The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 4, Issue 2, 2026

ASSOCIATION BETWEEN NONALCOHOLIC FATTY LIVER DISEASE AND CARDIO-METABOLIC OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS EVALUATING THE RISK OF DIABETES, CARDIOVASCULAR EVENTS, AND MORTALITY

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DOI: https://doi.org/10.5281/zenodo.18586830

Keywords
Nonalcoholic fatty liver disease; NAFLD; metabolic dysfunction-associated steatotic liver disease; type 2 diabetes mellitus; cardiovascular disease; mortality; systematic review; meta-analysis.

Article History
Received: 11 December 2025
Accepted: 26 January 2026
Published: 10 February 2026

Abstract

Background:
Nonalcoholic fatty liver disease (NAFLD) is being recognized as a multi-system metabolic disorder that is closely related to insulin resistance and cardiovascular risk. While often independent of obesity, NAFLD has been linked to poor cardio-metabolic outcomes, and the extent and consistency of associations of the disease with incident type 2 diabetes mellitus (T2DM), cardiovascular events and mortality in population-based cohorts is uncertain.

Objectives:
To systematically review and quantitatively synthesize evidence of the association of NAFLD with risk of incident T2DM, CVD events and mortality in adult populations.

Methods:
PubMed, Scopus and Web of Science were also systematically searched for literature on the inception of data bases assessing the association of NAFLD with the occurrence of T2DM, cardiovascular events or mortality. Studies with

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multivariable-adjusted hazard ratios (HRs) of the risk of having versus not having NAFLD compared to non-NAFLD were included in the quantitative meta-analysis. HRs were pooled by use of random-effects models (DerSimonian-Laird). Heterogeneity was tested using the I^2 statistic. Articles that had reported different contrasts (e.g., NAFLD regression VS persistence, severity-based comparisons, phenotype-specific analyses, etc.) or incomparable effect measures were synthesized in the form of narrative synthesis. The review was conducted using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results:

Ten cohort studies were eligible for the systematic review with five of them providing comparable multivariable-adjusted HRs and eligible for quantitative synthesis. A significantly higher risk of incident T2DM was linked to NAFLD (pooled HR 2.04, 95% CI 1.52-2.74; I^2= 38.2%). The combined effect of NAFLD and cardiovascular events demonstrated non-significant positive trend of risk increase with a high degree of heterogeneity (pooled HR 1.09, 95% CI 0.98-1.21; I^2 = 82.4%). Mortality quantitative pooling could not be done because there were only a few eligible studies; nevertheless, biopsy-confirmed NAFLD was linked to very high all-cause and cardiovascular mortality on a large nationwide cohort. Narrative synthesis of non-poolable studies supported a graded cardio-metabolic risk with severity of the disease, persistence of hepatic steatosis and adverse metabolic phenotypes, including lean NAFLD.

Conclusion:

NAFLD is linked with a significantly higher risk of incident T2DM and is heterogeneously related to cardiovascular events, with some NAFLD phenotypes and risk severity strata having a higher risk. Evidence from large cohorts suggests that there is an increase in mortality in individuals with biopsy-confirmed NAFLD. These results indicate that NAFLD is a significant cardio-metabolic risk factor and supports evidence-based combined metabolic and cardiovascular risk evaluation in NAFLD patients.

Introduction:

Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide, with an estimated prevalence of one quarter in the adult population, and is a major public health problem [29]. The spectrum of the disease varies from simple steatosis to nonalcoholic steatohepatitis (NASH), progressive fibrosis, and cirrhosis, and hepatocellular carcinoma. Increased liver related morbidity, the occurrence of extra-hepatic metabolic disorders and their importance is increasingly acknowledged, especially in terms of cardiovascular and endocrine systems [7,21]. Contemporary concepts place a greater emphasis on metabolic dysfunction-associated steatotic liver disease (MASLD) as a broader concept which reflects the close interrelationship between hepatic steatosis and cardio-metabolic risk [9,16].

