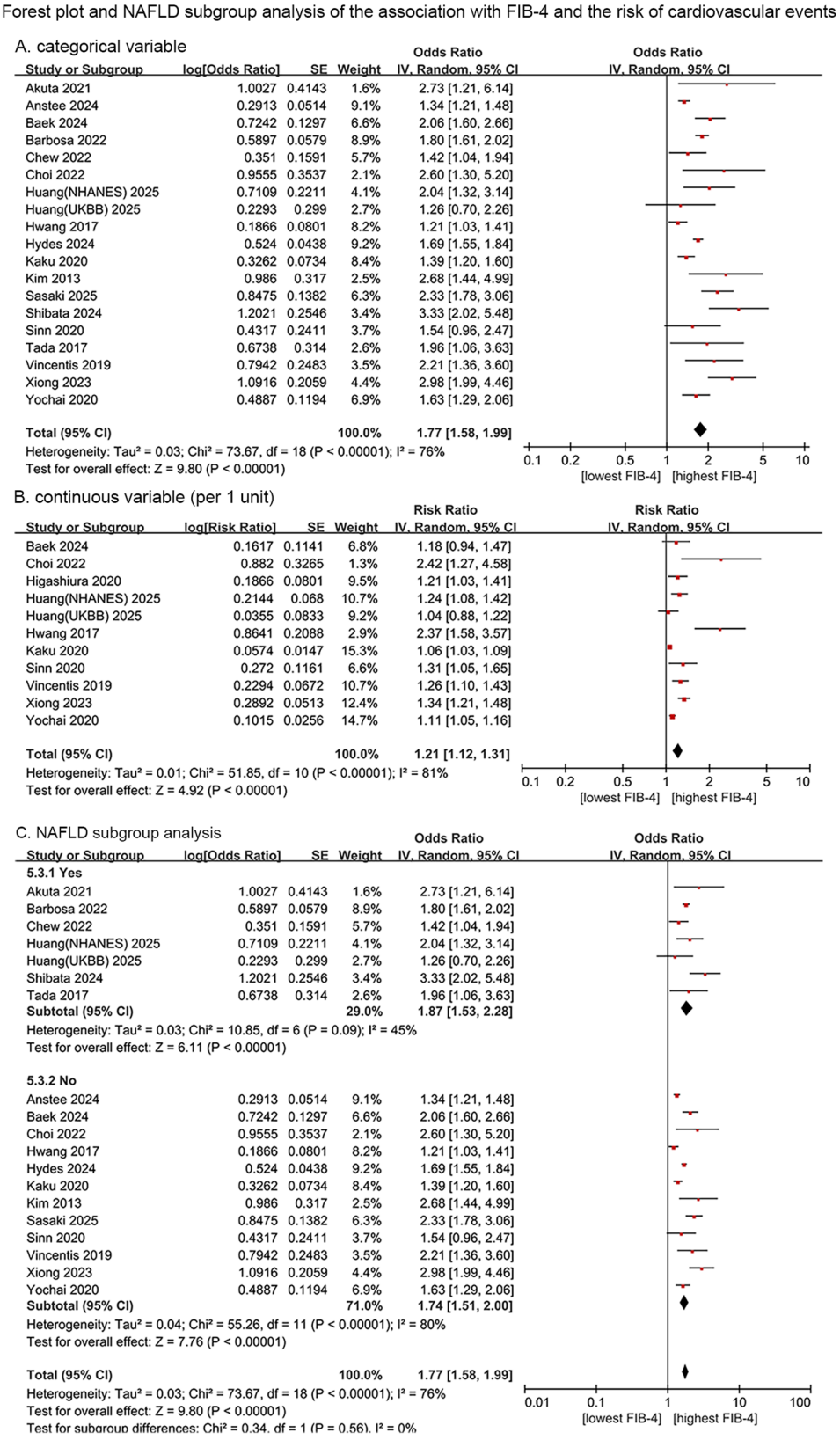


Fig. 2 Forest plot and NAFLD subgroup analysis of the association with FIB-4 and the risk of cardiovascular events. FIB-4 was analyzed as category variables (highest vs. lowest) (**A**); FIB-4 was analyzed as continuous variable (per 1 unit) (**B**); NAFLD subgroup analysis (**C**). In the forest plot, the diamond indicates the pooled estimate. Red boxes are relative to study size and the black vertical lines indicate 95% CIs around the effect size estimate. FIB-4: Fibrosis 4 score; CVD: cardiovascular disease; NAFLD: non-alcoholic fatty liver disease

