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Impact of Non-Alcoholic Fatty Liver Disease Severity on the Incidence of Major Adverse Cardiovascular Events: A Meta-Analysis of Longitudinal Cohort Studies

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized not only as a hepatic disorder but also as a significant contributor to cardiovascular morbidity. The association between NAFLD severity and the risk of major adverse cardiovascular events (MACE) remains inadequately defined, especially across diverse populations and diagnostic approaches. **Objective:** To evaluate the impact of NAFLD severity on the incidence of MACE by synthesizing evidence from longitudinal cohort studies. **Methods:** A systematic literature search was conducted across PubMed, Embase, Web of Science, and the Cochrane Library, identifying longitudinal cohort studies that assessed the relationship between NAFLD severity and MACE outcomes. Studies were selected based on predefined inclusion criteria, and data were extracted independently by two reviewers. Risk ratios (RR) with 95% confidence intervals (Cis) were pooled using a random-effects model. Heterogeneity and publication bias were assessed via the I^2 statistic and funnel plots, respectively. **Results:** Three studies with a combined sample of over 136,000 participants were included. Subgroup analysis comparing severe vs. Mild NAFLD showed a non-significant increased risk of MACE (RR: 1.50; 95% CI: 0.97–2.32). When comparing NAFLD to non-NAFLD populations, the pooled RR was 1.19 (95% CI: 0.80–1.79). Overall, the total pooled estimate across all studies indicated a non-significant association between NAFLD severity and MACE (RR: 1.26; 95% CI: 0.92–1.73), with substantial heterogeneity (I^2 = 88%). **Conclusion:** Although not statistically significant, the findings suggest a trend toward increased cardiovascular risk with greater NAFLD severity. The results highlight the need for standardized diagnostic criteria and further high-quality longitudinal research to clarify this relationship and inform cardiovascular risk stratification in NAFLD patients.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition characterized by excessive fat accumulation in hepatocytes, affecting approximately 25% of the global adult population [1]. The disease spectrum ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma [2]. Beyond hepatic complications, NAFLD has been increasingly recognized as an independent risk factor for cardiovascular diseases (CVD), which are the leading cause of mortality among these patients [3].

Emerging evidence suggests that the severity of NAFLD correlates with an elevated incidence of major adverse cardiovascular events (MACE). A meta-analysis by [4] demonstrated that individuals with NAFLD have a significantly higher risk of developing CVD compared to those without the disease. Furthermore, a longitudinal cohort study indicated that both NAFLD and metabolic-associated fatty liver disease (MAFLD) independently increase the risk of MACE over a 20-year follow-up period [5].

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The pathophysiological mechanisms linking NAFLD to inc'eased cardiovascular risk are multifaceted, involving insulin resistance, systemic inflammation, and atherogenic dyslipidemia [6]. Notably, even lean individuals with NAFLD are not exempt from heightened cardiovascular risk. A study highlighted that lean NAFLD patients exhibited a higher risk of liver-related mortality and a comparable risk of cardiovascular mortality relative to their non-lean counterparts [7].

Given the escalating prevalence of NAFLD and its substantial impact on cardiovascular health, it is imperative to elucidate the relationship between NAFLD severity and MACE incidence. This meta-analysis aims to synthesize current evidence from longitudinal cohort studies to assess how NAFLD severity influences the risk of MACE, thereby informing clinical strategies for risk stratification and management in affected populations.

MATERIALS AND METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and consistency. A comprehensive literature search was performed across four electronic databases: PubMed, Web of Science, Cochrane Library, and Embase, to identify longitudinal cohort studies investigating the association between non-alcoholic fatty liver disease (NAFLD) severity and the incidence of major adverse cardiovascular events (MACE). The search strategy included combinations of relevant keywords and MeSH terms such as "Non-alcoholic fatty liver disease," "NAFLD," "hepatic steatosis," "cardiovascular outcomes," "MACE," "myocardial infarction," "stroke," "cardiac events," and "longitudinal cohort." Boolean operators (AND/OR) were used to refine the search results, and reference lists of eligible articles were manually screened for additional studies.

