Long-Term Cardiovascular outcomes Differ Across Metabolic Dysfunction-Associated Fatty Liver Disease Subtypes

Hokyou Lee
Yonsei University College of Medicine
Tae Seop Lim
Yonsei University College of Medicine
Seung Up Kim (ksukorea@yuhs.ac)
Yonsei University College of Medicine https://orcid.org/0000-0002-9658-8050
Hyeon Chang Kim
Yonsei University College of Medicine

Research Article

Keywords: Metabolic dysfunction-associated fatty liver disease, non-alcoholic fatty liver disease, fatty liver, cardiovascular disease, subtype

Posted Date: April 20th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1508843/v1

Abstract

Background & Aims: The new metabolic dysfunction-associated fatty liver disease (MAFLD) criteria include three distinct subtypes: MAFLD with diabetes mellitus (DM), overweight/obese (OW), or lean/normal weight with metabolic dysfunction. We investigated whether long-term cardiovascular disease outcomes differ across the MAFLD subtypes.

Methods: From a nationwide health screening database, we included 8,412,730 participants (48.6% male) aged 40-64 years, free of cardiovascular disease history, between 2009 and 2010. Participants were categorized into non-MAFLD, OW-MAFLD, lean-MAFLD, and DM-MAFLD. The primary outcome was a composite cardiovascular disease event, including myocardial infarction, ischemic stroke, heart failure, or cardiovascular disease-related death. The presence of advanced liver fibrosis was estimated using a BARD score ≥2.

Results: Among the study participants, 3,087,640 (36.7%) had MAFLD, among which 2,424,086 (78.5%), 170,761 (5.5%), and 492,793 (16.0%) had OW-MAFLD, lean-MAFLD, and DM-MAFLD, respectively. Over a median follow-up period of 10.0 years, 169,433 new cardiovascular disease events occurred. With the non-MAFLD group as reference, multivariable-adjusted hazard ratios (95% confidence intervals) for cardiovascular disease events were 1.16 (1.15-1.18), 1.23 (1.20-1.27), and 1.82 (1.80-1.85) in the OW-MAFLD, lean-MAFLD, and DM-MAFLD groups, respectively. Participants with lean-MAFLD or DM-MAFLD had a higher cardiovascular disease risk than those with OW-MAFLD, irrespective of metabolic abnormalities or comorbidities. The presence of advanced liver fibrosis was significantly associated with a higher cardiovascular disease risk in each MAFLD subtype.

Conclusion: Long-term cardiovascular disease outcomes differed across the MAFLD subtypes. Further studies are required to investigate whether preventive or therapeutic interventions should be optimized according to the MAFLD subtypes.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a global health problem with 25% prevalence [1]. The prevalence of NAFLD is rapidly increasing due to lifestyle changes, such as sedentary habits, unhealthy food, and high calorie intake, and it is becoming a major health burden [2]. NAFLD is associated with metabolically unhealthy status and has a disadvantage in that it does not reflect the heterogeneity of the disease because it lacks “positive” criteria related to metabolic dysfunction [3].

Recently, the concept of metabolic dysfunction associated fatty liver disease (MAFLD) has been proposed based on positive inclusion criteria, in which MAFLD is diagnosed when there is an evidence of hepatic steatosis accompanied by metabolic dysfunction regardless of etiologies [2]. The new MAFLD definition has the advantage to better reflect the characteristics of the disease associated with metabolic dysfunction without evaluating the ambiguity of average alcohol intake. Several studies have shown that

MAFLD might be better than NAFLD in identifying high-risk patients among those with fatty liver disease (FLD) [4, 5].

FLD can progress to cirrhosis or hepatocellular carcinoma or cause hepatic complications. However, in patients with FLD, deaths from cardiovascular disease (CVD) are more common than those from liver disease, probably due to the close association of FLD with other metabolic dysfunctions [1]. Recent studies have shown that MAFLD is more useful than NAFLD in identifying patients who are at a high risk of CVD development [4, 5]. While MAFLD was proposed to overcome heterogeneity in the clinical course of NAFLD, MAFLD also can be divided into three subtypes—overweight/obese (OW), lean/normal weight, and diabetes mellitus (DM)—among which the difference in prognosis, if any, is not well known.

Thus, this study investigates whether CVD risk varies according to the MAFLD subtype using a nationwide health screening database.

Methods

Data source

We accessed the nationwide health information database of the National Health Insurance Service (NHIS), a single provider of universal healthcare coverage in Korea. The NHIS database contains de-identified sociodemographic details, reimbursement claims with International Classification of Disease, 10th revision (ICD-10) coding, health check-up results, and death information for the entire Korean population. This data source has been described in previous studies [4]. The current study protocol was in accordance with the principles of the 1975 Declaration of Helsinki, and the study was approved by the Institutional Review Board of Yonsei University Health System, Seoul, Korea (#Y-2019-0081). Informed consent was waived because this was a retrospective study of de-identified, routinely collected data.

Study population

We identified 10,186,076 adults aged 40 to 64 years who underwent routine NHIS health examinations between 2009–2010. If a participant underwent multiple examinations during this period, the first record was used as the baseline. After excluding participants with incomplete information (n = 601,677), previous CVD (n = 601,601), previous cancer (n = 555,343), or < 1 year of follow-up (n = 14,725), a final analytical sample of 8,412,730 participants (Supplementary Fig. 1) was included in the study.

Measurements and key variables

Clinical and biochemical measurements and questionnaire-based lifestyle information were collected during biennial health examinations in centers designated and overseen for quality control according to relevant laws and regulations. Details of the health examinations are described elsewhere [6]. The collected variables included body mass index (BMI), waist circumference, blood pressure, blood chemistry, tobacco use, alcohol consumption, and exercise frequency. OW, DM, hypertension, and dyslipidemia were defined according to the Korean clinical guidelines (Supplementary Table 1).