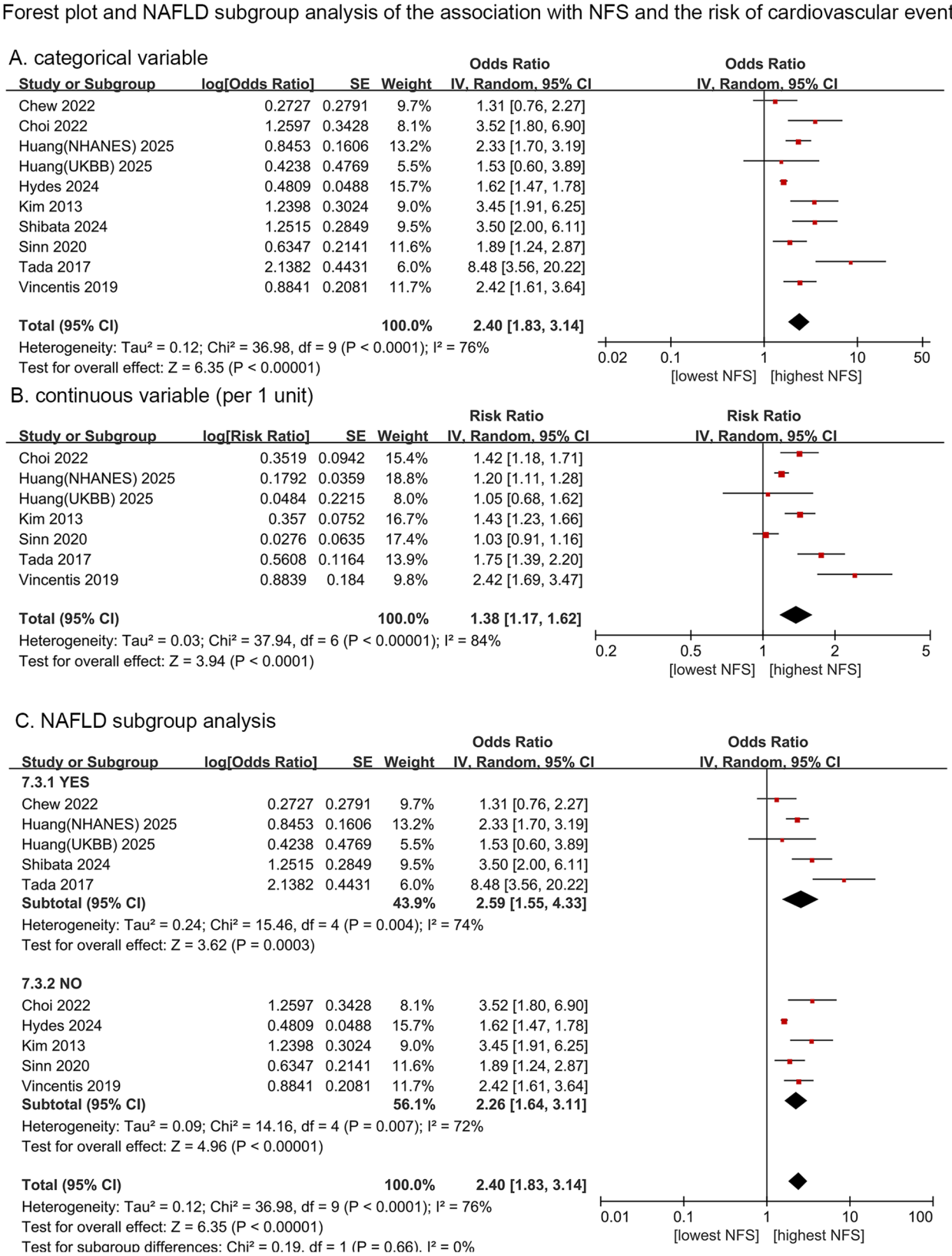


Fig. 3 Forest plot and NAFLD subgroup analysis of the association between NFS with the risk of cardiovascular events. NFS was analyzed as category variables (highest vs. lowest) (**A**); NFS was analyzed as continuous variable (per 1 unit) (**B**); NAFLD subgroup analysis (**C**). In the forest plot, the diamond indicates the pooled estimate. Red boxes are relative to study size and the black vertical lines indicate 95% CIs around the effect size estimate. NFS: NAFLD fibrosis score; CVD: cardiovascular disease; NAFLD: non-alcoholic fatty liver disease