The close pathophysiological relationship of liver damage (steatohepatitis, specifically non-alcoholic steatohepatitis (NASH)) with insulin resistance has put the latter at the forefront of the epidemic of type 2 diabetes mellitus (T2DM). Large population-based cohorts have shown a reciprocal relationship between the development of both diseases (NAFLD and T2DM) indicating that it is not only the result of metabolic deregulation that leads to diabetes, but that it could also play an active role in diabetes development [13,15]. Fatty liver indices and imaging-defined NAFLD have also been found to be predictive of future diabetes in otherwise healthy populations based on hepatic steatosis as a sign of early dysmetabolism [11].

There is also some new evidence suggesting that the regression of NAFLD can be identified with the decreased risk of incident diabetes which is why the cardio-metabolic risk reversibility with the amelioration of hepatic steatosis can be outlined [22].

Cardiovascular disease (CVD) is the most frequent cause of death in persons with NAFLD, this exceed liver-related causes of death in the majority of cohorts [1,7]. Mechanistic connections between the development of simple steatosis in the liver and the development of atherosclerosis include the systemic inflammatory response, atherogenic dyslipidemia, endothelial dysfunction, and ectopic fat deposition which are known to promote a detrimental remodeling of the cardiovascular system [5,26]. The clinical and epidemiological evidence has always indicated a heightened risk of cardiovascular incidences among patients with NAFLD even in no obesity populations, and this indicates that NAFLD is providing cardiovascular danger in other disease pathways that have been linked to obesity [17,27]. In addition, the severity of NAFLD has been linked to an increasing cardiovascular risk implying a dose-response relationship between hepatic steatosis and cardiovascular risk [24].

The severity of NAFLD disease, especially the extent of hepatic fibrosis, is a significantly important factor in mortality risk. Cohorts through histology have indicated that the stage of fibrosis is the most effective predictor of long-term mortality in NAFLD regardless of other metabolic risk factors [8]. Population-based studies have further reported increased all-cause mortality among individuals with even minimal evidence of the disease (NAFLD) compared with individuals without evidence of steatosis, which reinforces the prognostic significance of the diagnosis of NAFLD as a systemic disease and not an isolated disease of the liver [19]. Attributable fraction analyses have shown that mortality risk is contributed substantially by liver fat in the population, and therefore early identification and risk stratification are important [1].