Medication use, concomitant liver disease, and Charlson Comorbidity Index (CCI) were determined from the claims data during a look-back period of two years prior to the baseline. DM and liver diseases were not counted toward the CCI as these were key covariables and determinants of the MAFLD subtype. Excessive drinking (≥ 30 g/day in men and ≥ 20 g/day in women) and concomitant liver diseases were defined as previously described [4].

Hepatic steatosis was assessed using the fatty liver index (FLI; Supplementary Table 1) described by the European Clinical Practice Guidelines as an acceptable alternative to imaging modalities for large epidemiologic studies [7]. FLI was validated in the Korean population with an area under the receiver operating characteristic curve of 0.87, although the cutoff should be lower than that for the Western populations [8]. The lower cutoff of FLI ≥ 30 was used, as in previous Korean studies [4]. Another steatosis model, Simple NAFLD Score (SNS, ≥ 8) [8], developed and validated in the Korean population, was used in the sensitivity analysis.

MAFLD was defined as the presence of hepatic steatosis with one or more of the following criteria: (1) DM; (2) OW (BMI ≥ 23 kg/m^2); or (3) at least 2 metabolic abnormalities (MA) described in Supplementary Table [2]. From these criteria, three mutually exclusive subtypes of MAFLD were derived: (1) MAFLD with DM (“DM-MAFLD”); (2) OW MAFLD without DM (“OW-MAFLD”); or (3) lean/normal-weight MAFLD with ≥ 2 MA but without DM (“lean-MAFLD”). Participants with the DM-MAFLD or OW-MAFLD subtypes may have had overlapping diagnostic components (e.g., DM + OW or OW + MA), which were further parsed in subsequent analyses. The presence of advanced liver fibrosis was estimated using a BARD score ≥ 2 (Supplementary Table 1).

Outcomes

The primary outcome was a composite CVD event, defined as the first hospitalization for MI (ICD-10: I21-I23), ischemic stroke (ICD-10: I63), or heart failure (ICD-10: I50), or CVD-related death (ICD-10: I00-I99) [9] recorded through December 31, 2019. If a participant had > 1 event during the follow-up period, the first event was counted as the primary outcome. The secondary outcomes were liver cancer (the first hospitalization with ICD-10 code C22) [10] and all-cause death, each assessed separately; if > 1 type of event had occurred, the first occurrence of each type of event was counted as an outcome. Participants who did not have any event were censored at the date of death, last follow-up, or December 31, 2019, whichever came first. Death was ascertained by linkage to the national registry via resident registration numbers.

Statistical analysis

Baseline characteristics were reported as frequency and percentage or median and interquartile range. Incidence rates were calculated as the number of events per 100,000 person-years of follow-up. The cumulative incidence of CVD events was estimated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated using Cox proportional hazards models. The proportionality of hazards was confirmed via graphical inspection of log-minus-log plots and Schoenfeld residuals. HRs were adjusted for age, sex, household income quartile, residential area, CCI, aspirin use,

non-steroidal anti-inflammatory drug use, concomitant liver disease, alcohol consumption, tobacco use, exercise frequency, hypertension, and dyslipidemia. Covariables were selected *a priori* based on possible associations with MAFLD and CVD [11, 12].

Three sensitivity analyses were performed. First, the associations of MAFLD subtypes with CVD events were explored in subgroups stratified by sex, age, and comorbidities. Heterogeneity between subgroups was examined in terms of relative risk ratio (RRR) calculated from multiplicative interaction between the subgrouping variable and MAFLD subtypes [9]. Second, a lower threshold of ≥ 1 instead of ≥ 2 MA for MAFLD criteria was used to relieve stringency, considering the lack of fasting insulin and C-reactive protein data in our study. Third, another validated steatosis model, SNS ≥ 8, was used to define MAFLD. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of the study participants are presented in Table 1. The study included 8,412,730 participants (median age, 50 years; 48.6% male), among whom 3,087,640 (36.7%) had MAFLD. Among those with MAFLD, 2,424,086 (78.5%) were classified as OW-MAFLD, 170,761 (5.5%), as lean-MAFLD, and 492,793 (16.0%), as DM-MAFLD. Participants with MAFLD were more likely to be male, living in a rural area, heavy drinking, and having unfavorable cardiovascular risk factors than those without MAFLD. Participants with DM-MAFLD were on average older, more likely to be poor, and more likely to have comorbid conditions than those with other MAFLD subtypes. Participants with lean-MAFLD were more likely to be male, be heavy drinkers, have a poor lifestyle, and have higher triglyceride levels than those with other MAFLD subtypes.

Table 1
Baseline characteristics by presence and subtypes of MAFLD

Variable	Non-	MAFLD		
	MAFLD	OW-MAFLD	Lean-MAFLD	DM-MAFLD
	(n = 5,325,090)	(n = 2,424,086)	(n = 170,761)	(n = 492,793)
% Among total N	63.3	28.8	2.0	5.9
% Among MAFLD	-	78.5	5.5	16.0
Age, years	49 [44–55]	50 [44–56]	51 [46–56]	53 [48–58]
Sex				
Female	3,478,403 (65.3)	684,852 (28.3)	27,536 (16.1)	132,965 (27.0)
Male	1,846,687 (34.7)	1,739,234 (71.7)	143,225 (83.9)	359,828 (73.0)
Household income quartile*				
Q4, highest	1,898,352 (35.6)	952,423 (39.3)	56,852 (33.3)	164,851 (33.5)
Q3	1,286,164 (24.2)	624,977 (25.8)	46,032 (27.0)	130,261 (26.4)
Q2	1,038,595 (19.5)	437,029 (18.0)	35,685 (20.9)	98,226 (19.9)
Q1, lowest	1,101,979 (20.7)	409,657 (16.9)	32,192 (18.9)	99,455 (20.2)
Residential area				
Metropolitan	2,503,237 (47.0)	1,071,932 (44.2)	77,483 (45.4)	217,471 (44.1)

Values as frequency (%) or median [interquartile range].

