Comparative effects of non-alcoholic fatty liver disease and metabolic dysfunction-associated fatty liver disease on risk of incident cardiovascular events: a meta-analysis of about 13 million individuals

Alessandro Mantovani, MD[1], Alessandro Csermely, MD[1], Herbert Tilg, MD[2], Christopher D. Byrne, MB BCh, PhD[3,4], Giovanni Targher, MD[1]

[1]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
[2]Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology & Metabolism, Medical University Innsbruck, Innsbruck, Austria
[3]Nutrition and Metabolism, Faculty of Medicine, University of Southampton, UK
[4]Southampton National Institute for Health and Care Research Biomedical Research Centre, University Hospital Southampton, Southampton General Hospital, Tremona Road, Southampton, UK

Running title: NAFLD, MAFLD and CVD risk prediction

Word count: 600 words. n=1 **Table**, n=1 **Figure** *plus* online-only supplementary material.

Address for correspondence:
Prof. Giovanni Targher, MD
Section of Endocrinology, Diabetes and Metabolism
Department of Medicine
University and Azienda Ospedaliera Universitaria Integrata
Piazzale Stefani, 1
37126 Verona, Italy
Phone: +39-045-8123110
E-mail: giovanni.targher@univr.it

We read with interest the report on comparative risks of liver-related and cardiovascular disease (CVD) outcomes among lean and obese patients with non-alcoholic fatty liver disease (NAFLD) by Younes et al. [1]. Recently, international experts proposed redefining NAFLD as metabolic dysfunction-associated fatty liver disease (MAFLD) [2]. The impact of this name change on CVD risk prediction is not known.

We performed a meta-analysis of observational cohort studies (by searching PubMed, Scopus and Web of Science from database inception to June 30, 2022) that *simultaneously* used the NAFLD and MAFLD definitions for examining the risk of CVD events associated with both definitions, amongst adults with and without either NAFLD or MAFLD, and in which hepatic steatosis was diagnosed by imaging techniques or blood biomarkers/scores. The primary outcomes were CVD mortality, nonfatal CVD events, or both. Data from selected studies were extracted, and meta-analysis was performed using random-effects models to obtain summary hazard ratios (HR) with 95% CIs. In the case of studies reporting HRs with varying degrees of covariate adjustment, those reflecting the maximum extent of adjustment for confounding factors were extracted. The study was registered on Open Science Framework, number osf.io/gtvqm. **Supplementary Table S1** and **Figure S1** summarize the syntax used as well as the results of search and selection processes.

We identified 7 cohort studies with aggregate data on 13,318,377 middle-aged individuals (52.5% men; mean age 51 years; mean BMI 25 kg/m^2) and 201,399 incident cases of CVD events over a median follow-up of 7.0 (interquartile range 5-13) years [3, 4, 5, 6, 7, 8, 9]. The overall prevalence of MAFLD and NAFLD was 30.8% and 24.8%, respectively. As shown in **Table 1**, most of these studies recruited participants either from general populations or large health examination check-up programs, in which fatty liver was diagnosed by ultrasonography (n=3 studies) or blood biomarkers/scores (n=4). Six studies were carried out in Asia; one study was carried out in the United States. One study reported data only on CVD mortality, 3 studies reported data only on nonfatal CVD events, and 2 studies reported data on the combined CVD outcome.

Figure 1 shows that each of the two definitions were associated with a higher risk of fatal or nonfatal CVD events (pooled random-effects HR 1.50, 95%CI 1.30-1.72 for MAFLD vs. no-MAFLD; and pooled random-effects HR 1.27, 95%CI 1.12-1.45 for NAFLD vs. no-NAFLD, respectively). These risks were independent of age, sex, smoking or other traditional CVD risk factors (as specified in Table 1). Although MAFLD identified a greater number of CVD events than NAFLD, the risk for incident CVD events associated with either definition was not significantly different (Z-score=1.66, p=0.097 by comparison of pooled random-effects HRs for the two definitions). Meta-regression analyses did not show any effect of body mass index or percentage of diabetes at baseline on the association between each of the two definitions and risk of CVD events (**supplementary Figure S2**).

This meta-analysis comparing the long-term risk of CVD events associated with NAFLD or MAFLD definitions is the first and most comprehensive assessment to date. The quality of the selected studies was acceptable, suggesting an overall medium-low risk of bias, according to the Newcastle-Ottawa scale (NOS) (Table 1). Funnel plot did not reveal any significant publication bias (**supplementary Figure S3**). Our meta-analysis has some important limitations, e.g., the relatively small number of cohort studies (mostly from Asian countries), the methods used for diagnosing hepatic steatosis, and the incomplete adjustment for potential confounders (including the change in status of the exposure variable between baseline and follow-up). Additionally, none of the included studies had any data on non-invasive tests for liver fibrosis in order to compare potential differences of NAFLD and MAFLD definitions on risk of CVD events, according to severity of liver disease.