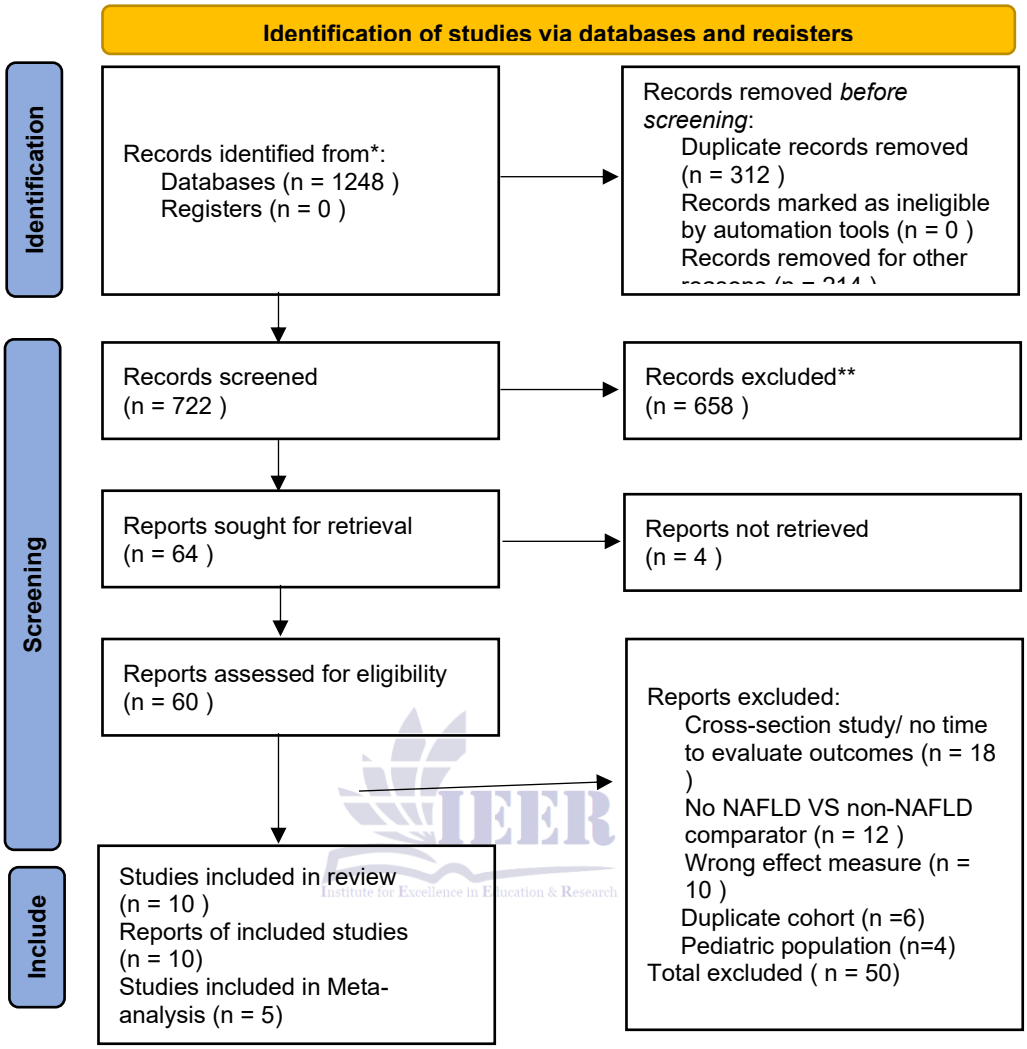
Despite increasing awareness that NAFLD is a cardio-metabolic risk state, available evidence has been heterogeneous regarding outcome definitions, modalities of diagnostic procedures for diagnosis of the disease and effect estimates across populations [28,29]. While there are several systematic reviews and meta-analyses that have investigated associations of cirrhosis (NAFLD) with individual outcomes such as T2DM or cardiovascular disease, there is still room for an updated synthesis of incident diabetes, cardiovascular events, and mortality in a unified analytic framework [3,15,28]. Such an approach is especially relevant in the context of changing disease definitions (NAFLD VS MASLD) and new knowledge concerning phenotype-specific risks, including lean NAFLD and different metabolic profiles [9,21].

Accordingly, the current systematic review and meta-analysis was carried out to comprehensively assess the link between NAFLD and major cardio-metabolic outcomes, such as incident T2DM, cardiovascular events and mortality. This research aims to highlight the level and stability of cardio-metabolic risk in NAFLD as well as provide a basis of clinical risk assessment and prevention interventions in this expanding patient group by synthesizing the data of large population-based cohorts and contextualizing the quantitative results with qualitative evidence.

Methods:

This systematic review and meta-analysis were both conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The aim was to conduct the synthesis of cohort-based evidence assessing the relationship between nonalcoholic fatty liver disease (NAFLD) and principal cardio-metabolic outcomes, such as incident type 2 diabetes mellitus (T2DM), cardiovascular events, and mortality.

Figure 1: PRISMA Flow Diagram:



Sources and search strategy Data:

A systematic search of the literature was conducted in PubMed (MEDLINE), Scopus, and Web of Science from database inception until December 2025. The search strategy was a combination of controlled vocabulary and free text terms associated with NAFLD and cardio-metabolic outcomes, including "nonalcoholic fatty liver disease," "NAFLD," "metabolic dysfunction-associated steatotic liver disease," "MASLD," "type 2 diabetes," "incident diabetes," "cardiovascular disease," "myocardial infarction," "stroke," "cardiovascular events," "mortality" and "death." Reference lists of eligible articles and relevant reviews were manually searched for further studies.