*Household income categorized based on quartiles among the entire Korean population.

†Not counting diabetes or liver diseases.

‡ALT > 35 IU/L in men and > 25 IU/L in women, according to the American Association for the Study of Liver Disease recommendation.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese; UNL, upper limit of normal.

Variable	Non-		MAFLD	
Urban	1,897,925 (35.6)	865,160 (35.7)	57,986 (34.0)	167,625 (34.0)
Rural	923,928 (17.4)	486,994 (20.1)	35,292 (20.7)	107,697 (21.9)
Charlson Comorbidity Index†				
0	3,890,167 (73.1)	1,786,498 (73.7)	130,940 (76.7)	348,155 (70.6)
1	1,322,150 (24.8)	581,433 (24.0)	36,491 (21.4)	125,445 (25.5)
≥2	112,773 (2.1)	56,155 (2.3)	3,330 (2.0)	19,193 (3.9)
Presence of other conditions				
Overweight/Obese	2,249,059 (42.2)	2,424,086 (100)	0	444,227 (90.1)
Diabetes mellitus	274,333 (5.2)	0	0	492,793 (100)
Hypertension	1,031,876 (19.4)	932,142 (38.5)	69,018 (40.4)	288,944 (58.6)
Dyslipidemia	1,324,106 (24.9)	1,427,320 (58.9)	128,492 (75.2)	362,027 (73.5)
Viral hepatitis	183,372 (3.4)	88,185 (3.6)	5,688 (3.3)	25,376 (5.1)
Other liver disease	46,801 (0.9)	28,067 (1.2)	2,325 (1.4)	9,877 (2.0)
Alcohol consumption				
None	3,384,043 (63.5)	1,025,096 (42.3)	46,634 (27.3)	212,672 (43.2)
Moderate	1,564,041 (29.4)	946,221 (39.0)	71,123 (41.7)	173,406 (35.2)

Values as frequency (%) or median [interquartile range].

*Household income categorized based on quartiles among the entire Korean population.

†Not counting diabetes or liver diseases.

‡ALT > 35 IU/L in men and > 25 IU/L in women, according to the American Association for the Study of Liver Disease recommendation.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese; UNL, upper limit of normal.

Variable	Non-		MAFLD	
Excessive	377,006 (7.1)	452,769 (18.7)	53,004 (31.0)	106,715 (21.7)
Tobacco use				
Never	3,903,013 (73.3)	1,116,723 (46.1)	50,819 (29.8)	216,455 (43.9)
Past	564,204 (10.6)	548,768 (22.6)	32,962 (19.3)	108,872 (22.1)
Current	857,873 (16.1)	758,595 (31.3)	86,980 (50.9)	167,466 (34.0)
Exercise frequency				
≥3/week	1,364,742 (25.6)	589,042 (24.3)	35,616 (20.9)	128,896 (26.2)
1–2/week	1,345,709 (25.3)	720,086 (29.7)	50,096 (29.3)	130,606 (26.5)
None	2,614,639 (49.1)	1,114,958 (46.0)	85,049 (49.8)	233,291 (47.3)
Body mass index, kg/m^2	22.5 [21.0-24.1]	26.1 [24.8–27.8]	22.1 [21.3–22.6]	26.1 [24.3–28.0]
Waist circumference, cm	76 [71–81]	88 [84–92]	81 [78–84]	88 [84–93]
Systolic BP, mm Hg	120 [110–130]	128 [119–135]	130 [120–138]	130 [120–139]
Diastolic BP, mm Hg	74 [70–80]	80 [73–86]	80 [75–88]	80 [75–88]
Total cholesterol, mg/dL	193 [171–217]	207 [184–232]	205 [180–232]	202 [176–230]
Triglyceride, mg/dL	89 [66–120]	167 [123–230]	221 [173–295]	185 [133–263]
HDL-cholesterol, mg/dL	56 [48–66]	49 [42–57]	50 [41–60]	48 [41–57]
LDL-cholesterol, mg/dL	115 [95–137]	120 [97–143]	105 [79–132]	110 [84–137]
Fasting glucose, mg/dL	92 [85–100]	96 [89–105]	100 [91–108]	140 [127–168]

Values as frequency (%) or median [interquartile range].

*Household income categorized based on quartiles among the entire Korean population.

†Not counting diabetes or liver diseases.

‡ALT > 35 IU/L in men and > 25 IU/L in women, according to the American Association for the Study of Liver Disease recommendation.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese; UNL, upper limit of normal.

Variable	Non-		MAFLD	
AST, IU/L	21 [18–26]	26 [21–32]	28 [23–37]	27 [21–36]
ALT, IU/L	18 [14–23]	28 [21–39]	28 [21–40]	31 [22–45]
ALT > ULN‡	667,078 (12.5)	893,151 (36.8)	62,202 (36.4)	227,134 (46.1)
Follow-up, years	10.0 [9.4–10.4]	10.1 [9.4–10.4]	10.1 [9.4–10.4]	10.0 [9.4–10.4]
Values as frequency (%) or median [interquartile range].				
*Household income categorized based on quartiles among the entire Korean population.				
†Not counting diabetes or liver diseases.				
‡ALT > 35 IU/L in men and > 25 IU/L in women, according to the American Association for the Study of Liver Disease recommendation.				
AST, aspartate aminotransferase; ALT, alanine aminotransferase; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese; UNL, upper limit of normal.				