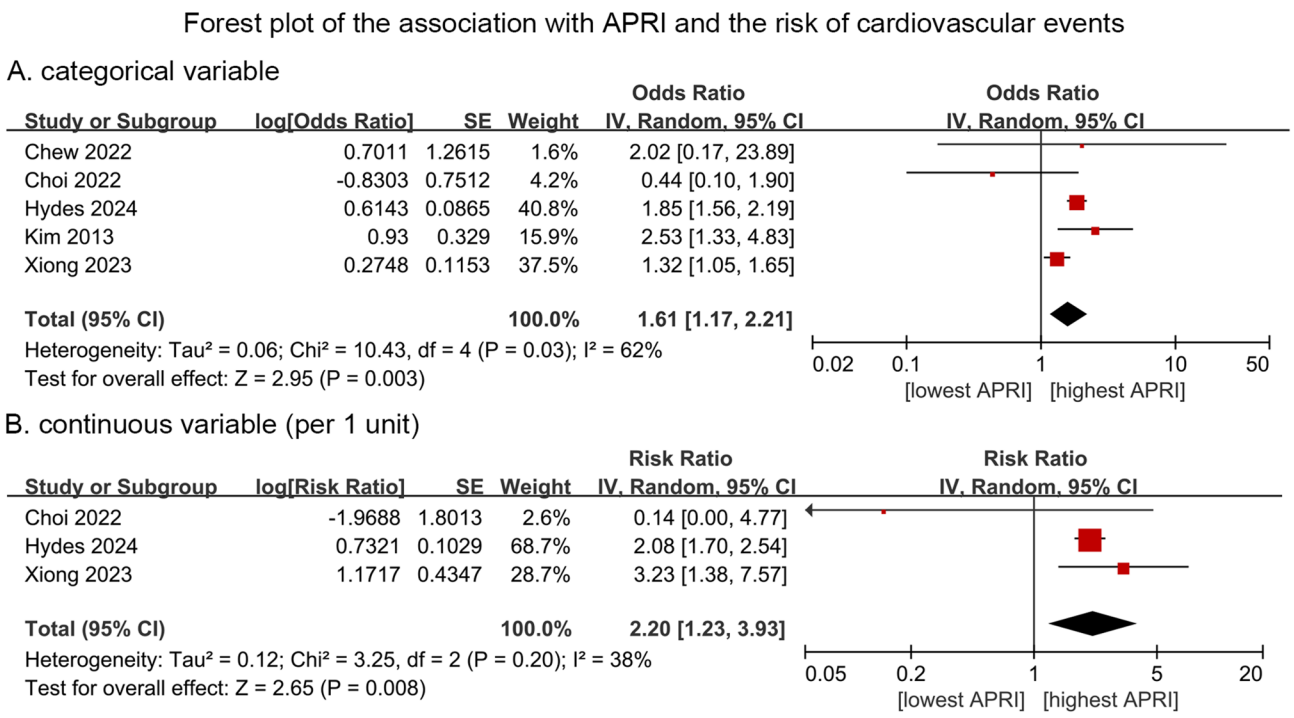


Fig. 4 Forest plot of the association between APRI with the risk of cardiovascular events. APRI was analyzed as category variables (highest vs. lowest) (**A**); APRI was analyzed as continuous variable (per 1 unit) (**B**); In the forest plot, the diamond indicates the pooled estimate. Red boxes are relative to study size and the black vertical lines indicate 95% CIs around the effect size estimate. APRI: aspartate transaminase platelet ratio index; CVD: cardiovascular disease

from 19 longitudinal studies with a total of 1,481,875 participants, demonstrated that both FIB-4 and NFS are significantly associated with CVD events. FIB-4 and NFS risk estimates for cardiovascular events were similar in patients with NAFLD and without NAFLD. We are the firstly meta-analysis that assess the impact of NALFD on the association between FIB-4 score and NFS associated cardiovascular risk.