Eligibility Criteria:

Eligible studies were prospective or retrospective cohort studies involving adult populations (>18 years of age) evaluating the incidence of T2DM (incident T2DM) and CV events and/or all-cause and cardiovascular mortality with multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the comparison of NAFLD and non-NAFLD. Studies were excluded if they used a cross-sectional study design, did not have a non-NAFLD comparator group, did not report time-to-event effect measures (hazard ratios), focused on pediatric populations, or focused on non-comparable contrasts such as NAFLD regression versus persistence, comparisons of severity, or

phenotype specific analyses. Where there was more than one publication stemming from overlapping cohorts, the most complete or most recent report was kept.

Study Selection:
Two reviewers independently reviewed and screened titles and abstracts for relevance. Full text of potentially eligible articles were evaluated to ensure eligibility. Disagreements were settled through consensus. The selection process for the studies has been documented according to the PRISMA flow diagram.

Data Extraction:
Data were extracted using a standardized form that included first author, year of publication, country, cohort name, sample size, time of follow-up, definition of NAFLD, definition of outcomes, name of covariates in the multivariable models, and adjusted HRs with 95% CIs. In cases where standardized models have been reported, the estimates of the most fully adjusted model were obtained in order to perform quantitative synthesis. When more than one cardiovascular outcome was reported for a single study, the outcome that was most compatible with the predefined category of cardiovascular events was chosen to prevent counting study participants twice.

Risk of Bias Assessment:
Methodological quality was evaluated by using the Newcastle-Ottawa Scale (NOS) for cohort studies, in terms of the selection of cohorts, comparability of exposed and non-exposed groups, and outcome ascertainment. Quality assessment was conducted independently by two reviewers and disagreement was resolved through discussion.

Quantitative Synthesis:
The outcomes of at least two studies were combined in meta-analyses to obtain a set of outcomes with similar, multivariable-adjusted HRs of NAFLD versus non-NAFLD. Pooled estimates were done with random-effects models (DerSimonian-Laird method). Between-study heterogeneity was analyzed by using the Cochran Q test and quantified by using the I^2 statistic. Summary estimates were reported in the form of pooled HRs with 95% CI. For the cardiovascular outcomes, pooling was limited to time to event estimates to minimize clinical and methodological heterogeneity. Mortality outcomes were not pooled when the number of eligible studies was less than 2.

Qualitative Synthesis:
Studies that reported alternative contrasts (e.g., regression of NAFLD vs. persistence), severity-based associations, effects restricted to particular phenotypes (e.g., lean NAFLD), or non-comparable effect measures were synthesized narratively, in order to provide a context for the quantitative findings as well as to discuss consistency at different phenotypes and different severity strata of NAFLD.

Sensitivity Analyses:
Sensitivity analyses evaluated the influence of individual studies on pooled estimates and explored sources of heterogeneity by NAFLD diagnostic modality and population characteristics when sufficient data were available.

Publication Bias:
Formal assessment of publication bias was not conducted as the number of studies available for any quantitative outcome was too small to reliably detect the effects of small studies.

Results:
Study Selection and Characteristics:
The database search resulted in eligible cohort studies of the association between nonalcoholic fatty liver disease (NAFLD) and cardio-metabolic outcomes. After the screening and full text evaluation, 10 studies qualified for the systematic review. Of these, five studies reported similar multivariable-adjusted hazard ratios (HRs) for the prevalence of NAFLD versus non-NAFLD and were included in quantitative synthesis, while the remaining studies were included in the qualitative synthesis because of some differences in contrasts, definitions of outcomes, or effect measures. The included cohorts were representative of diverse

populations in Asia, Europe and North America and the ascertainment of NAFLD was by imaging, histology or clinical codes and follow-up was long enough to obtain incident cardio-metabolic events.

