

ASSOCIATION BETWEEN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND CARDIOVASCULAR OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growingly recognized multisystem disorder, but the relationship between MASLD and cardiovascular outcomes is not fully understood.

Objective: To comprehensively review and measure the relationship between MASLD and cardiovascular outcomes.

Methods: Longitudinal cohort studies reporting adjusted associations of MASLD, metabolic dysfunction-associated fatty liver disease (MAFLD), or non-alcoholic fatty liver disease (NAFLD) with clinical cardiovascular outcomes were included. Relative effect estimates were pooled using random-effects models. The following were assessed: heterogeneity, prediction intervals, disease-definition subgroups, sensitivity analyses, cohort overlap, and small-study effects.

Results: 19 cohort studies were selected. The composite analysis of cardiovascular disease or major adverse cardiovascular events was based on 10 independent estimates. There was an association with increased composite cardiovascular risk with steatotic liver disease (pooled relative effect 1.48, 95% CI 1.25–1.75; $I^2=96.9\%$), but the prediction interval extended beyond the null (0.82–2.68). Pooled associations were significant for MASLD (1.48, 95% CI 1.17–1.88) and MAFLD (1.62, 95% CI 1.10–2.38), but inconclusive for NAFLD (1.31, 95% CI 0.99–1.74). Increased risks were also observed for heart failure (1.46, 95% CI 1.06–2.00), myocardial infarction (1.34, 95% CI 1.13–

1.58), ischemic stroke (1.14, 95% CI 1.11–1.17), and atrial fibrillation (1.17, 95% CI 1.02–1.35). There was no significant difference in cardiovascular mortality (1.35, 95% CI 0.84–2.18).

Conclusion: There was substantial heterogeneity, different definitions of the disease, and different effect measures, which should be taken into account when interpreting the association of MASLD with multiple cardiovascular outcomes.

INTRODUCTION:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now known to be a multisystem disease, not just a liver disease. It focuses on the presence of hepatic steatosis and cardiometabolic abnormalities such as obesity, insulin resistance, dyslipidaemia, hypertension, and type 2 diabetes. Previously, longitudinal studies using the non-alcoholic fatty liver disease (NAFLD) nomenclature revealed that cardiovascular disease is an important factor in long-term morbidity and mortality [2,8,20]. Further, more recent studies using the metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolically associated hepatic steatosis (MASLD) criteria have also shown the cardiovascular relevance of metabolically associated hepatic steatosis [4,21,27].

The link between MASLD and cardiovascular disease could be due to the interplay between hepatic and systemic metabolic dysfunction. Atherosclerosis, myocardial dysfunction and cardiac electrical instability may be caused by insulin resistance, atherogenic dyslipidaemia, chronic inflammation, endothelial dysfunction, oxidative stress and prothrombotic activity. The cardiovascular risk might not be limited to people who are obese; there is also an increased cardiovascular risk reported in non-obese and non-overweight people with fatty liver disease [3,45]. These findings indicate that hepatic steatosis and related metabolic changes could be clinically useful parameters other than anthropometric parameters.

Population-based cohorts, national insurance databases, health-screening programs, community studies, and histology-confirmed cohorts have all been associated with fatty liver disease and composite cardiovascular disease and major

adverse cardiovascular events [12,27,36,40,44]. There are also associations with myocardial infarction [7,39,43] and ischemic stroke [6,39,41], as well as with heart failure and hospitalization for heart failure [6,41] and atrial fibrillation and other cardiac arrhythmias [5,32,38]. Longitudinal histology-based studies also indicate that the cardiovascular and mortality risk could be different based on the degree of hepatic fibrosis [9,13,14,35,36].

Although evidence is growing, the magnitude and consistency of cardiovascular risk remain unclear. Various definitions of NAFLD, MAFLD, and MASLD have been used in studies, and hepatic steatosis has been detected by ultrasonography, liver histology, diagnostic codes, the fatty liver index, or clinical algorithms. Differences also exist in cardiovascular endpoints, comparator groups, covariate adjustment, and follow-up duration. Also, investigators have reported various effect measures such as hazard ratios, subdistribution hazard ratios, and risk ratios. The results of cardiovascular mortality have been more variable [10,16,22,25]. There is also the risk of double counting when the studies are quantitatively synthesized because of potential overlap of participants across studies from the same national databases.

Thus, the purpose of this systematic review and meta-analysis was to assess the relationship between MASLD and poor cardiovascular outcomes in prospective cohort studies. The main goal was to measure the relationship between the composite cardiovascular disease or major adverse cardiovascular events. Secondary endpoints included cardiovascular mortality, myocardial infarction, ischemic stroke, heart failure, and atrial fibrillation; comparisons of estimates based on the

different definitions of MASLD, MAFLD, and NAFLD; and analyses of heterogeneity, prediction intervals, sensitivity analyses, small study effects, and overlapping cohorts.

Methods:

Study Design and Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines were followed for this systematic review and meta-analysis. There was no prospective registration of the review protocol. A systematic search was conducted in PubMed/MEDLINE and Europe PMC from 1st January 2021 to 23rd August 2026. Google Scholar was used as an additional source to find other eligible publications. The reference lists and citation records of relevant articles were also searched to find studies that were not identified by the database search.

Controlled vocabulary and free text terms were used in the search for steatotic liver disease and cardiovascular outcomes. The keywords used were “metabolic dysfunction-associated steatotic liver disease,” “MASLD,” “metabolic dysfunction-associated fatty liver disease,” “MAFLD,” “non-alcoholic fatty liver disease,” “NAFLD,” “cardiovascular disease,” “major adverse cardiovascular events,” “myocardial infarction,” “stroke,” “heart failure,” “atrial fibrillation,” and “cardiovascular mortality.” Boolean operators “AND” and “OR” were used to combine the terms. Only studies involving human subjects and published in English were searched. Studies that included the older terms MAFLD or NAFLD were included when the exposure definition was hepatic steatosis with metabolic dysfunction, or when there was clinically relevant evidence appropriate for the prespecified analyses, given the recent introduction of the term MASLD.