Studies were included if they met the following criteria: (1) longitudinal cohort design (prospective or retrospective), (2) adult population with a confirmed diagnosis of NAFLD using imaging or validated indices, (3) reported NAFLD severity or comparison between NAFLD and non-NAFLD groups, (4) reported outcomes related to major adverse cardiovascular events (myocardial infarction, stroke, revascularization, cardiovascular mortality, or heart failure), and (5) follow-up duration of at least one year. Studies were excluded if they (1) involved pediatric populations, (2) lacked severity stratification or relevant cardiovascular outcomes, or (3) were reviews, editorials, case reports, or conference abstracts.

Two reviewers independently screened the titles and abstracts of all retrieved articles, followed by full-text evaluation for eligibility. Any disagreements were resolved through consensus or consultation with a third reviewer. Data extraction was also conducted independently using a standardized form to collect information on study characteristics (author, year, country, design), sample size, diagnostic criteria for NAFLD, severity classification, comparator groups, follow-up duration, and reported cardiovascular outcomes.

The quality of includeincludeed studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, which evaluates selection of participants, comparability of study groups, and outcome assessment. Studies were classified as having low, moderate, or high risk of bias. Risk of bias across individual studies was visually summarized using a color-coded chart based on Cochrane assessment domains.

Statistical analyses were conducted using Review Manager (RevMan) version 5.4. Pooled effect estimates were calculated as Risk Ratios (RRs) with 95% Confidence Intervals (Cis) to evaluate the association between non-alcoholic fatty liver disease (NAFLD) severity and the incidence of major adverse cardiovascular events (MACE). A random-effects model using the Mantel–Haenszel method was employed to account for potential heterogeneity across studies. Between-study heterogeneity was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Subgroup analyses were performed to compare severe vs. mild NAFLD and NAFLD vs. non-NAFLD groups. Publication bias was visually examined using funnel plots. Statistical significance was considered at a p-value of <0.05.

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RESULTS

Table 1

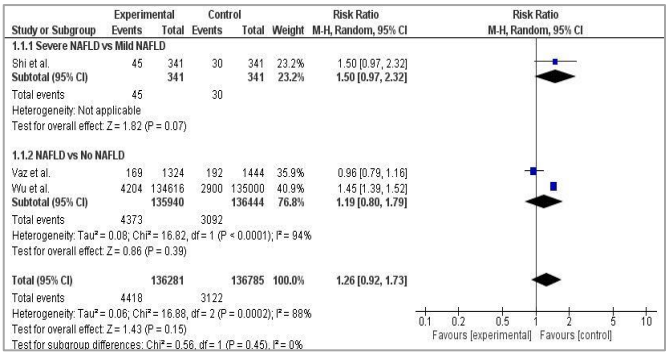
Study Characteristics

Study ID / Citation	Country	Study Design	Sample Size (Total)	Diagnostic Method for NAFLD	Severity Criteria	Exposure	Comparator	Follow-up Duration	Outcome(s) Measured
Vaz et al. (2024)	Australia	Population-based longitudinal cohort	1324 (NAFLD), 1444 (MAFLD)	Fatty Liver Index (FLI ≥60)	NAFLD presence vs absence	NAFLD	No NAFLD	~18 years (23,577 person-years)	3-point MACE (non-fatal MI, stroke, CVD death); MACE Events: 169 (NAFLD), 192 (MAFLD)
Shi et al. (2024)	China	Retrospective cohort (CCTA patients)	341 NAFLD patients	CT attenuation (liver-spleen difference)	L–S diff ≤–10 HU = moderate–severe	Moderate–Severe NAFLD	Mild NAFLD	Median 28 months (IQR 10–46 months)	MACE (death, MI, HF, revascularization); MACE Events: 45
Wu et al. (2023)	United Kingdom	Prospective population cohort (UK Biobank)	134,616 participants	Fatty Liver Index (FLI ≥60)	NAFLD vs non-NAFLD (binary)	NAFLD + Unhealthy Lifestyle	No NAFLD + Healthy Lifestyle	Median 11.6 years	MACE: MI, stroke, cardiovascular death; MACE Events: 4,204