CVD risk according to MAFLD presence and subtypes

During a median follow-up of 10.0 years, 169,433 new CVD events occurred. The CVD incidence rates per 100,000 person-years were 143.3 in the non-MAFLD group, 262.0 in the OW-MAFLD group, 370.1 in the lean-MAFLD group, and 564.9 in the DM-MAFLD group. The cumulative incidence of CVD events was the highest in the DM-MAFLD group, followed by the lean-MAFLD, OW-MAFLD, and non-MAFLD groups in descending order (Fig. 1). After adjustment for sociodemographic factors, CCI, medication, lifestyle, and liver diseases, the HRs (95% CI) for CVD events were 1.35 (1.34–1.37) in the OW-MAFLD group, 1.49 (1.45–1.53) in the lean-MAFLD group, and 2.26 (2.23–2.30) in the DM-MAFLD group, in comparison with the non-MAFLD group (Table 2, model 3). After further adjustment for hypertension and dyslipidemia, the corresponding HRs (95% CI) were 1.16 (1.15–1.18), 1.23 (1.20–1.27), and 1.82 (1.80–1.85), respectively (Table 2, model 4).

Table 2
Cardiovascular disease risk according to presence and subtypes of MAFLD

Group	Events	Person-yrs	Rate*	Hazard ratio (95% confidence interval)			
				Model 1	Model 2	Model 3	Model 4
Non-MAFLD	74,875	52,246,291	143.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
OW-MAFLD	61,960	23,646,386	262.0	1.83 (1.81–1.85)	1.35 (1.34–1.37)	1.35 (1.34–1.37)	1.16 (1.15–1.18)
Lean-MAFLD	6,081	1,643,205	370.1	2.59 (2.52–2.66)	1.65 (1.61–1.70)	1.49 (1.45–1.53)	1.23 (1.20–1.27)
DM-MAFLD	26,517	4,694,364	564.9	3.96 (3.91–4.02)	2.42 (2.39–2.46)	2.26 (2.23–2.30)	1.82 (1.80–1.85)
*Rate per 100,000 person-years.							
Model 1 was unadjusted.							
Model 2 was adjusted for age and sex.							
Model 3 was further adjusted for household income quartile, residential area, Charlson Comorbidity Index, aspirin use, non-steroidal anti-inflammatory drug use, past liver disease, alcohol consumption, tobacco use, and exercise frequency.							
Model 4 was further adjusted for hypertension and dyslipidemia.							
DM, diabetes mellitus; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese.							

Comparison of outcomes across MAFLD subtypes

Among participants with MAFLD, those with lean-MAFLD (HR, 1.10; 95% CI, 1.07–1.13) and DM-MAFLD (HR, 1.65; 95% CI, 1.63–1.68) were at a significantly higher risk for CVD events than those with OW-MAFLD (Table 3, model 4). For the secondary outcomes (15,629 liver cancer occurrences and 95,601 all-cause deaths among participants with MAFLD), lean-MAFLD and DM-MAFLD were associated with a significantly higher risk compared with OW-MAFLD (Table 3). Multivariable-adjusted HRs (95% CI) for liver cancer development and all-cause death, respectively, were 1.32 (1.24–1.41) and 1.81 (1.77–1.85) in the lean-MAFLD group and 2.07 (2.00-2.14) and 1.79 (1.76–1.82) in the DM-MAFLD group, in comparison with the OW-MAFLD group (Table 3, model 4).

Table 3
Comparison of primary and secondary outcomes across MAFLD subtypes

Group	Events	Person-yrs	Rate*	Hazard ratio (95% confidence interval)			
				Model 1	Model 2	Model 3	Model 4
Composite CVD events							
OW-MAFLD	61,960	23,646,386	262.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Lean-MAFLD	6,081	1,643,205	370.1	1.41 (1.38–1.45)	1.25 (1.22–1.28)	1.14 (1.11–1.17)	1.10 (1.07–1.13)
DM-MAFLD	26,517	4,694,364	564.9	2.16 (2.13–2.20)	1.84 (1.82–1.87)	1.75 (1.72–1.78)	1.65 (1.63–1.68)
Liver cancer							
OW-MAFLD	9,826	23,859,454	41.2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Lean-MAFLD	1,037	1,661,949	62.4	1.52 (1.42–1.62)	1.28 (1.20–1.36)	1.13 (1.06–1.20)	1.32 (1.24–1.41)
DM-MAFLD	4,766	4,785,935	99.6	2.42 (2.34–2.51)	2.06 (1.99–2.13)	1.85 (1.78–1.91)	2.07 (2.00-2.14)
All-cause death							
OW-MAFLD	58,603	23,886,686	245.3	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Lean-MAFLD	9,776	1,664,696	587.3	2.40 (2.35–2.45)	2.08 (2.04–2.13)	1.79 (1.75–1.83)	1.81 (1.77–1.85)
DM-MAFLD	27,222	4,798,184	567.3	2.32 (2.29–2.35)	1.92 (1.89–1.95)	1.81 (1.78–1.84)	1.79 (1.76–1.82)

*Rate per 100,000 person-years.

Model 1 was unadjusted.

Model 2 was adjusted for age and sex.

Group	Events	Person-yrs	Rate*	Hazard ratio (95% confidence interval)
Model 3 was further adjusted for household income quartile, residential area, Charlson Comorbidity Index, aspirin use, non-steroidal anti-inflammatory drug use, past liver disease, alcohol consumption, tobacco use, and exercise frequency.				
Model 4 was further adjusted for hypertension and dyslipidemia.				
DM, diabetes mellitus; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese.				