Eligibility, Study Selection, and Data Extraction

Original longitudinal cohort studies were eligible if they included adults with either MASLD, MAFLD, or NAFLD; an appropriate comparison group without the liver disease; reported incident cardiovascular outcomes during follow-up; and an

adjusted effect estimate with a corresponding 95% confidence interval. HRs, SDHRs, and RRs were acceptable. Studies had to report at least one of the prespecified outcomes: composite cardiovascular disease or major adverse cardiovascular events, heart failure, cardiovascular mortality, myocardial infarction, stroke, or atrial fibrillation.

Cross-sectional studies, case reports, case series, reviews, meta-analyses, editorials, commentaries, conference abstracts with inadequate data, and studies with only surrogate cardiovascular markers were excluded. Studies that failed to report an adjusted effect estimate and/or an appropriate non-steatotic liver disease comparator were also excluded. For multiple publications that included overlapping populations, the publication with the most relevant outcome, the longest follow-up, the largest sample size, or the most complete adjustment was chosen for each analysis. Nineteen original longitudinal cohort studies were eligible and included in the systematic review.

Titles and abstracts were reviewed for relevance, and then full-text articles were assessed for eligibility. A standard extraction form was used to extract data. Data gathered consisted of the first author, year of publication, country of origin, data source, study design, number of patients, participant characteristics, definition of liver disease, definition of the comparator, duration of follow-up, definition of the cardiovascular outcome, number of events, effect measure, adjusted effect estimate, 95% confidence interval, and covariates included in the statistical model. The primary analysis was based on the estimate of the most fully adjusted model. If results were reported for multiple eligible subgroups of liver disease, estimates were extracted separately only when this did not lead to double counting of the same individuals in a pooled analysis.

Outcomes and Management of Overlapping Cohorts

The main outcome was incident composite cardiovascular disease or major adverse cardiovascular events. Secondary outcomes were heart failure, cardiovascular mortality, myocardial infarction, stroke, and atrial fibrillation. The

original investigators reported outcome definitions that were accepted due to the variability in the composition of the composite outcomes. The differences were taken into account when interpreting statistical heterogeneity.

Potential overlap in population was explored by comparing the country, database, recruitment period, participant characteristics, and outcome definitions of the studies included. Studies with overlapping populations (Korean National Health Insurance Service or UK Biobank) for the same outcome were not combined in the same outcome-specific analysis if they were the same study population and outcome. The study with the most relevant and fully adjusted estimate was kept. But articles from the same database might result in different outcome analyses if they assessed different endpoints and did not include the same pooled estimate.

Risk of Bias Assessment

The methodological quality of the studies included in the cohort studies was assessed using the Newcastle–Ottawa Scale. This tool evaluates three areas: selection of study population, comparability of the exposed and comparison groups, ascertainment of outcomes, and follow-up. A maximum of 9 points were possible for studies. A score range of 7-9 was regarded as low risk of bias, 5-6 as moderate risk of bias, and < 5 as high risk of bias. Risk-of-bias assessments were not used as a basis for excluding studies from the pooled findings or sensitivity analyses, but rather were used in interpreting the pooled findings and sensitivity analyses.

Statistical Analysis

Logarithmically transformed and pooled effect estimates and 95% confidence intervals were calculated using the generic inverse-variance method. Random-effects models were used for all meta-analyses because there were anticipated differences in clinical and methodological approaches across populations, definitions of liver disease, definitions of outcomes, follow-up periods, and adjustment models. The restricted

maximum-likelihood method was used to estimate between-study variance. The pooled effects were back-transformed to the original ratio scale and presented with 95% confidence intervals.

Relative effect measures (hazard ratios, subdistribution hazard ratios, and risk ratios) were used because the cardiovascular outcomes were generally uncommon and the studies included in the analysis assessed longitudinal associations. Sensitivity analyses were conducted to explore implications of the combination of different effect measures. These measures were not pooled with odds ratios unless they could be reasonably considered to be a risk ratio and were clinically similar.

Cochran's Q test, between-study variance estimate (τ^2), and I^2 statistic were used to assess statistical heterogeneity. Low, moderate, and high heterogeneity were defined as I^2 values of around 25%, 50%, and 75%, respectively. Due to the limited power of this test, a two-sided Q-test probability value < 0.10 was taken as evidence of heterogeneity. For analyses with enough studies to describe the range in which the effect of a future similar study might be expected, 95 per cent prediction intervals were calculated.

Separate meta-analyses were performed for composite cardiovascular outcomes, heart failure, cardiovascular mortality, myocardial infarction, stroke, and atrial fibrillation. Subgroup analyses were performed based on the terminology and diagnostic criteria of the original studies, such as MASLD, MAFLD, and NAFLD. Sensitivity analyses were conducted by excluding studies with limited or clinically different comparator groups, excluding influential studies, limiting analysis to hazard ratios, and excluding overlapping cohorts. To check for any single study that had an undue effect on the pooled estimate, leave-one-out analyses were conducted.

Only for an outcome with 10 or more independent studies, small-study effects were assessed by inspection of the funnel plots and by Egger's regression test. The Egger test was not applied to outcomes with fewer than 10 studies, due to the limited reliability of Egger's test in small meta-analyses. Pooled effect estimates were

considered statistically significant if the two-sided p-value was < 0.05 . All analyses were conducted in Python 3.12 using well-known statistical packages for inverse-variance random-effects meta-analysis.