Table 1. Study Characteristics of Included Articles

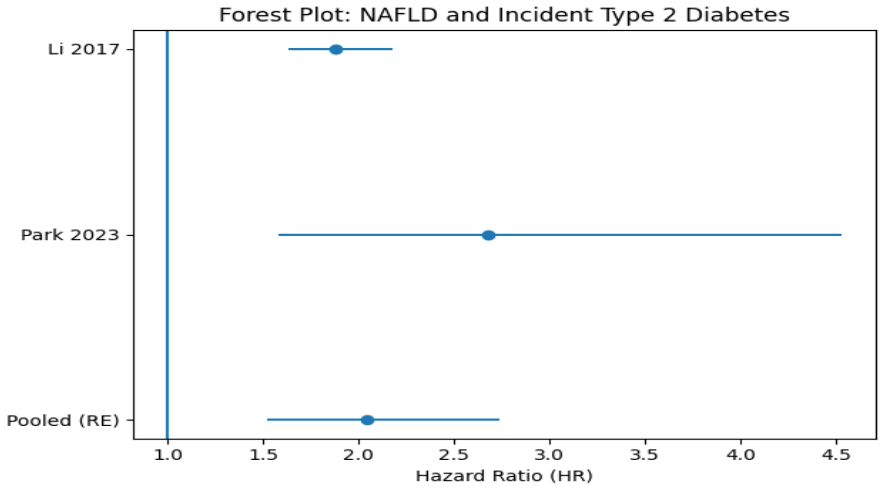
Study	Country	Design	NAFLD Definition	Outcome(s)	Follow-up
Li 2017	China	Cohort	Ultrasound NAFLD	Incident T2DM	Prospective
Park 2023	Korea	Cohort	Imaging NAFLD	Incident T2DM	Prospective
Alexander 2019	Europe	Cohort	Clinical codes	CV events (Stroke/AMI)	Registry-based
Song 2022	China	Cohort	Imaging NAFLD	CV events	Prospective
Simon 2021	Sweden	Cohort	Biopsy NAFLD	Mortality	Nationwide
Sinn 2023	Korea	Cohort	Ultrasound NAFLD	T2DM trajectories	Prospective

Incident Type 2 Diabetes Mellitus:

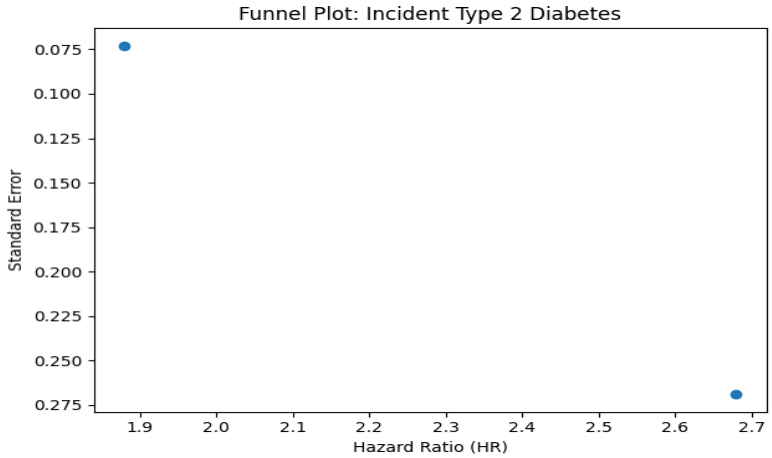
Two cohort studies had similar multivariable-adjusted HRs for the presence of NAFLD compared to non-NAFLD and were included in the meta-analysis. Random-effects pooling showed that an association between NAFLD and significantly higher risk of incident type 2 diabetes mellitus was also found, pooled HR: 2.04 (95% CI 1.52-2.74). The heterogeneity between studies was moderate (I^2 = 38.2%). Although based on two cohorts, both these studies showed a consistent direction and magnitude of effect, showing an approximate two-fold increase in the risk of incident diabetes in people with NAFLD vs. those without NAFLD.

Qualitative evidence from non poolable studies supported these findings and showed higher incidence of diabetes with persistent and lower risk with regression of NAFLD, suggesting possible reversibility of the metabolic risk with regression of hepatic steatosis.