Further studies from different countries are needed to test whether MAFLD better predicts incident CVD events than NAFLD. However, our findings further emphasize that clinicians should have a high index of suspicion that MAFLD individuals can have co-existing CVD.

ACKNOWLEDGEMENTS

Contributors: GT designed the study. AM, AC and GT did the literature search, with arbitration by AC. AM and GT analyzed the data and did the figures. All authors interpreted the data. GT and CDB wrote the manuscript draft. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest: The authors have no competing financial interests to declare.

Funding source: There was no funding source for this study.

FIGURE LEGEND

Figure 1. Forest plots and pooled estimates of the prognostic effect of either MAFLD (A) or NAFLD (B) on the risk of developing fatal and nonfatal CVD events in 7 eligible cohort studies that simultaneously used the NAFLD and MAFLD definitions.

REFERENCES

1. Younes R, Govaere O, Petta S, Miele L, Tiniakos D, Burt A*, et al.* Caucasian lean subjects with non-alcoholic fatty liver disease share long-term prognosis of non-lean: time for reappraisal of BMI-driven approach? Gut 2022;**71**:382-90.
2. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M*, et al.* A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;**73**:202-9.
3. Niriella MA, Ediriweera DS, Kasturiratne A, De Silva ST, Dassanayaka AS, De Silva AP*, et al.* Outcomes of NAFLD and MAFLD: Results from a community-based, prospective cohort study. PLoS One 2021;**16**:e0245762.
4. Yoneda M, Yamamoto T, Honda Y, Imajo K, Ogawa Y, Kessoku T*, et al.* Risk of cardiovascular disease in patients with fatty liver disease as defined from the metabolic dysfunction associated fatty liver disease or nonalcoholic fatty liver disease point of view: a retrospective nationwide claims database study in Japan. J Gastroenterol 2021;**56**:1022-32.
5. Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. J Hepatol 2021;**75**:1284-91.
6. Jeong S, Oh YH, Choi S, Chang J, Kim SM, Son JS*, et al.* Metabolic Dysfunction-Associated Fatty Liver Disease Better Predicts Incident Cardiovascular Disease. Gut Liver 2021.
7. Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. Clin Gastroenterol Hepatol 2021;**19**:2138-47 e10.
8. Liang Y, Chen H, Liu Y, Hou X, Wei L, Bao Y*, et al.* Association of MAFLD with diabetes, chronic kidney disease, and cardiovascular disease: a 4.6-year cohort study in China. J Clin Endocrinol Metab 2022;**107**:88-97.
9. Moon JH, Kim W, Koo BK, Cho NH, Innovative Target Exploration of NAFLD (ITEN) consortium. Metabolic dysfunction-associated fatty liver disease predicts long-term mortality and cardiovascular disease. Gut Liver 2022;**16**:433-42.

Table 1. Eligible cohort studies examining the association between either MAFLD or NAFLD definition and the risk of developing fatal and/or nonfatal cardiovascular events (ordered by publication year; *n* = 7 studies).