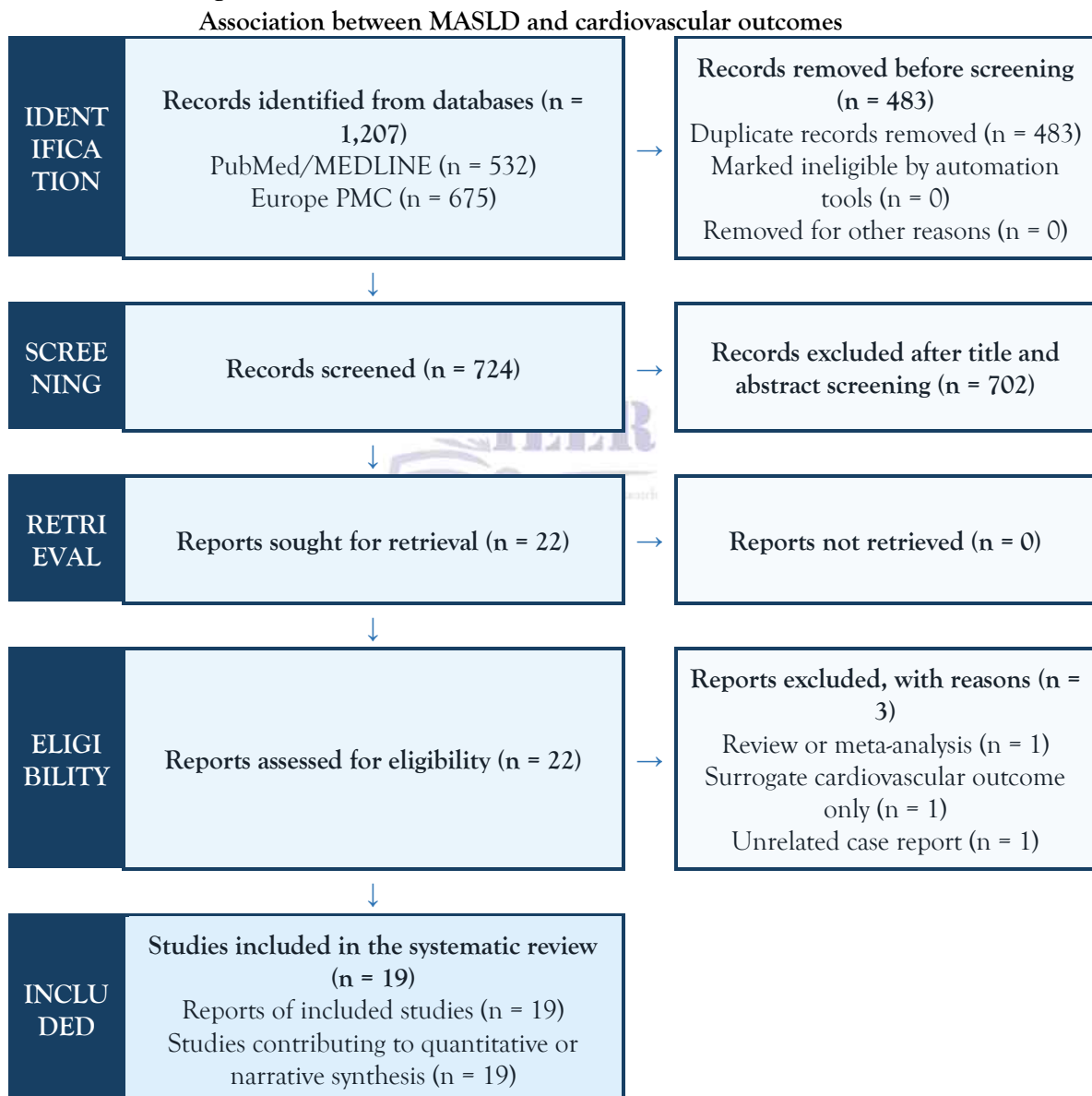
Results:

Study selection

Nineteen original longitudinal cohort studies were eligible and included in the systematic review. All

retained studies reported clinical cardiovascular outcomes and could be used for quantitative or narrative synthesis with an adjusted relative-effect estimate. Reviews, meta-analyses, case reports, non-longitudinal investigations, or studies reporting only surrogate cardiovascular markers were not included.

PRISMA 2020 Flow Diagram



Note. Database Counts were obtained from a reproducible search completed on 12 August 2026. All boxes, numbers, and exclusion reasons are editable Word content.

Characteristics of Included Studies

The 19 studies were published from 2021 to 2026, and the studies took place in Asia, Europe, Australia and the United States. The number of participants in individual study populations ranged from 2,985 to 5,666,728, and follow-up ranged from 4.0 to 22.8 years. The investigations included population-based prospective and retrospective cohorts, national insurance

databases, health-screening cohorts, community cohorts, and one national histopathology cohort. The most common way to detect hepatic steatosis was by using the fatty liver index. Other studies employed ultrasonography, claims algorithms, or liver histology. The exposure groups of contemporary MASLD criteria, MAFLD criteria, and legacy NAFLD were kept. Cardiovascular outcomes were composite CVD or MACE, cardiovascular mortality, myocardial infarction, ischemic stroke, heart failure, and cardiac arrhythmias.

Table 1. Characteristics of the 19 included cohort studies

Study	Country	Sample	Follow-up	Exposure	Outcome
Baek 2024	South Korea	104,399	10.6 y	MASLD; FLI/FIB-4	Incident CVD
Ma 2022	United Kingdom	215,245	To 2020	NAFLD; FLI	MACE/CV death/MI/stroke
Huang 2021	United States	12,480	22.8 y	MAFLD/NAFLD; ultrasound	CV mortality
Chang 2025	Taiwan	26,676	6 y	MASLD among SLD	HF/HF hospitalization/HFpEF
Mayen 2024	Europe	15,784	15.6 y	FLI/MAFLD	CV mortality
Park 2022	South Korea	240,301	6.7 y	Dynamic NAFLD; FLI	HF/CV mortality
Simon 2023	Sweden	63,062	10.8 y	Histology MASLD	Arrhythmias
Wei 2023	China	98,685	14.0 y	MAFLD; ultrasound	Heart failure
Yoneda 2021	Japan	>1.5 million	4 y	MAFLD/NAFLD	Incident CVD
Jeong 2022	South Korea	333,389	5.5 y	MAFLD; K-NAFLD	Incident CVD
Moon 2022	South Korea	8,919	15.7 y	MAFLD/NAFLD; FLI	CVD/mortality
Niriella 2021	Sri Lanka	2,985	7 y	MAFLD/NAFLD; ultrasound	Fatal/nonfatal CVD
Vaz 2024	Australia	1,444	~20 y	MAFLD/NAFLD; FLI	MACE/CV death/AF
Moon 2023	South Korea	351,068	9 y	MASLD/MetALD/ALD	MI/stroke composite
Chung 2025	South Korea	5,666,728	10.6 y	MASLD; FLI	MACE/MI/stroke/HF
Yin 2025	Taiwan	303,589	10.4 y	Ultrasound MASLD	Multiple CVD outcomes
Huber 2025	Germany	14,575	5.0 y	MASLD; FLI	MACE/eMACE

Hirooka 2026	Japan	24,384	5.2 y	Ultrasound MASLD	CVD/hypertension
Feng 2026	United Kingdom	486,156	13.8 y	SLD; FLI/FIB-4	CV mortality

Risk of bias

All studies included were observational cohorts. Several common weaknesses were found, such as the use of surrogate markers or administrative algorithms to define steatotic liver disease, residual confounding, and differences in definitions of cardiovascular outcomes and possible overlap between national database cohorts. Most studies used multivariable adjustment and longitudinal outcome ascertainment, but the covariates included in the final models differed across studies. Population overlap was dealt with at the synthesis stage by only including one estimate from an overlapping source population in each outcome-specific model.