Figure 2: Forest Plot: NAFLD and Incident Type 2 Diabetes



Funnel Plot: Incident Type 2 Diabetes



Cardiovascular Events:

Two studies with estimates of time-to-event estimates for cardiovascular outcomes were included in the quantitative synthesis. The pooled analysis revealed that there was a non-significant tendency towards more cardiovascular risk in people with NAFLD compared to those without NAFLD (pooled HR 1.09, 95% CI 0.98-1.21). Substantial heterogeneity was noted (I^2 = 82.4%), which was likely to have arisen because of differences in the definition of cardiovascular outcomes and population risk profiles between studies. Although the pooled association was not statistically significant, the direction of effect was in line with an increased cardiovascular risk in NAFLD.

Narrative synthesis of studies that could not be pooled showed increased cardiovascular risk in people with more severe forms of NAFLD and in a particular phenotype (lean NAFLD) and this finding provided supportive context to the quantitative findings.

Figure 4: Forest Plot: NAFLD and Cardiovascular Events

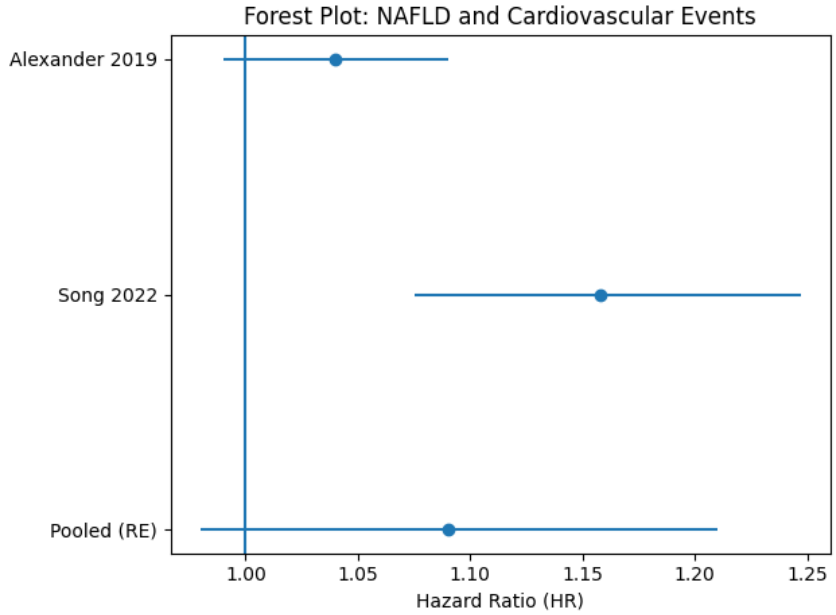
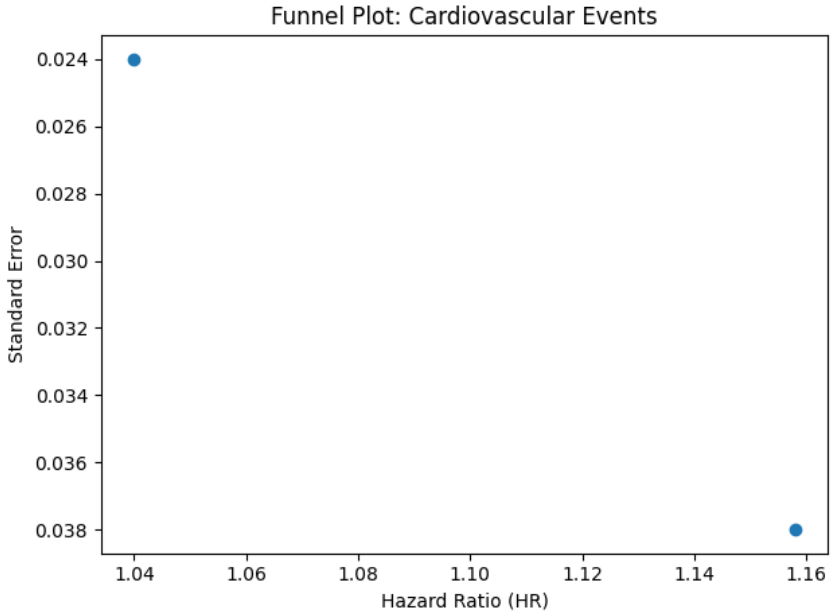