CVD outcome according to MAFLD components and liver fibrosis

To further delineate the joint associations of overlapping MAFLD diagnostic components, we categorized participants into seven mutually exclusive groups according to the combined presence of DM, OW, and MA (Fig. 2). Herein, the presence of MA was defined as having ≥ 2 MA components in non-DM participants or ≥ 1 MA component other than high fasting glucose in DM participants. Lean-MAFLD was associated with a higher CVD risk than was OW-MAFLD, with or without MA. Likewise, among participants with DM-MAFLD, lean participants had a higher CVD risk than those with OW. The presence of MA in addition to OW or DM was associated with further excess risk of CVD events.

The presence of advanced liver fibrosis (BARD score ≥ 2) in each MAFLD subtype was associated with a higher CVD risk, with the greatest excess risk observed in the lean-MAFLD subtype (Fig. 3). Compared to OW-MAFLD without advanced liver fibrosis, OW-MAFLD with advanced liver fibrosis and lean-MAFLD with advanced liver fibrosis were associated with higher CVD risk, whereas lean-MAFLD without advanced liver fibrosis was not. With or without advanced liver fibrosis, DM-MAFLD was associated with the highest CVD risk among MAFLD subtypes.

Sensitivity analyses

We conducted the following sensitivity analyses. First, when stratified by sex, age, and comorbidities, the associations of MAFLD subtypes with CVD events were generally consistent in all subgroups. No significant heterogeneity was found in the association of lean-MAFLD (vs. OW-MAFLD) with CVD events across each subgroup (95% CI for RRR included 1), except in the subgroup with concomitant liver diseases, in which the HR was greater than that in the subgroup without liver diseases (RRR, 1.07; 95% CI, 1.01–1.13; Supplementary Table 2). DM-MAFLD (vs. OW-MAFLD) was associated with a significantly higher CVD risk in all subgroups, although the HRs were generally smaller in the subgroups with higher absolute risk (Supplementary Table 3). Second, using the lower threshold of ≥ 1 instead of ≥ 2 MA for MAFLD criteria, the HRs for CVD events associated with MAFLD subtypes were similar in terms of point estimates to those in the main analysis (Supplementary Table 4). Third, using another validated biochemical steatosis model (SNS ≥ 8), the associations of MAFLD subtypes with CVD events were compatible with those observed using the FLI (Supplementary Table 5).

Discussion

In this nationwide study of 8 million middle-aged population under routine health screening, the CVD risk increased in the following order: non-MAFLD, OW-MAFLD, lean-MAFLD, and DM-MAFLD. Even after appropriate adjustment for confounders, the order of the CVD risk was maintained. Similar trends were observed for the risk of liver cancer development and all-cause death.

Our study had several clinical implications. First, we confirmed that patients with MAFLD, with any subtype, were at a higher risk of CVD events than those without MAFLD. Previous observational studies have shown that NAFLD is significantly associated with a higher risk of CVD development [13], and that CVD, rather than liver-related complications or extrahepatic malignancies, is the primary cause of death in patients with NAFLD [1]. Despite this close association between NAFLD and CVD, the NAFLD criteria might have a potential pitfall of including “metabolically healthy” subjects, not having DM, hypertension, dyslipidemia, or obesity, with negligible risk of CVD. Such patients with NAFLD who do not satisfy the new MAFLD criteria are at a significantly lower risk of CVD [4]. we focused on subjects with MAFLD with “metabolically unhealthy” status and found that CVD incidence rates are much higher in MAFLD subgroups than those in the control group. In addition, extending this prior knowledge, we further evaluated the overlapping components between MAFLD subtypes by dividing them into seven mutually exclusive groups. In the OW-MAFLD, OW with MA conferred a higher CVD risk than OW without MA, whereas in the DM-MAFLD subtype, the presence of MA was associated with a higher CVD risk in both OW and non-OW patients. Our results suggest that the presence of MA in patients with OW-MAFLD and DM-MAFLD further increases the CVD risk.

Second, among the MAFLD subtypes, DM-MAFLD conferred the highest risk for CVD events. This is not surprising as DM has been recognized as a major risk factor for CVD [14]. DM is associated with inflammatory and thrombotic condition, and endothelial cell dysfunction and oxidative stress due to insulin resistance and hyperglycemia; such processes can, in turn, lead to the development of atherosclerosis and CVD [15]. Several studies using a large claims database reported that DM increases CVD risk in patients with NAFLD or MAFLD [4, 16]. Our study extends this prior knowledge by demonstrating that the DM-MAFLD subtype may be a strong predictor of future CVD events.

Third, lean-MAFLD was associated with a higher CVD risk than OW-MAFLD. There have been controversies regarding the different prognoses between obese and non-obese patients with NAFLD. A meta-analysis reported that obesity in NAFLD could predict worse long-term outcomes [17], while others reported that non-obese NAFLD increased CVD risk and CVD-related mortality [18, 19]. Another study showed similar event-free survival between obese and lean patients with NAFLD [20]. In our study, the high CVD risk of lean-MAFLD compared to OW-MAFLD might be due to the influence of fibrotic burden. Several previous studies have revealed that advanced liver fibrosis in patients with FLD is not only a major risk factor for liver cancer or liver-specific mortality but is also closely related to CVD risk [21, 22]. Indeed, in this study, lean-MAFLD with advanced fibrosis had an increased CVD risk compared to OW-MAFLD without advanced fibrosis, whereas lean MAFLD without advanced fibrosis did not. This result

supports the hypothesis that the extent of liver fibrosis may play a role in CVD risk. Although our data could not provide information regarding muscle mass, the prevalence of sarcopenia might have also influenced the CVD risk difference between lean and OW-NAFLD. A recent study proved the independent associations among NAFLD, fibrosis, sarcopenia, and CVD [21]. “Metabolically unhealthy” lean patients may have less lean body mass, especially muscle mass, which may have an impact on poor CVD outcome [21, 23]. In addition, it is known that, unlike visceral fat, subcutaneous fat plays a role in protecting organs against lipotoxicity, and leg fat is associated with a low CVD risk [24]. Therefore, obese patients with a large muscle mass and little visceral fat tissue may have a good prognosis.