Quantitative synthesis

Table 2. Summary of random-effects meta-analyses

Outcome	k	Pooled effect (95% CI)	I ² (%)	Tau ²	Interpretation
Composite cardiovascular disease / MACE	10	1.48 (1.25-1.75)	96.9	0.061	Significant
MASLD subgroup	5	1.48 (1.17-1.88)	97.0	0.069	Significant
MAFLD subgroup	4	1.62 (1.10-2.38)	91.5	0.118	Significant
NAFLD subgroup	4	1.31 (0.99-1.74)	73.2	0.055	Not significant
Heart failure	4	1.46 (1.06-2.00)	92.3	0.099	Significant
Cardiovascular mortality	3	1.35 (0.84-2.18)	94.6	0.170	Not significant
Myocardial infarction	2	1.34 (1.13-1.58)	94.6	0.014	Significant
Ischemic stroke	2	1.14 (1.11-1.17)	0.0	0.000	Significant
Atrial fibrillation	2	1.17 (1.02-1.35)	91.3	0.010	Significant

Composite cardiovascular disease and major adverse cardiovascular events

Ten independent cohort estimates were included in the exploratory composite cardiovascular analysis. To avoid double counting, only one estimate from overlapping national cohorts of Koreans for the same outcome was included, and UK Biobank estimates were not duplicated in the same model. The synthesis included adjusted HRs, subdistribution HRs, and RRs only as an overall relative-effect analysis, and thus disease-definition subgroups and sensitivity analyses have more interpretive value. The composite cardiovascular

outcomes were associated with an increased risk of steatotic liver disease (pooled relative effect 1.48, 95% CI 1.25-1.75). Heterogeneity was considerable ($Q=290.57$, $p<0.001$; $I^2=96.9\%$; $\tau^2=0.061$). The 95% prediction interval was 0.82-2.68, which included the null, suggesting that there was significant variation between settings.

The smaller group of Sri Lankans with the highest effect estimate was excluded, leaving a pooled effect of 1.45 (95% CI 1.23-1.71). Leave-one-out estimates were between 1.41 and 1.54, and were all statistically significant.

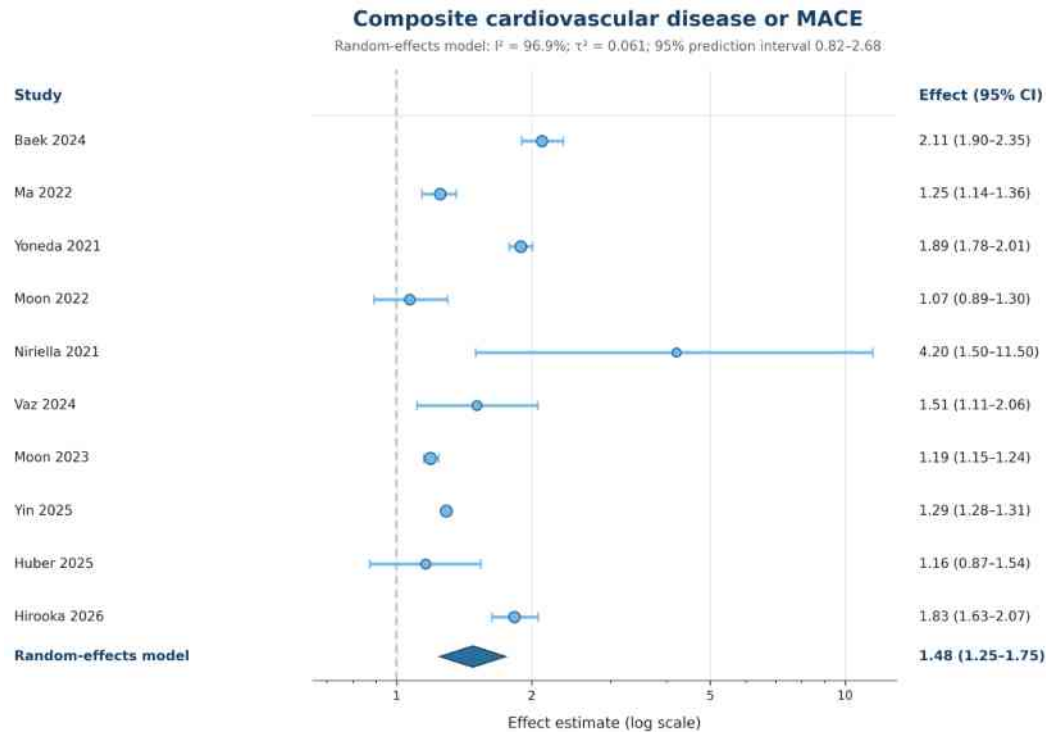


Figure 2. Forest plot for composite cardiovascular disease or major adverse cardiovascular events. Squares show study estimates and horizontal lines show 95% confidence intervals; the diamond shows the random-effects estimate.

Subgroup analysis by disease definition

Five studies applying contemporary MASLD criteria showed an increased risk of composite cardiovascular outcomes (pooled relative effect 1.48, 95% CI 1.17-1.88; $I^2=97.0\%$). Four MAFLD

studies also showed increased risk (pooled relative effect 1.62, 95% CI 1.10-2.38; $I^2=91.5\%$). The legacy NAFLD subgroup produced a smaller, statistically inconclusive association (pooled relative effect 1.31, 95% CI 0.99-1.74; $I^2=73.2\%$).