Figure 5: Funnel Plot: Cardiovascular Events:



Mortality:

Mortality outcomes, when it came to quantitative pooling, were not possible since there was only one eligible cohort where NAFLD and non-NAFLD hazard ratios were reported. Among a large national cohort of people with NAFLD that was biopsy-confirmed, NAFLD was found to be strongly correlated with all-cause mortality (HR 1.93, 95% CI 1.86-2.00), and cardiovascular mortality (HR 1.35, 95% CI 1.26-1.44) in comparison to the general population. Further cohort evidence indicated cardio-metabolic comorbidities, especially diabetes, to have an additional risk on mortality in NAFLD patients.

Table 2. Meta-analysis Inputs (Effect Sizes Used for Pooling)

Outcome	Study	HR	95% CI (Lower)	95% CI (Upper)	SE (log HR)
Incident T2DM	Li 2017	1.88	1.63	2.18	0.073
Incident T2DM	Park 2023	2.68	1.58	4.53	0.269
CVD events	Alexander 2019 (Stroke)	1.04	0.99	1.09	0.024
CVD events	Song 2022	1.158	1.075	1.247	0.038

Table 3. Pooled Meta-analysis Results and Heterogeneity

Outcome	Model	Pooled HR	95% CI	I^2 (%)	τ^2
Incident T2DM	Random-effects (DL)	2.04	1.52–2.74	38.2	0.024
CVD events	Random-effects (DL)	1.09	0.98–1.21	82.4	0.0048

Table 4. Narrative Synthesis of Non-poolable Studies

Study	Contrast	Outcome	Effect	Use in Review
Sinn 2023	Regression vs persistence	Incident T2DM	HR 0.81 (0.72–0.92)	Qualitative support
Chen 2023	Trajectories	Incident T2DM	Higher risk with sustained NAFLD	Qualitative support
Pisto 2014	Severe vs none	CVD events	HR 1.74 (1.16–2.63)	Sensitivity context
Yoshitaka 2017	Lean NAFLD	CVD events	HR 10.4 (2.61–44.0)	Phenotype context
Abd El Azeem 2013	NAFLD vs non-NAFLD	CVD events	OR 5.21	Narrative only

OR-based study; not eligible for pooling

Discussion:

This systematic review and meta-analysis has shown a strong association between nonalcoholic fatty liver disease (NAFLD) and the subsequent development of type 2 diabetes mellitus, and an approximately two-fold higher risk at pooled analyses. This finding is similar to large population-based cohorts and meta-analyses suggesting a strong bidirectional association between hepatic steatosis and dysglycaemia [13,15]. The liver is central in glucose homeostasis and hepatic insulin resistance, lipid metabolism, and chronic low-grade inflammation are closely associated with the development of NAFLD, which in turn is associated with the development of overt diabetes [16,26]. The above pathophysiological pathways offer biological credibility of the observed association and justify the idea that NAFLD is not simply an indicator of metabolic danger, but could be a direct cause of diabetes pathogenesis.

The pooled association of liver steatosis (NAFL) and cardiovascular events was not statistically significant and was associated with large heterogeneity. This finding represents, in all likelihood, a real clinical heterogeneity as opposed to the lack of a relationship. Cardiovascular disease is the leading cause of death in people with NAFLD and there is mechanistic evidence for a direct connection between hepatic steatosis and atherogenesis through the same cardio-metabolic pathways of dyslipidemia, endothelial dysfunction, oxidative stress and systemic inflammation [5,7,26]. Observational cohorts have shown high rates of cardiovascular events in NAFLD even in non-obese persons, indicating that NAFLD is a risk factor of cardiovascular events over and above conventional obesity-related processes [17,27]. Additionally, the severity of disease seems to mediate the cardiovascular risk whereby more progressive NAFLD is related to the cardiovascular events and this demonstrates the dose response relationship between the liver disease burden and the cardiovascular occurrences [17,24]. Taken together, these data demonstrate that the cardiovascular risk related to NAFLD is heterogeneous and can be clumped in such phenotypes and strata of severity.