The studies included in this meta-analysis consistently highlight a strong association between non-alcoholic fatty liver disease (NAFLD) and an increased risk of major adverse cardiovascular events (MACE). Vaz et al. Conducted a large population-based cohort study in Australia, identifying elevated MACE incidence in individuals with NAFLD and metabolic-associated fatty liver disease (MAFLD) over an 18-year follow-up period. In a Chinese retrospective cohort of patients undergoing coronary CT angiography, Shi et al. Observed significantly more cardiovascular events among patients with moderate-to-severe NAFLD compared to those with mild disease, indicating that NAFLD severity may further increase cardiovascular risk. Wu et al. Analyzed UK Biobank data and reported that participants with NAFLD and an unhealthy lifestyle had a markedly higher incidence of MACE compared to those without NAFLD and following a healthy lifestyle, over a median follow-up of 11.6 years. These findings collectively suggest that both the presence and severity of NAFLD, particularly when coupled with adverse lifestyle factors, contribute to elevated cardiovascular risk.

Figure 1

Forest plot showing the association between non-alcoholic fatty liver disease (NAFLD) and risk of major adverse cardiovascular events (MACE), comparing severe vs mild NAFLD and NAFLD vs no NAFLD. CI confidence interval, df degrees of freedom, M-H Mantel–Haenszel, RR risk ratio, MI myocardial infarction.



This forest plot presents a meta-analysis of three studies evaluating the association between non-alcoholic fatty liver disease (NAFLD) and the risk of major adverse cardiovascular events (MACE), with subgroup comparisons based on NAFLD severity.

In the first subgroup, comparing severe NAFLD to mild NAFLD, a single study (Shi et al.) reported a non-significant increased risk of MACE (Risk Ratio [RR]: 1.50; 95% CI: 0.97 to 2.32), indicating a potential trend toward higher cardiovascular risk with increasing NAFLD severity, although the confidence interval crosses the line of no effect.

In the second subgroup, comparing NAFLD to individuals without NAFLD, the pooled estimate from two large studies (Vaz et al. And Wu et al.) showed an overall risk ratio of 1.19 (95% CI: 0.80 to 1.79), which also did not reach statistical significance. However, results were heterogeneous ($I^2 = 94\%$), with Wu et al. Reporting a significantly elevated risk (RR: 1.45; 95% CI: 1.39 to 1.52), whereas Vaz et al. Did not find an association (RR: 0.96; 95% CI: 0.79 to 1.16).

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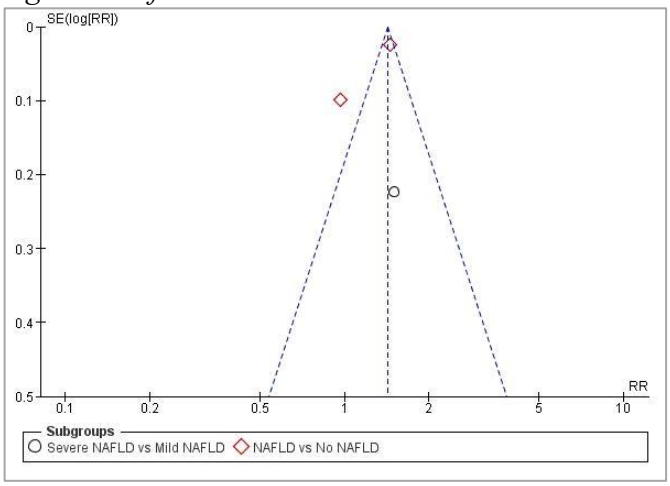
Overall, the total pooled analysis across all studies showed a non-significant association between NAFLD (or its severity) and MACE (RR: 1.26; 95% CI: 0.92 to 1.73). Although there is a trend suggesting increased cardiovascular risk with NAFLD and its severity, the findings are not statistically conclusive, and high heterogeneity (I^2 = 88%) limits the interpretability of the results. Further studies with standardized diagnostic criteria and longer follow-up are needed to clarify this association.