Author, Ref.	Study characteristics	Methods for diagnosing hepatic steatosis	CVD outcomes (number of total events)	Covariate adjustment	Main findings	NOS scale
Niriella et al.[3]	Population-based cohort study: 2,985 Sri Lankan individuals (median age 53 years; 63% women; 29.4% T2DM). The prevalence of NAFLD and MAFLD was 31.5% (n=940) and 33.1% (n=990). Mean follow-up: 7 years	US	Nonfatal myocardial infarction, stroke, coronary revascularization procedures, or cardiovascular death (n=47)	Age, sex	Compared with those without MAFLD, subjects with MAFLD had increased risk of fatal and/or nonfatal cardiovascular events (aHR 4.2, 95%CI 1.5-11.5). Compared with those without NAFLD, subjects with NAFLD had increased risk of fatal and/or nonfatal cardiovascular events (aHR 3.7, 95%CI 1.3-10.3)	8
Yoneda et al.[4]	Population-based cohort study: 1,542,688 South Korean individuals (mean age 46 years; mean BMI 25 kg/m^2; 37% women; 17.8% T2DM) were included in the NAFLD cohort, while 2,452,949 individuals (mean age 46 years; mean BMI 25 kg/m^2; 38% were women; 18% T2DM) were included in the MAFLD cohort. The prevalence of NAFLD and MAFLD was 9.2% (n=142,158), and 9.7% (n=237,242). Median follow-up: 4 years	FLI	Nonfatal coronary heart disease or stroke (n=6,715)	Age, sex, smoking, LDL-cholesterol, statin use	Compared with those without MAFLD, subjects with MAFLD had increased risk of nonfatal cardiovascular events (aHR 1.89, 95%CI 1.78-2.01). Compared with those without NAFLD, subjects with NAFLD did not have a higher risk of cardiovascular events (aHR 1.02, 95%CI 0.92-1.14)	7
Kim et al.[5]	Population-based cohort study: 7,761 United States individuals (mean age 41 years; mean BMI 26 kg/m^2; 50% women; 7% T2DM) from the Third National Health and Nutrition Examination Survey (1988-1994). The prevalence of NAFLD and MAFLD was 29.5% (n=2,438) and 25.9% (n=2,256). Median follow-up: 23 years	US	Cardiovascular death (n=576)	Age, sex, race/ethnicity, marital status, education, smoking, sedentary lifestyle, ALT	Compared with those without MAFLD, subjects with MAFLD had increased risk of cardiovascular death (aHR 1.24, 95%CI 1.01-1.51). Compared with those without NAFLD, subjects with NAFLD did not have a higher risk of cardiovascular death (aHR 1.09, 95%CI 0.88-1.35)	9
Jeong et al.[6]	Nationwide health screening database: 333,389 South Korean participants (mean age 57 years; mean BMI 23.9 kg/m^2; 46% women; 9.6% T2DM) from the Korean National Health Insurance Service database, who received a health examination between 2009 and 2010. The prevalence of MAFLD and NAFLD was 12.6% (n=41,915) and 7% (23,190). Mean follow-up: 5.5 years	K-NAFLD score*	Hospitalization due to nonfatal coronary heart disease or stroke (n=10,370)	Age, sex, insurance premium, BMI, smoking, alcohol consumption, physical activity, ALT, Charlson comorbidity index	Compared with those without MAFLD, subjects with MAFLD had increased risk of nonfatal cardiovascular events (aHR 1.71, 95%CI 1.22-2.41). Compared with those without NAFLD, subjects with NAFLD had increased risk of nonfatal cardiovascular events (aHR 1.55, 95%CI 1.44-1.65)	7
Lee et al.[7]	Nationwide health screening database: 8,962,813 South Korean participants (mean age 50 years; 52% women) from the National Health Insurance Service.	FLI	Nonfatal myocardial infarction, stroke, heart failure, or cardiovascular death (n=182,423)	Age, sex, household income, residential area, smoking, physical activity, estimated glomerular	Compared with those without MAFLD, subjects with MAFLD had increased risk of fatal and nonfatal cardiovascular events (aHR 1.52, 95%CI 1.51-1.54). Compared with those without NAFLD, subjects with NAFLD	7

	The prevalence of NAFLD and MAFLD was 28.0% (n=2,509,588) and 37.3% (n=3,343,129). Median follow-up: 10.1 years			filtration rate, Charlson comorbidity index	had increased risk of fatal and nonfatal cardiovascular events (aHR 1.41, 95%CI 1.40-1.43)	
Liang et al.[8]	Population-based cohort study: 6,873 Chinese individuals (mean age 62 years; mean BMI 25 kg/m^2; 58% women; 20% T2DM). The prevalence of NAFLD and MAFLD was 40.3% (n=2,545) and 46.7% (n=2,950). Mean follow-up: 4.6 years	US	Nonfatal coronary heart disease or stroke (n=296)	Age, sex, education, smoking, physical activity	Compared with those without MAFLD, subjects with MAFLD had increased risk of nonfatal cardiovascular events (aHR 1.44, 95%CI 1.15-1.81). Compared with those without NAFLD, subjects with NAFLD had increased risk of nonfatal cardiovascular events (aHR 1.48, 95%CI 1.17-1.88)	8
Moon et al.[9]	Population-based cohort study: 8,919 South Korean patients (mean age 52 years, mean BMI 24.4 kg/m^2; 52% women; 11.7% T2DM). The prevalence of NAFLD and MAFLD was 12.8% (n=1,142) and 16.9% (n=1,509). Mean follow-up: 15.7 years	FLI	Nonfatal myocardial infarction, coronary heart disease, or cerebrovascular disease (n=972)	Age, sex, BMI, smoking, alcohol intake, T2DM, hypertension, dyslipidemia, chronic kidney disease, viral hepatitis, plasma CRP	Compared with those without MAFLD, subjects with MAFLD did not have increased risk of nonfatal cardiovascular events (aHR 1.08, 95%CI 0.89-1.31). Compared with those without NAFLD, subjects with NAFLD did not have a higher risk of cardiovascular events (aHR 0.99, 95%CI 0.82-1.21)	7

Note: *K-NAFLD score was calculated as follows = (0.913 * sex [2, if female; 1, if male] + 0.089 * waist circumference + 0.032 * [systolic blood pressure + fasting serum glucose] + triglycerides * 0.007 + alanine aminotransferase * 0.105 − 20.929).

Abbreviations: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; FLI, fatty liver index; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NOS, Newcastle-Ottawa quality assessment scale; T2DM, type 2 diabetes mellitus; US, ultrasonography.