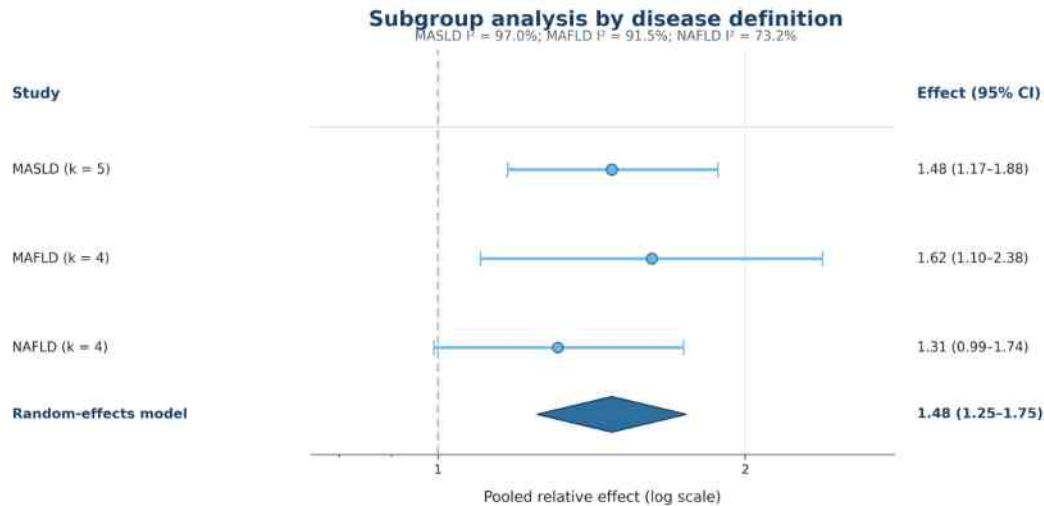


Figure 3. Random-effects subgroup estimates according to MASLD, MAFLD and legacy NAFLD definitions.

Cardiovascular mortality

Three independent cohorts were analyzed in the main cardiovascular mortality study. The pooled association was not statistically significant (pooled HR 1.35, 95% CI 0.84-2.18), with considerable heterogeneity ($Q=37.22$, $p<0.001$; $I^2=94.6\%$; $\tau^2=0.170$). The 95% prediction interval was 0.17-10.63. The pooled HR of 1.68 (95% CI 1.49-

1.90) was significant when the NHANES III estimate was excluded.

Feng et al. was not combined with the earlier UK Biobank estimate because of population overlap. In that study, SLD was associated with cardiovascular mortality (HR 1.57, 95% CI 1.50-1.64), with a graded increase across low, intermediate, and high FIB4 categories: HR 1.34, 2.08, and 2.88, respectively.

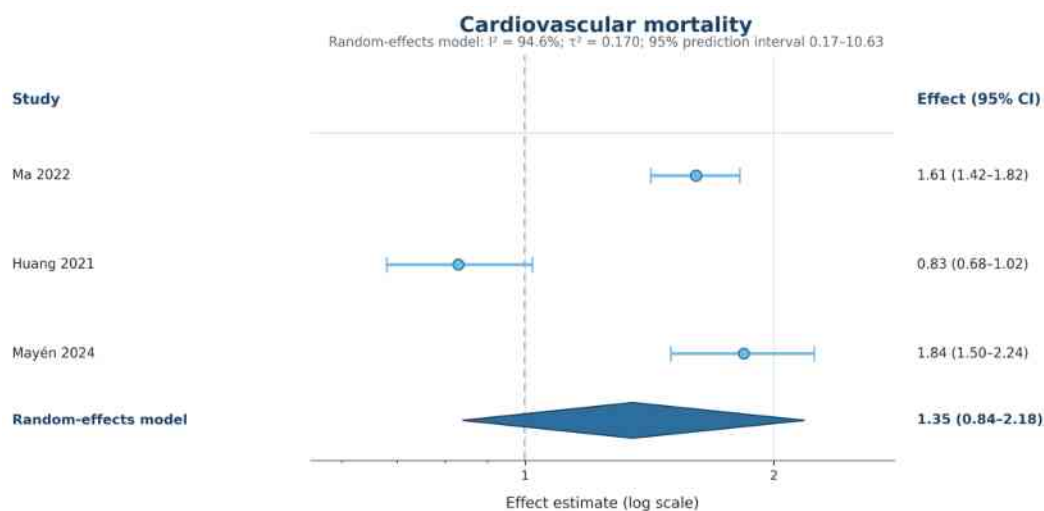


Figure 4. Forest plot for cardiovascular mortality.

Heart failure

Four independent cohorts were included in the exploratory heart-failure meta-analysis. MASLD or MAFLD was associated with incident heart failure (pooled relative effect 1.46, 95% CI 1.06-2.00; $Q=38.87$, $p<0.001$; $I^2=92.3\%$; $\tau^2=0.099$). The prediction interval was 0.47-4.49 and crossed the null. Chang et al. compared MASLD with non-MASLD among patients who already had SLD and reported an SHR, whereas the other cohorts used general-population comparators. Excluding this

restricted-comparator study reduced the pooled estimate to 1.25 (95% CI 1.13-1.38; $I^2=89.7\%$), although heterogeneity remained high.

The Taiwanese cohort reported associations with incident HF (subdistribution HR 2.59, 95% CI 1.84-3.64), HF hospitalization (2.30, 95% CI 1.31-4.04), and HFpEF (1.91, 95% CI 1.27-2.86). Regression of hepatic steatosis was associated with lower risks of incident HF (HR 0.80, 95% CI 0.69-0.93) and hospitalized HF (HR 0.65, 95% CI 0.51-0.81) than persistent steatosis.