Fourth, in our study, the risk for liver cancer and all-cause death varied across MAFLD subtypes similarly as for CVD events. DM is known to be a major risk factor for liver cancer development [25]. In addition, a recent study revealed that the risk of advanced liver fibrosis increased in the order of OW, lean, and DM-MAFLD subtypes [26]. Therefore, in our study, differences in fibrotic burden between each MAFLD subtype may affect the differences in liver cancer risk. In this study, all-cause mortality was lowest in OW-MAFLD and similarly higher in lean- and DM-MAFLD in most adjusted models. This finding is supported by a recent study based on the National Health and Nutrition Examination Survey III data [27], which showed that both lean- and DM-MAFLD might have higher risk of all-cause death than OW-MAFLD. This may be because OW-MAFLD subtype includes “metabolically healthy” patients except for high BMI [18].

Our study has several strengths. To the best of our knowledge, this is the first study to evaluate the long-term risk of CVD events, liver cancer development, and all-cause death according to the MAFLD subtypes. Based on the NHIS database, the single provider of universal healthcare coverage in Korea, with a large sample size of approximately 8 million subjects, and a median follow-up period of 10 years, we could compare the CVD risk among MAFLD subtypes with adequate statistical power and minimized risk of selection bias, which was further confirmed after adjustment for various confounders. Additionally, the large sample size allowed us to investigate the influence of fibrotic burden on CVD risk in each MAFLD subtype. Despite the strengths of our study, we are also aware of its limitations. First, in this study, FLD was defined by FLI without histology or imaging techniques. However, recent guidelines suggest that non-invasive markers such as FLI are acceptable alternatives for defining FLD in large epidemiologic studies [2, 7]. Second, only the BARD score was used to evaluate advanced liver fibrosis due to the limited availability of variables in the Korean NHIS database required to calculate other noninvasive surrogates such as fibrosis-4 index or NAFLD fibrosis score [4, 28]. Third, our study included only middle-aged Koreans; caution should be exercised when applying the results of this study to other populations or age groups. Finally, since there was no insulin and high-sensitivity C-reactive protein values in this database, MA were defined only with the remaining five factors; however, sensitivity analysis showed similar trends of CVD risk according to MAFLD subgroups.

In conclusion, long-term CVD outcomes differed across the MAFLD subtypes. Further studies are warranted to investigate whether preventive or therapeutic interventions should be optimized according to the MAFLD subtypes.

Declarations

Funding

This study was supported by the Technology Innovation Program (20013712) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interests

None to declare

Author contributions

All authors conceived and designed the study. Hokyou Lee conducted statistical analyses, and all authors interpreted the findings. Hokyou Lee and Tae Seop Lim drafted the manuscript. Seung Up Kim and Hyeon Chang Kim critically reviewed the manuscript for key intellectual content. All authors approved the final manuscript. Seung Up Kim and Hyeon Chang Kim are the guarantors, and as such, had full access to the data and take responsibility for its integrity and accuracy.

Ethics approval

The current study protocol was in accordance with the principles of the 1975 Declaration of Helsinki, and the study was approved by the Institutional Review Board of Yonsei University Health System, Seoul, Korea (#Y-2019-0081).

Consent to participate

Informed consent was waived because this was a retrospective study of de-identified, routinely collected data.

Consent for publication

Informed consent was waived because this was a retrospective study of de-identified, routinely collected data.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84. https://doi.org/10.1002/hep.28431.
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(1):202–9. https://doi.org/10.1016/j.jhep.2020.03.039.

3. Eslam M, Sanyal AJ, George J. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020;158(7):1999–2014.e1991. https://doi.org/10.1053/j.gastro.2019.11.312.
4. 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(10):2138–47.e2110. https://doi.org/10.1016/j.cgh.2020.12.022.
5. Tsutsumi T, Eslam M, Kawaguchi T, Yamamura S, Kawaguchi A, Nakano D, et al. MAFLD better predicts the progression of atherosclerotic cardiovascular risk than NAFLD: Generalized estimating equation approach. Hepatol Res. 2021;51(11):1115–28. https://doi.org/10.1111/hepr.13685.
6. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open. 2017;7(9):e016640. https://doi.org/10.1136/bmjopen-2017-016640.
7. EASL-EASD-EASO. Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402. https://doi.org/10.1016/j.jhep.2015.11.004.
8. Lee YH, Bang H, Park YM, Bae JC, Lee BW, Kang ES, et al. Non-laboratory-based self-assessment screening score for non-alcoholic fatty liver disease: development, validation and comparison with other scores. PLoS ONE. 2014;9(9):e107584. https://doi.org/10.1371/journal.pone.0107584.
9. Lee H, Yano Y, Cho SMJ, Park JH, Park S, Lloyd-Jones DM, et al. Cardiovascular Risk of Isolated Systolic or Diastolic Hypertension in Young Adults. Circulation. 2020;141(22):1778–86. https://doi.org/10.1161/CIRCULATIONAHA.119.044838.
10. Seo HJ, Oh IH, Yoon SJ. A comparison of the cancer incidence rates between the national cancer registry and insurance claims data in Korea. Asian Pac J Cancer Prev. 2012;13(12):6163–8. https://doi.org/10.7314/apjcp.2012.13.12.6163.
11. Fan JG, Saibara T, Chitturi S, Kim BI, Sung JJ, Chutaputti A, et al. What are the risk factors and settings for non-alcoholic fatty liver disease in Asia-Pacific? J Gastroenterol Hepatol. 2007;22(6):794–800. https://doi.org/10.1111/j.1440-1746.2007.04952.x.
12. Bhatnagar A. Environmental Determinants of Cardiovascular Disease. Circ Res. 2017;121(2):162–80. https://doi.org/10.1161/CIRCRESAHA.117.306458.
13. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol. 2016;65(3):589–600. https://doi.org/10.1016/j.jhep.2016.05.013.
14. Fox CS, Coady S, Sorlie PD, D'Agostino RB, Sr., Pencina MJ, Vasan RS, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation. 2007;115(12):1544–50. https://doi.org/10.1161/circulationaha.106.658948.
15. King RJ, Grant PJ. Diabetes and cardiovascular disease: pathophysiology of a life-threatening epidemic. Herz. 2016;41(3):184–92. https://doi.org/10.1007/s00059-016-4414-8.
16. 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(11):1022–32. https://doi.org/10.1007/s00535-021-01828-6.