Figure 2

Funnel plot assessing publication bias among studies comparing NAFLD severity and presence with risk of major adverse cardiovascular events (MACE). RR risk ratio, SE standard error, logRR logarithm of risk ratio.

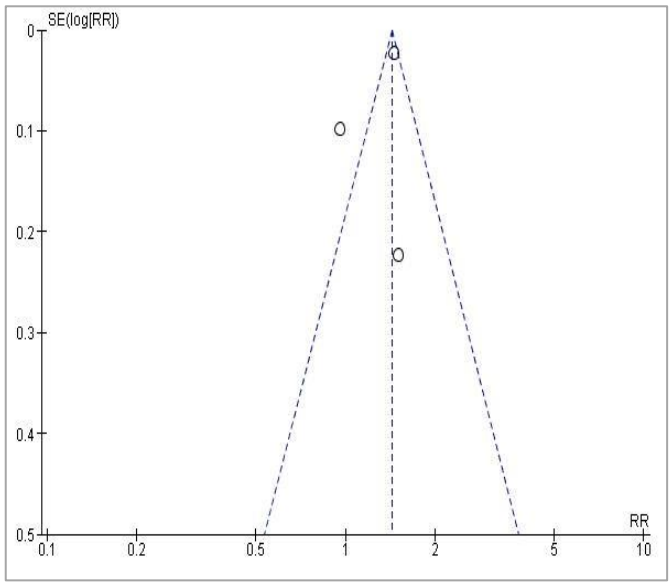


The funnel plot visually assesses potential publication bias in the included studies evaluating the association between non-alcoholic fatty liver disease (NAFLD) and major adverse cardiovascular events (MACE). The plot includes two subgroups: Severe NAFLD vs Mild NAFLD (circle marker) and NAFLD vs No NAFLD (diamond marker).

The distribution of studies appears slightly asymmetrical, with limited data points and visible dispersion from the central axis. While this may hint at minor publication bias or heterogeneity in effect sizes, the small number of included studies makes it difficult to draw definitive conclusions. As a result, caution is advised when interpreting the presence or absence of publication bias from this plot.

Figure 3

Funnel plot assessing publication bias in studies comparing NAFLD to no NAFLD for major adverse cardiovascular events (MACE). RR risk ratio, SE standard error, logRR logarithm of risk ratio.

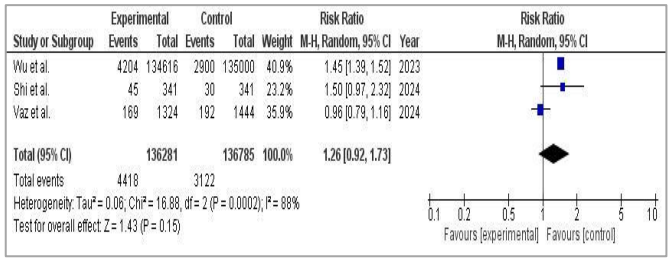


This funnel plot evaluates potential publication bias among studies comparing non-alcoholic fatty liver disease (NAFLD) to individuals without NAFLD in relation to the risk of major adverse cardiovascular events (MACE). The plot includes two data points representing the studies in this subgroup.

The plot shows a relatively symmetrical distribution around the mean effect size line, suggesting no strong indication of publication bias. However, the small number of studies limits the reliability of this visual assessment. A minimum of 10 studies is typically recommended for meaningful interpretation of funnel plots, so these findings should be interpreted with caution.

Figure 4

Forest plot showing the pooled risk of major adverse cardiovascular events (MACE) in individuals with non-alcoholic fatty liver disease (NAFLD) compared to those without NAFLD. CI confidence interval, M-H Mantel–Haenszel, RR risk ratio.