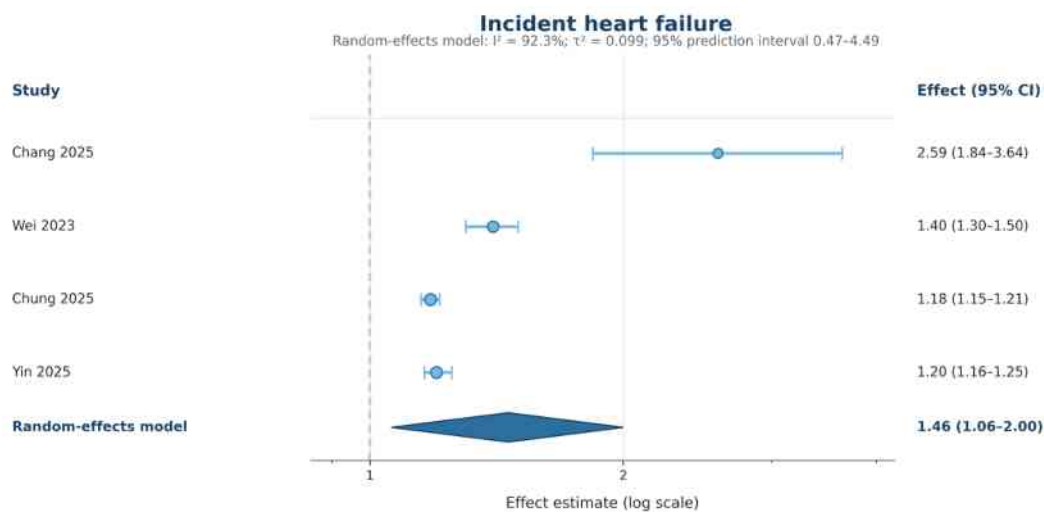


Figure 5. Forest plot for incident heart failure.

Myocardial infarction

Two independent MASLD cohorts reported myocardial infarction. MASLD was associated with increased MI risk (pooled effect 1.34, 95% CI 1.13-1.58), although heterogeneity was

considerable ($Q=18.64$, $p<0.001$; $I^2=94.6\%$; $\tau^2=0.014$). Because only two estimates were available, this result should be interpreted cautiously.

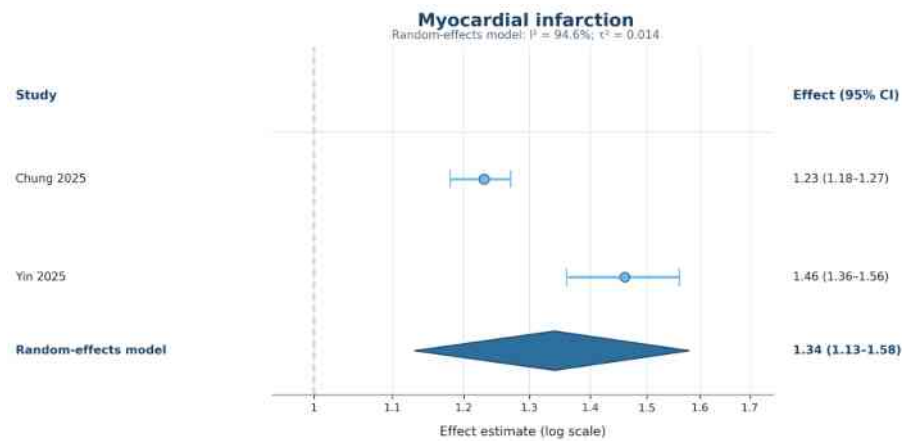


Figure 6. Forest plot for myocardial infarction.

Ischemic stroke

Two independent cohorts reported ischemic stroke. MASLD was associated with a modest but statistically significant increase in stroke risk

(pooled effect 1.14, 95% CI 1.11-1.17). The study estimates were consistent ($Q=0.84$, $p=0.36$; $I^2=0\%$; $\tau^2=0$).

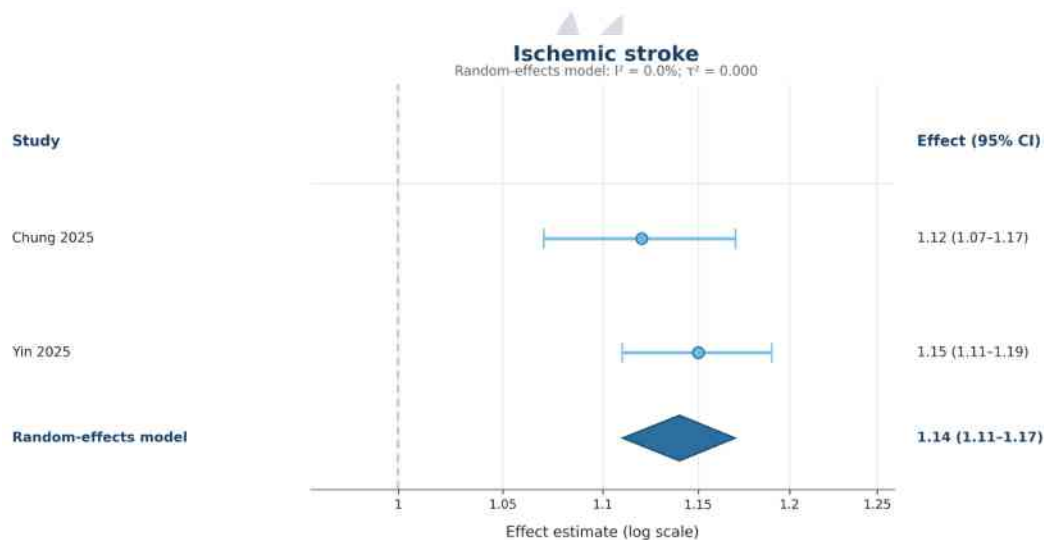


Figure 7. Forest plot for ischemic stroke.

Atrial fibrillation and other arrhythmias

Two independent studies reported atrial fibrillation. MASLD was associated with increased AF risk (pooled effect 1.17, 95% CI 1.02-1.35), with substantial heterogeneity ($Q=11.44$, $p<0.001$; $I^2=91.3\%$; $\tau^2=0.010$).

The Swedish histology cohort additionally found associations with any cardiac arrhythmia (HR

1.30, 95% CI 1.22-1.38), ventricular arrhythmia or cardiac arrest (1.53, 95% CI 1.30-1.80), bradyarrhythmia (1.26, 95% CI 1.06-1.48) and other supraventricular arrhythmias (1.27, 95% CI 1.00-1.62). These endpoints were summarized narratively because only one study reported each category.