Our results bring into an interesting question, can LFs improve the predictive ability for the cardiovascular events by adding to traditional models? Recent research suggests impressive results. Xiong et al. demonstrated that incorporating LFs significantly improved the C-statistics, integrated discrimination improvement and net reclassification index for CVD prediction based on 4,164 hypertensive participants without a history of CVD in a community-based prospective cohort [44]. A retrospective analysis of 17,244 participants took utility of LFS as a marker of CVD outcomes, including coronary heart disease, myocardial infarction, congestive heart failure, and stroke, with an area under the receiver operating curve ranging from 0.61 to 0.66 [45]. Despite these findings, comprehensive studies examining whether LFs can serve as new predictors of CVD risk when added to established risk scores, such as the Framingham 10-year CVD risk score, are limited. Our results provide exploratory insights and further study are needed.

Age is a well-known predictor for CVD. Previous articles also reported age difference in the diagnostic ability of LFs for liver fibrosis. Jang et al. revealed that the association between FIB-4 index and the disease did not significantly vary with age ($p = 0.15$). However, a pronounced effect was observed in participants aged 65 and above, with a threefold increase in risk (OR: 3.32, 95% CI: 1.39–7.85) compared to the younger cohort (OR: 1.34, 95% CI: 0.77–2.32) [12]. This suggests a heightened impact of the FIB-4 index on cerebral small vessel disease among the elderly. Further subgroup analysis indicated a stable relationship between FIB-4, NFS, and CVD events across age groups, yet hinted at a stronger connection in the elderly (Online Table S8). Adjei-Mosi's theory on age-related SIRT1 changes potentially exacerbating liver fibrosis underscores the complex interplay between aging, metabolic syndromes, and increased CVD risk [46]. The higher prevalence of metabolic syndrome and diabetes in older adults further elevates CVD incident and mortality rates, underscoring the critical role of age in exacerbating liver fibrosis and cardiovascular events [47, 48]. These findings call for more in-depth research to uncover the mechanisms behind age's amplifying effect on these health issues.

Diabetes is a major risk factor for cardiovascular events in individuals with NAFLD. Data from 30,895 American adults, including 12.9% with diabetes, Wong et al.

identified an association between diabetes, increased FIB-4 scores, and atherosclerotic cardiovascular disease [49]. Further subgroup analysis indicated a stable relationship between FIB-4 and CVD events across diabetes groups, yet hinted at a stronger connection in adjust for diabetes group (Online Table S8).Conversely, Pennisi's study of 542 patients, 11.4% of whom had type 2 diabetes, suggests that diabetes may affect the accuracy of FIB-4, NFS, and similar assessments in those with NAFLD [50]. Kim's et al., involving 363 patients (32.8% diabetes), further highlights the FIB-4 score's limitations in detecting advanced liver fibrosis among diabetics [51]. These findings underline the need for further research to determine if diabetes directly impacts liver fibrosis scores.

Ballestri et al. demonstrated a strong correlation between liver fibrosis biomarkers (APRI, FIB-4, Forns Index) and cardiovascular risk scores in predicting 10-year fatal and non-fatal CVD events. These non-invasive scores showed good accuracy for detecting advanced fibrosis, with marginally superior performance in NAFLD patients versus viral liver disease (e.g., FIB-4 AUROC 0.91 vs. 0.88). Notably, NFS, HFS, and BARD exhibited excellent negative predictive values (96–97%) for excluding advanced fibrosis in NAFLD [52]. We showed NAFLD has no significant impact in the association between the FIB-4 and CVD events (with NAFLD, FIB-4: OR 1.87, 95% CI 1.53–2.28; without NAFLD, FIB-4: OR 1.74, 95% CI 1.51-2.00, P for interaction = 0.56, Fig. 2C). Our recent study showed a positive association between FIB-4, NFS, and APRI scores and the prevalence of heart failure in the general U.S. population and, independent of traditional risk factors [53]. This supports the idea that these scores can identify cardiovascular risk in a general population, not just in patients with known liver conditions. We propose that the ability of scores like FIB-4 and NFS to predict cardiovascular events in individuals without clinically diagnosed liver disease stems from the fact that their components reflect systemic pathophysiological processes that are common to both liver fibrosis and cardiovascular disease. These scores may be acting as composite biomarkers for multisystemic subclinical pathology rather than being specific to the liver: cytokine-driven chronic inflammation (e.g., IL-6, TNF-α), endothelial dysfunction and atherosclerosis, and metabolic health and insulin resistance [54]. Emerging non-invasive tools like FibroScan-AST score can identify high-risk nonalcoholic steatohepatitis-a critical NAFLD stage preceding severe fibrosis [55]. Early detection during the reversible stage of non-alcoholic hepatitis is crucial, as targeted interventions may prevent the progression of cirrhosis and alleviate cardiovascular complications [56]. Overall, the non-invasive fibrosis score has a certain predictive effect on non-liver disease patients.