17. Lu FB, Hu ED, Xu LM, Chen L, Wu JL, Li H, et al. The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2018;12(5):491–502. https://doi.org/10.1080/17474124.2018.1460202.
18. Golabi P, Paik J, Fukui N, Locklear CT, de Avilla L, Younossi ZM. Patients With Lean Nonalcoholic Fatty Liver Disease Are Metabolically Abnormal and Have a Higher Risk for Mortality. Clin Diabetes. 2019;37(1):65–72. https://doi.org/10.2337/cd18-0026.
19. Yoshitaka H, Hamaguchi M, Kojima T, Fukuda T, Ohbora A, Fukui M. Nonoverweight nonalcoholic fatty liver disease and incident cardiovascular disease: A post hoc analysis of a cohort study. Med (Baltim). 2017;96(18):e6712. https://doi.org/10.1097/md.0000000000006712.
20. Leung JC, Loong TC, Wei JL, Wong GL, Chan AW, Choi PC, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology. 2017;65(1):54–64. https://doi.org/10.1002/hep.28697.
21. Han E, Lee YH, Kim YD, Kim BK, Park JY, Kim DY, et al. Nonalcoholic Fatty Liver Disease and Sarcopenia Are Independently Associated With Cardiovascular Risk. Am J Gastroenterol. 2020;115(4):584–95. https://doi.org/10.14309/ajg.0000000000000572.
22. Tamaki N, Kurosaki M, Takahashi Y, Itakura Y, Inada K, Kirino S, et al. Liver fibrosis and fatty liver as independent risk factors for cardiovascular disease. J Gastroenterol Hepatol. 2021;36(10):2960–6. https://doi.org/10.1111/jgh.15589.
23. Kim Y, Han E, Lee JS, Lee HW, Kim BK, Kim MK, et al. Cardiovascular Risk Is Elevated in Lean Subjects with Nonalcoholic Fatty Liver Disease. Gut Liver. 2021. https://doi.org/10.5009/gnl210084.
24. Han E, Lee YH, Lee BW, Kang ES, Lee IK, Cha BS. Anatomic fat depots and cardiovascular risk: a focus on the leg fat using nationwide surveys (KNHANES 2008–2011). Cardiovasc Diabetol. 2017;16(1):54. https://doi.org/10.1186/s12933-017-0536-4.
25. Polesel J, Zucchetto A, Montella M, Dal Maso L, Crispo A, La Vecchia C, et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. Ann Oncol. 2009;20(2):353–7.
26. Sohn W, Kwon HJ, Chang Y, Ryu S, Cho YK. Liver Fibrosis in Asians With Metabolic Dysfunction-Associated Fatty Liver Disease. Clin Gastroenterol Hepatol. 2021. https://doi.org/10.1016/j.cgh.2021.06.042.
27. Chen X, Chen S, Pang J, Tang Y, Ling W. Are the different MAFLD subtypes based on the inclusion criteria correlated with all-cause mortality? J Hepatol. 2021;75(4):987–9. https://doi.org/10.1016/j.jhep.2021.06.013.
28. Lee JI, Lee HW, Lee KS, Lee HS, Park JY. Effects of Statin Use on the Development and Progression of Nonalcoholic Fatty Liver Disease: A Nationwide Nested Case-Control Study. Am J Gastroenterol. 2021;116(1):116–24. https://doi.org/10.14309/ajg.0000000000000845.