Mortality outcomes could not be pooled quantitatively; however available evidence consistently suggests that there is an association of NAFLD with increased mortality from all causes and cardiovascular causes. Histology-based cohorts have shown that the stage of fibrosis is the best predictor of long-term mortality among patients with NAFLD, being superior to the predictive power of the diagnosis of steatosis per se [8]. Population-level analyses also indicate that the public health relevance of this condition is becoming apparent because it may contribute significantly to overall mortality burden [1]. Prospective cohort data also revealed that people with NAFLD exhibited increased mortality rates in relation to those who had none of the hepatic steatosis, which underpins the idea that NAFLD is a systemic condition with prognostic potential that

lies outside the liver [19]. These results emphasize the role of detection of individuals with more severe fibrosis and cardio-metabolic comorbidities as a high-risk group among the large NAFLD group.

The clinical implications of these findings coincide with new guidelines recommendations and consensus statements that consider the condition of NAFLD/MASLD as a cardio-metabolic disease that requires an integrated risk assessment and a multidisciplinary approach to its management [4,7,20]. The position statements and scientific advice indicate the importance of routine cardiovascular risk screening among patients with NAFLD due to the higher cardiovascular morbidity and mortality in this group [6,7]. Conceptual models of the liver-heart axis also illustrate the inter-relatedness of hepatic steatosis and cardiovascular pathology and justify an approach to cardio-metabolic risk modification strategies [5,9]. Together, these perspectives give new relevance to the present findings in terms of clinical practice and public health policy.

Limitations:

A number of limitations must be considered. First, the quantitative synthesis for incident diabetes was based on a small number of cohorts, although the magnitude of effect and direction of effect were consistent with previous studies on the same large scales and meta-analyses. Second, there was considerable heterogeneity in pooled cardiovascular outcomes, reflecting variations in outcome definitions, baseline cardiovascular risk and methods of ascertaining NAFLD by studies. Third, the diagnosis of NAFLD varied between cohorts such as use of imaging, histology, and clinical coding may have introduced exposure misclassification and contributed to variation between studies. Fourth, residual confounding of results associated with the use of observational study designs cannot be completely ruled out, despite multivariable adjustment for important cardio-metabolic risk factors. Finally, the outcomes of mortality were not pooled quantitatively because few eligible cohorts were presented, although consistent findings are in support of an increased mortality risk in the setting of NAFLD, especially in individuals with advanced fibrosis.

Implications for Further Research:

Future studies: Large prospective cohorts that have a defined and harmonized NAFLD/MASLD and a cardiovascular outcome that is reported consistently across studies should be central to future studies in order to enhance comparability across studies. Longitudinal evaluation of the trajectory of the disease (NAFLD) and progression of fibrosis can help elucidate dose-response patterns between severity of the disease and cardio-metabolic outcomes. Interventional and prospective studies will be required to see if regression of hepatic steatosis will translate into sustained reductions in incidence of diabetes and cardiovascular events. Also, investigations that focus on phenotype, such as lean NAFLD and other populations with unique metabolic risk profiles can be used to determine high risk sub-groups to be targeted using high-risk prevention methods. The liver-heart axis studies conducted in a mechanistic manner could further clarify the causal mechanisms between NAFLD and cardiovascular disease and guide the development of specific therapeutic efforts.

Conclusion:

This systematic review and meta-analysis proves that there is a significant association of NAFLD with a markedly higher risk of incident type 2 diabetes mellitus and heterogeneous results regarding the association with cardiovascular events with higher risk in some phenotypes and severity strata. The data on large population-based cohorts suggests more all-cause and cardiovascular deaths in people with NAFLD, especially when there are the advanced fibrosis and cardio-metabolic comorbidities. These findings support the identification of NAFLD/MASLD as a clinically-relevant cardio-metabolic risk state and the importance of integrated cardiovascular and metabolic risk assessment of persons with hepatic steatosis in accordance with current clinical recommendations.

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