What do we update?

The meta-analysis by Yi et al. (n = 155,382) linked liver fibrosis score to increased CVD risk in NAFLD patients [43]. Mantovani et al. identified NAFLD as a critical predictor of cardiovascular events, noting that the risk increases with NAFLD severity, especially during the fibrosis phase [57]. Our previous research also highlighted those individuals with elevated baseline levels of FIB-4 or NFS faced worse outcomes in the context of existing cardiovascular diseases [15]. Our recent work highlights a positive association between FIB-4, NFS, and APRI scores and the prevalence of heart failure, independent of liver diseases [53]. Extending these findings, our study revealed that the LFS is significantly linked to a higher risk of cardiovascular events. FIB-4 and NFS risk estimates for cardiovascular events were similar in patients with NAFLD and without NAFLD. These results showed LFS may be a predictor for patients without liver diseases. To our knowledge, this is the first meta-analysis exploring the NAFLD stratified relationship between LFS and the risk of cardiovascular events.

Strength and limitation

This is the first meta-analysis to demonstrate an NAFLD stratified association between LFS and CVD events. Based on pooled results from cohort studies, we showed FIB-4 and NFS risk estimates for cardiovascular events were not influenced by concomitant NAFLD. The inclusion of cohorts and large sample size makes the robustness of present study. However, several limitations should be noted. First, we observed significant heterogeneity across the studies. This variability could stem from differences in baseline characteristics of the study populations. Second, the number of included studies is limited. Our use of comprehensive cardiovascular outcomes (rather than analyzing events such as stroke separately) may lead to imbalanced results in our publication bias assessment. Although no evidence of publication bias cannot be ruled out, larger prospective studies are needed to confirm our results. Third, due to data restriction, we cannot directly evaluate the NAFLD-stratified predictive ability of LFs on CVD events. Last, the binary classification of covariate adjustment failed to capture the differences in adjustment strategies in various studies, which oversimplified complex adjustment practices and could not assess the impact of adjustment comprehensiveness.

Conclusion

In conclusion, the evidence from cohort studies indicates an association between FIB-4 and NFS scores and higher CVD events. FIB-4 and NFS risk estimates for cardiovascular events were not influenced by concomitant NAFLD. These results showed LFS may be a predictor for patients without or without liver diseases. Further prospective research is imperative, particularly among patients without liver diseases.

Abbreviations

APRI	Aspartate transaminase/platelet ratio index
BMI	Body mass index
BARD	Body mass index aspartate transaminase alanine aminotransferase ratio Diabetes
CVD	Cardiovascular disease
CIs	Confidence intervals
FIB-4	Fibrosis 4 score
AST	Glutamic oxaloacetic transaminase
ALT	Glutamic pyruvic transaminase
GRADE	Grading of Recommendations Assessment, Development and Evaluation system
HR	Hazard ratio
LFS	Liver fibrosis score
NFS	Nonalcoholic fatty liver disease fibrosis score
NAFLD	Nonalcoholic fatty liver disease
OR	Odds ratio
PLT	Platelet
PICOS	Population, intervention, comparison, outcome and study design
ULN	Upper limit of normal

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-23883-x.

Supplementary Material 1.

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Authors' contributions
X-L was responsible for the entire project and revised the draft. L-L and L-L conducted the research selection, data extraction, statistical analysis, and data interpretation. L-L drafted the first edition of the manuscript. All authors (J-Z, L-L, L-L, Y.F-W, L.F-H, Z.L-F, D.J-Z, T.L-F, H.L-Z, X-G, X.P-Y, L-X, P-Y, W.T-W) participated in the interpretation of the results and prepared the manuscript of the final version.

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Data availability
All data generated or analyzed during this study are included in this published article [and its Online information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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