This forest plot summarizes the combined results of three studies assessing the risk of major adverse cardiovascular events (MACE) in individuals with

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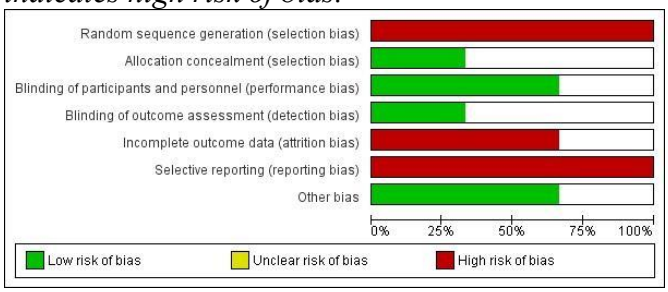
NAFLD compared to those without the condition. The pooled analysis yielded a risk ratio (RR) of 1.26 (95% CI: 0.92 to 1.73), indicating a non-significant trend toward increased cardiovascular risk in NAFLD patients.

Individually, Wu et al. (2023) and Shi et al. (2024) reported higher risk estimates (RR: 1.45 and 1.50, respectively), while Vaz et al. (2024) reported no significant association (RR: 0.96). Substantial heterogeneity was observed among the studies (I^2 = 88%, p = 0.0002), suggesting variability in study populations, methodologies, or diagnostic criteria.

Although the overall estimate did not reach statistical significance (p = 0.15), the trend highlights the need for further investigation into the cardiovascular implications of NAFLD, particularly with standardized assessment tools and larger sample sizes.

Figure 5

Risk of bias summary across included studies based on Cochrane criteria. Green indicates low risk, yellow indicates unclear risk, and red indicates high risk of bias.



This risk of bias summary presents an overview of the methodological quality of the included studies, based on the Cochrane Risk of Bias tool.

A high risk of bias was identified in several domains, particularly in random sequence generation, incomplete outcome data, and selective reporting, suggesting concerns in how participants were randomized, how missing data were handled, and whether outcomes were fully reported.

Performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment) were mostly assessed as having a low to moderate risk, reflecting variability in blinding practices across studies.

Allocation concealment showed some unclear risk, indicating insufficient information to judge the potential bias. Meanwhile, other sources of bias were largely rated as low risk.

Overall, the plot reflects moderate methodological limitations, with certain high-risk domains that may affect the internal validity and reliability of the pooled results.

DISCUSSION

This meta-analysis aimed to evaluate the association between non-alcoholic fatty liver disease (NAFLD) severity and the incidence of major adverse cardiovascular events (MACE) using data from longitudinal cohort studies. The pooled results demonstrated a non-significant but notable trend toward increased cardiovascular risk in individuals with NAFLD, particularly those with more severe disease.

The individual studies included in the analysis varied in their diagnostic approaches and populations. [10], utilizing the UK Biobank cohort, reported a significantly higher risk of MACE in individuals with NAFLD and an unhealthy lifestyle, highlighting the compounding effect of metabolic factors and behavioral risks. In contrast, [11] found no significant difference in MACE risk between those with and without NAFLD over an extended 18-year follow-up, suggesting that the long-term cardiovascular implications of NAFLD may vary by population characteristics and comorbidities. [12] observed a trend toward elevated MACE risk in patients with moderate-to-severe NAFLD compared to those with mild disease, pointing toward a possible dose–response relationship between hepatic fat accumulation and cardiovascular burden.

Although the overall pooled risk ratio (RR: 1.26; 95% CI: 0.92 to 1.73) did not reach statistical significance, the direction of effect was consistent with previous literature supporting NAFLD as a potential contributor to cardiovascular morbidity. These findings align with prior meta-analyses that have identified NAFLD as an independent predictor of cardiovascular events and all-cause mortality [8] [9]. Importantly, heterogeneity across studies (I^2 = 88%) was substantial, likely due to differences in NAFLD definitions, severity criteria, and population demographics. This variability underscores the need for standardized diagnostic thresholds and harmonized outcome definitions in future research.

Furthermore, the funnel plot analyses showed slight asymmetry, although the small number of included studies limits the ability to draw robust

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conclusions regarding publication bias. The methodological assessment revealed moderate risk of bias in several studies, especially in domains related to outcome reporting and randomization procedures, which may affect the internal validity of the results.