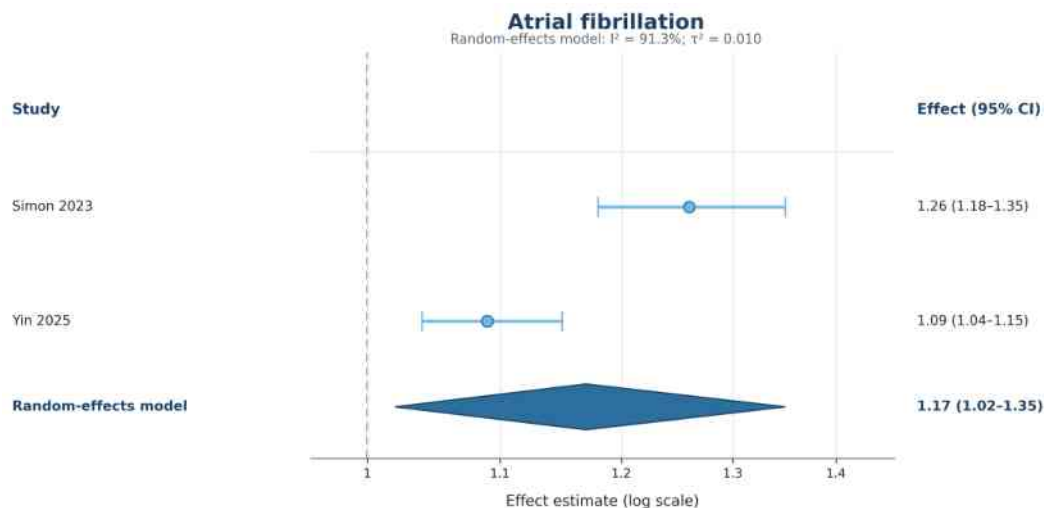


Figure 8. Forest plot for atrial fibrillation.

Influence of liver disease severity

Several studies showed associations that were severity-dependent. The Korean screening cohort showed that MASLD (FIB-4 ≥ 1.3) was associated with incident CVD (HR 2.27, 95% CI 1.87-2.76). The UK Biobank study revealed a gradual rise in cardiovascular deaths by FIB-4 category. The Swedish histology cohort also reported the highest absolute risks of arrhythmias in those with cirrhosis.

Sensitivity analyses and cohort overlap

Studies conducted by the Korean National Health Insurance Service (KNHIS) and publications from the UK Biobank were found to overlap. Each outcome model had only one estimate from an overlapping source population. Other estimates of sensitivity or narrative analysis were kept. The synthesis (pooled HR 1.34, 95% CI 0.84-2.15) was not materially changed when the earlier UK Biobank cardiovascular-mortality estimate was replaced with the later SLD analysis. When the age- and sex-adjusted Sri Lankan RR was not included in the composite analysis, the pooled relative effect was 1.45 (95% CI 1.23-1.71). Limiting the contemporary MASLD composite analysis to HRs yielded HR 1.69 (95% CI 1.21-2.35; $I^2=87.2\%$) with only three studies included.

Small-study effects and publication bias

Only composite cardiovascular outcomes were assessed formally, as this was the only analysis with at least 10 independent estimates. There was no statistically significant asymmetry ($p=0.22$) in the regression of Eggers. There was still significant clinical and statistical heterogeneity in interpretation. The other outcomes were not tested for publication bias due to the small number of independent studies (less than 10) in each outcome.

Overall Synthesis

Longitudinal evidence indicated that metabolic dysfunction-associated steatotic liver disease was associated with higher risks of composite cardiovascular events, heart failure, myocardial infarction, ischemic stroke, and atrial fibrillation. The main cardiovascular-mortality analysis was directionally positive but not statistically significant due to significant heterogeneity. The association was most consistent for ischemic stroke, and there was significant between-study variability for other outcome analyses. Heterogeneity may have been due to differences in disease definition, population, cardiovascular

endpoint, severity of fibrosis, adjustment strategy, and follow-up duration.

Discussion:

This meta-analysis of 19 longitudinal cohort studies suggests that definitions of MASLD and steatotic liver disease are linked to higher risk of composite cardiovascular outcomes, heart failure, myocardial infarction, ischemic stroke and atrial fibrillation. There was a positive, but not statistically significant, association with cardiovascular mortality. While most pooled estimates showed an increased risk, there was significant heterogeneity and prediction intervals that crossed the null for several outcomes, indicating that the magnitude of association is variable across populations and clinical settings.

The higher risk of composite cardiovascular disease or MACE was similar to what has been observed in large cohorts in other geographic regions [4,12,17,18,26,27,40,44]. This association was also present in leave-one-out and sensitivity analyses, even when the smaller Sri Lankan cohort with the largest estimate was excluded [28]. The large prediction interval, however, suggests that a similar relationship might not be seen in other populations in the future. Heterogeneity may have been due to differences in the characteristics of the participants, the definition of metabolic risk, the length of follow-up, the definition of steatosis, or the manner in which the covariate was adjusted.

The results were also affected by the definition of disease. The estimate was significantly associated in the MASLD and MAFLD subgroups, and was not significantly associated in the NAFLD subgroup. The metabolic abnormalities included in the MASLD and MAFLD criteria are also recognized cardiovascular risk factors, and may thus identify populations with a higher cardiometabolic burden [1,11,15,19,23,34]. However, these subgroup differences should not be viewed as evidence of a better cardiovascular prognostic performance of one definition, as the analyses were based on relatively small numbers of studies from various populations. They mainly illustrate that the definition of disease and the risk

factors used for diagnosis can have a significant impact on cardiovascular risk estimates.

The pooled estimate was affected by the choice of comparator, and MASLD/MAFLD was linked to incident heart failure. The other studies used general-population comparators [6], while Chang et al. compared MASLD with non-MASLD among those with preexisting steatotic liver disease. This limited-comparator study did not completely remove the association. Longitudinal evidence also shows that the presence of persistent steatosis is linked to increased risk of heart failure, and that regression of steatosis is linked to decreased risk of incident and hospitalized heart failure [29]. The Kailuan cohort also showed a correlation between MAFLD and the development of heart failure over the long-term follow-up [41]. The results indicate that the risk of heart failure might be different depending on the degree and duration of liver disease.

