

AASLD ABSTRACT

(Max.: 2500 characters excluding title and subheadings; no section for references.

Current: 2497/2498 characters depending upon *Results* section)

Title:

A systematic review and meta-analysis: Is metabolic dysfunction-associated steatotic liver disease associated with an increased risk of cardiovascular disease above that associated with shared risk factors?

Background:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with an increased risk of incident cardiovascular disease (CVD), the leading cause of death in people with MASLD. However, it is unclear whether liver disease is an independent risk factor (RF) for CVD or whether cardiometabolic RFs common to MASLD and CVD fully explain this risk. Equipose exists in the literature, with studies conducted in liver centres suggesting MASLD confers higher CVD risk regardless of metabolic RFs, but large epidemiological studies suggesting the converse. Mendelian epidemiology cannot resolve this question. A systematic review and meta-analysis was conducted to delineate the relationship between MASLD and CVD.

Methods:

To identify eligible studies, Medline, Embase, and Cochrane databases were interrogated from database inception to December 2024. Exclusion criteria incorporated: method of MASLD diagnosis (imaging, elastography or biopsy), alcohol intake (<30g/20g daily for males/females respectively), pre-existing CVD, and follow-up period. Cross-sectional studies were excluded. The primary outcome was overall incident CVD. Secondary endpoints were combined fatal/non-fatal CVD events (CVEs), atrial fibrillation (AF), acute coronary syndrome (ACS), CVD mortality, and stroke. Raw outcome data were extracted from selected studies, and meta-regression analyses performed using random-effects models to derive pooled odds ratios (ORs) with 95% confidence intervals (CIs).

Results:

Nineteen prospective and retrospective cohort studies with cardiovascular endpoints, were identified with aggregate data on 1,250,661 individuals. Median follow-up was 8.4 years (IQR 5.7-10.0). MASLD was associated with an increased risk of any incident CVD (OR 1.90 [1.27–2.84]; p=0.004). After adjustment for RFs or follow-up and in covariate-adjusted

models associations were statistically significant but confidence intervals for ORs spanned 1.0; adjustment for age, sex and cardiometabolic RFs (OR 1.62 [0.06–3.18]; $p=0.043$); adjustment for follow-up duration strengthened this association (OR 1.83 [0.03–3.63; $p=0.048$)). In covariate-adjusted models, MASLD was associated with CVEs (OR 1.52 [0.12–2.91]; $p=0.037$) and CVD mortality (OR 1.51 [0.03–2.99]; $p=0.049$). MASLD was associated with an increased risk of incident ACS, AF, and stroke, however eligible study numbers precluded full adjustment for all cardiometabolic RFs.

Conclusion:

MASLD is associated with nearly a 2 fold increase in the risk of incident CVD. After adjusting for common cardiometabolic RFs, this association is statistically significant but equivocal due to the relatively wide CIs for ORs calculated in fully adjusted models that indicate a need for caution when interpreting these data. Further high-quality studies are needed to conclusively determine the impact of MASLD as an independent RF for both overall CVD and specific cardiovascular outcomes. Our findings suggest greater vigilance for incident CVD may be warranted in MASLD patients, even after optimising cardiometabolic parameters.

Figure/Table:

Figure 1. Forest plot depicting unadjusted odds ratios for overall incident CVD risk in the MASLD vs. non-MASLD cohorts for the included studies.

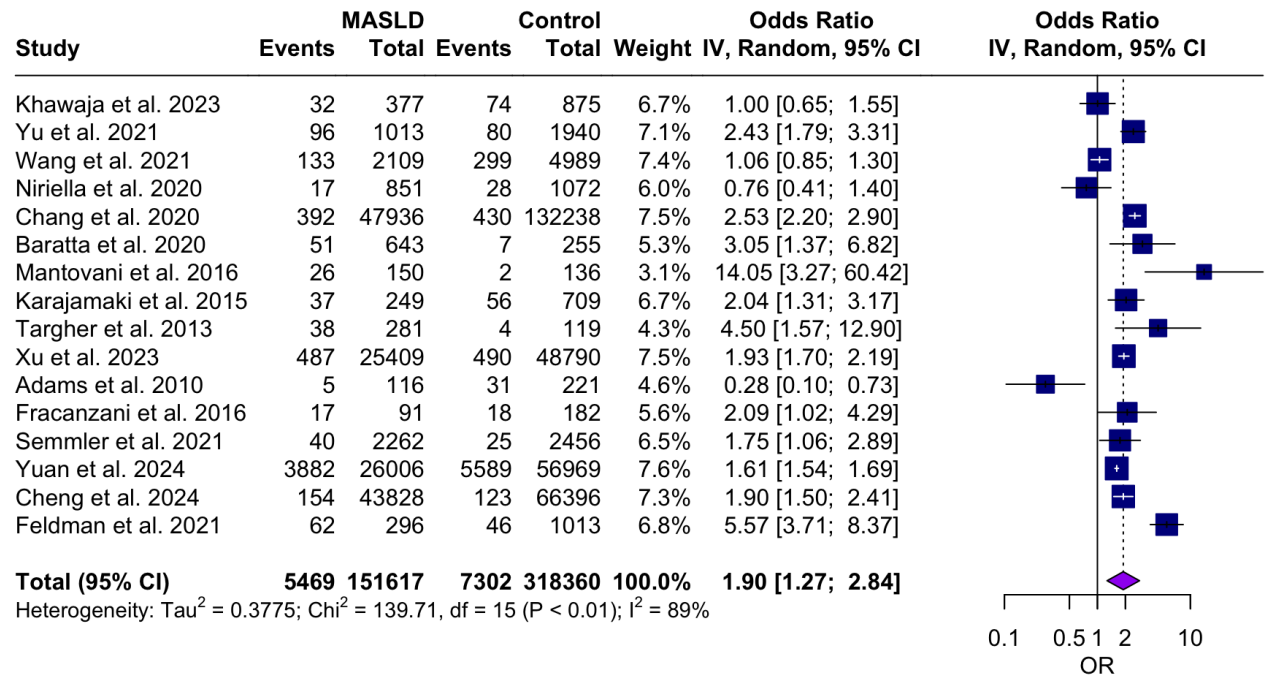


Figure 1. Forest plot depicting the risk of any incident CVD in the MASLD group as compared to the non-MASLD control group. Unadjusted odds ratios (ORs) are given for each of the individual studies included in the meta-analysis ($n=16$), with the pooled OR presented below along with heterogeneity statistics.