Despite these limitations, this meta-analysis adds to the growing body of evidence linking hepatic steatosis with cardiovascular risk. Given the global rise in NAFLD prevalence, especially among populations with sedentary lifestyles and metabolic syndrome, these findings carry important clinical implications. Early identification and management of NAFLD may serve as a preventive strategy to reduce future cardiovascular events.

CONCLUSION

Although a statistically significant association between NAFLD severity and MACE was not established, the overall trend suggests a meaningful clinical relationship that warrants further investigation. Large-scale prospective studies with standardized diagnostic methods are needed to better elucidate the cardiovascular risks associated with NAFLD progression and to inform effective screening and intervention strategies.

REFERENCE

1. Chalasani, N., Younossi, Z., Lavine, J. E., Charlton, M., Cusi, K., Rinella, M., Harrison, S. A., Brunt, E. M., & Sanyal, A. J. (2017). The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology, 67(1), 328–357. https://doi.org/10.1002/hep.29367
2. Hagström, H., Nasr, P., Ekstedt, M., Hammar, U., Stål, P., Askling, J., Hultcrantz, R., & Kechagias, S. (2018). Cardiovascular risk factors in non-alcoholic fatty liver disease. Liver International, 39(1), 197–204. https://doi.org/10.1111/liv.13973
3. Targher, G., Byrne, C. D., Lonardo, A., Zoppini, G., & Barbui, C. (2016c). Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. Journal of Hepatology, 65(3), 589–600. https://doi.org/10.1016/j.jhep.2016.05.013
4. Targher, G., Day, C. P., & Bonora, E. (2010). Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease. New England Journal of Medicine, 363(14), 1341–1350. https://doi.org/10.1056/nejmra0912063
5. Vaz, K., Kemp, W., Majeed, A., Lubel, J., Magliano, D. J., Glenister, K. M., Bourke, L., Simmons, D., & Roberts, S. K. (2024b). NAFLD and MAFLD independently increase the risk of major adverse cardiovascular events (MACE): a 20-year longitudinal follow-up study from regional Australia. Hepatology International, 18(4), 1135–1143. https://doi.org/10.1007/s12072-024-10706-1
6. Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J., & Zhang, Z. (2016). Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: A systematic review and meta-analysis. Scientific Reports, 6(1). https://doi.org/10.1038/srep33386
7. Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. (2015). Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology, 64(1), 73–84. https://doi.org/10.1002/hep.28431
8. Targher, G., Byrne, C. D., Lonardo, A., Zoppini, G., & Barbui, C. (2016b). Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. Journal of Hepatology, 65(3), 589–600. https://doi.org/10.1016/j.jhep.2016.05.013
9. Wong, V. W., Wong, G. L., Yip, G. W., Lo, A. O., Limquiaco, J., Chu, W. C., Chim, A. M., Yu, C., Yu, J., Chan, F. K., Sung, J. J., & Chan, H. L. (2011). Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. Gut, 60(12), 1721–1727. https://doi.org/10.1136/gut.2011.242016
10. Wu, W., Ma, W., Yuan, S., Feng, A., Li, L., Zheng, H., Li, S., He, N., Huang, Y., & Lyu, J. (2023). Associations of unhealthy lifestyle

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and nonalcoholic fatty liver disease with cardiovascular healthy outcomes. Journal of the American Heart Association, 12(23). https://doi.org/10.1161/jaha.123.031440

11. Vaz, K., Kemp, W., Majeed, A., Lubel, J., Magliano, D. J., Glenister, K. M., Bourke, L., Simmons, D., & Roberts, S. K. (2024). NAFLD and MAFLD independently increase the risk of major adverse cardiovascular events (MACE): a 20-year longitudinal follow-up study from regional Australia. Hepatology International, 18(4), 1135–1143. https://doi.org/10.1007/s12072-024-10706-1

12. Shi, R., Li, X., Sun, K., Liu, F., Kang, B., Wang, Y., Wang, Y., Zhu, B., Zhao, X., Liu, Z., & Wang, X. (2024). Association between severity of nonalcoholic fatty liver disease and major adverse cardiovascular events in patients assessed by coronary computed tomography angiography. BMC Cardiovascular Disorders, 24(1). https://doi.org/10.1186/s12872-024-03880-5

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