Insulin resistance, systemic inflammation, endothelial dysfunction, oxidative stress, dyslipidaemia, activation of the renin-angiotensin-aldosterone system and adverse cardiac remodelling are potential links between MASLD and heart failure and atherosclerotic events [3,14,21,35,42,45]. These mechanisms are, however, largely shared with obesity, diabetes and hypertension. Therefore, the present results do not demonstrate a direct link between hepatic steatosis and cardiovascular disease or whether it is a marker of cumulative metabolic dysfunction.

The pooled analyses also demonstrated increased risks of myocardial infarction and ischemic stroke. There was good consistency in the estimates of stroke among the two contributing cohorts, but large heterogeneity in the estimates of myocardial infarction [7,43]. Due to the limited number of independent studies that were used for each analysis, the apparent differences in consistency should be viewed with caution. There is the potential for residual confounding as diabetes, hypertension, obesity, dyslipidaemia, smoking, medication use, and socioeconomic status were not measured or adjusted for in all of the included studies.

An elevated risk for atrial fibrillation was also found, but with significant heterogeneity and a limited number of cohorts available, there is less certainty. The Swedish histology cohort found a higher risk of atrial fibrillation and other cardiac arrhythmias [38]. Other longitudinal studies have linked fatty liver disease with atrial fibrillation, especially in individuals with diabetes or more metabolic dysfunction [5,30,32]. This relationship may be mediated by systemic inflammation, autonomic dysfunction, and structural atrial remodelling, but additional outcome-specific evidence is needed.

The cardiovascular-mortality analysis was not as definitive. This variation between studies could be due to the different definitions of liver disease, the competing mortality risks, the length of follow-up, and the classification of cause of death [10,16,22,25]. The NHANES III estimate resulted in a statistically significant association when it was excluded. The UK Biobank estimate was not included in the earlier UK Biobank study due to population overlap and was reported to be associated with an increased risk of cardiovascular death, with a graded association across the FIB-4 categories [10,22]. The evidence available therefore suggests a possible association, but is not robust enough to give a reliable estimate of the risk of cardiovascular mortality.

A few studies showed higher cardiovascular associations with higher FIB-4 scores or more severe liver disease [4,10,33,36]. In histological and population-based cohorts, fibrosis severity has also been shown to be a significant predictor of long-term clinical outcomes [9,13,35]. Previous longitudinal studies also suggest that prognosis is more closely linked to the development of steatohepatitis or fibrosis than to uncomplicated steatosis [2,8,20]. Fibrosis assessment may thus provide a better cardiovascular risk stratification, but should not be seen as a surrogate for imaging- or histology-proven fibrosis.

Strengths and Limitations

In this review, 19 original longitudinal cohorts from various geographical regions were included, and clinical cardiovascular outcomes were

assessed, not surrogate markers. The most fully adjusted estimate was chosen from each study, and potentially overlapping populations from the Korean National Health Insurance Service and UK Biobank were handled separately for each outcome. Subgroup, leave-one-out, and sensitivity analyses were conducted, and prediction intervals were provided when applicable to indicate the potential variation of effects in other settings [31]. The main drawback is that all the studies included were observational, which means that it is not possible to conclude causality. There was potential for exposure misclassification due to the different methods of diagnosis of steatotic liver disease, including fatty liver indices, ultrasonography, histology, and administrative algorithms. Definitions of outcomes and adjustment models also varied. The exploratory primary analysis included HRs, subdistribution HRs, and RRs as relative-effect measures, but sensitivity analyses using only HRs were performed.

A number of secondary analyses had only two to four independent studies, which reduced the precision of pooled estimates and heterogeneity statistics. Assessment of publication bias was thus limited to the composite cardiovascular analysis. The results of Egger's test were not statistically significant, but small-study effects cannot be ruled out. Some pooled estimates also showed substantial heterogeneity and prediction intervals that crossed the null, which also reduces the generalizability of some of these estimates, as seen in previous evidence syntheses [24,30]. Other limitations include restricting to English-language articles and including studies that used previous NAFLD and MAFLD definitions.

Implication for Future Research

Future prospective studies should employ the same criteria for MASLD, well-defined comparator groups, and validated cardiovascular outcomes. Exposure misclassification would be minimized if imaging or histological confirmation of steatosis and fibrosis were available. Myocardial infarction, stroke, heart-failure phenotypes, atrial fibrillation, and cardiovascular mortality should be reported separately, and not just as composite outcomes.

The liver should also be assessed repeatedly to see if there is any improvement or worsening of liver disease and, if there is, whether it is matched by a change in cardiovascular risk [29]. Studies should be conducted to assess the value of fibrosis measures beyond known cardiovascular risk factors [9,13,33]. Individual-participant-data meta-analysis could be useful to standardize diagnostic criteria, outcome definitions and covariate adjustment, and to determine if associations vary by age, sex, ethnicity, diabetes, obesity, or fibrosis severity.

To determine if lifestyle modification, weight reduction, or pharmacological treatment of MASLD is effective at reducing cardiovascular events in addition to improving hepatic measures, interventional research is needed. In addition, cardiovascular effects should be assessed throughout the lifespan as steatotic liver disease in younger populations could be a marker of chronic cardiometabolic exposure [7,37].

Conclusion

The risks of composite cardiovascular events, heart failure, myocardial infarction, ischemic stroke, and atrial fibrillation were increased with the MASLD and related steatotic liver disease definitions. The link with cardiovascular death was not clear. These results provide evidence to support cardiovascular risk stratification in patients with MASLD, especially in those with metabolic comorbidities and/or advanced fibrosis. There is, however, significant variation, and the evidence is observational, so care should be taken in interpretation. Further prospective and interventional studies are required to establish whether the presence of MASLD is a risk factor for cardiovascular disease and whether intervention for liver and metabolic dysfunction decreases cardiovascular events.

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Note: A dagger (†) identifies one of the 19 included parent studies.