Figures

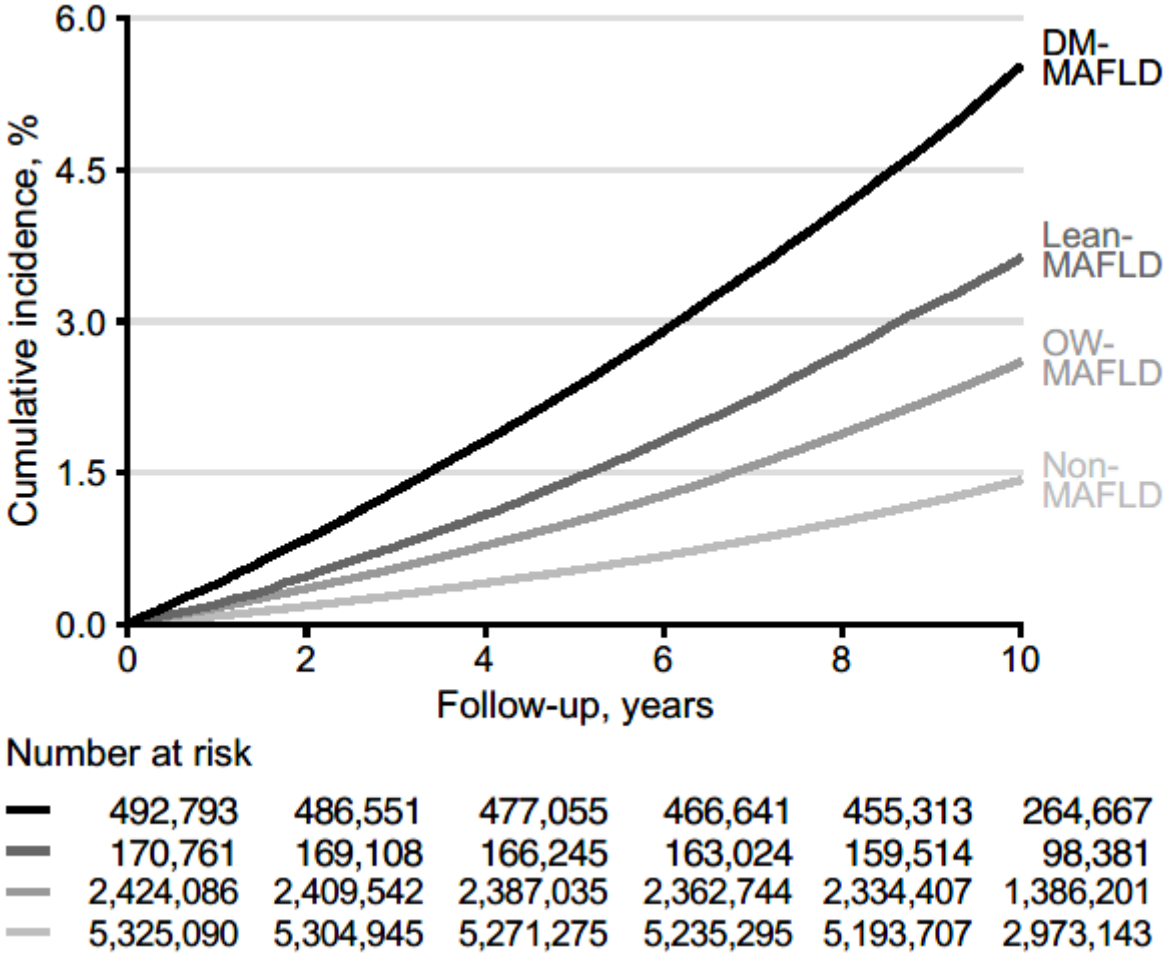

Figure 1

Cumulative incidence of cardiovascular events according to presence and subtypes of MAFLD

Cumulative incidence estimated by Kaplan-Meier methods.

CVD, cardiovascular disease; DM, diabetes mellitus; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese.

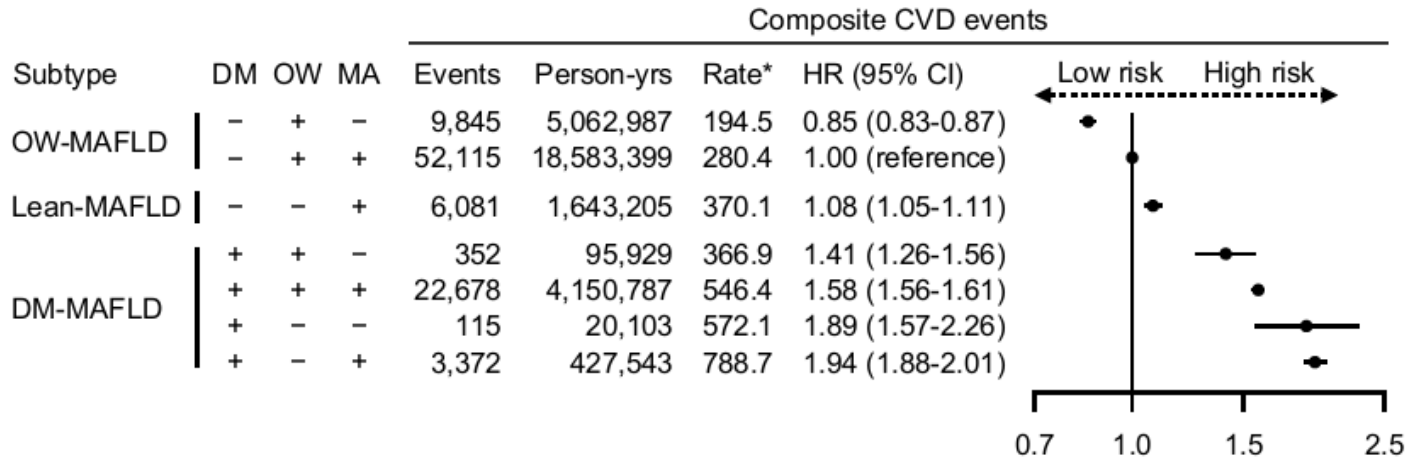

Figure 2

Cardiovascular disease risk according to MAFLD diagnostic components

*Rate per 100,000 person-years. HRs adjusted for age, sex, household income quartile, residential area, Charlson Comorbidity Index, aspirin use, non-steroidal anti-inflammatory drug use, concomitant liver disease, alcohol consumption, tobacco use, exercise frequency, hypertension, and dyslipidemia. MA+ denotes ≥2 MA in non-DM participants or ≥1 MA other than high fasting glucose in DM participants.

CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; MA, metabolic abnormality; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese.

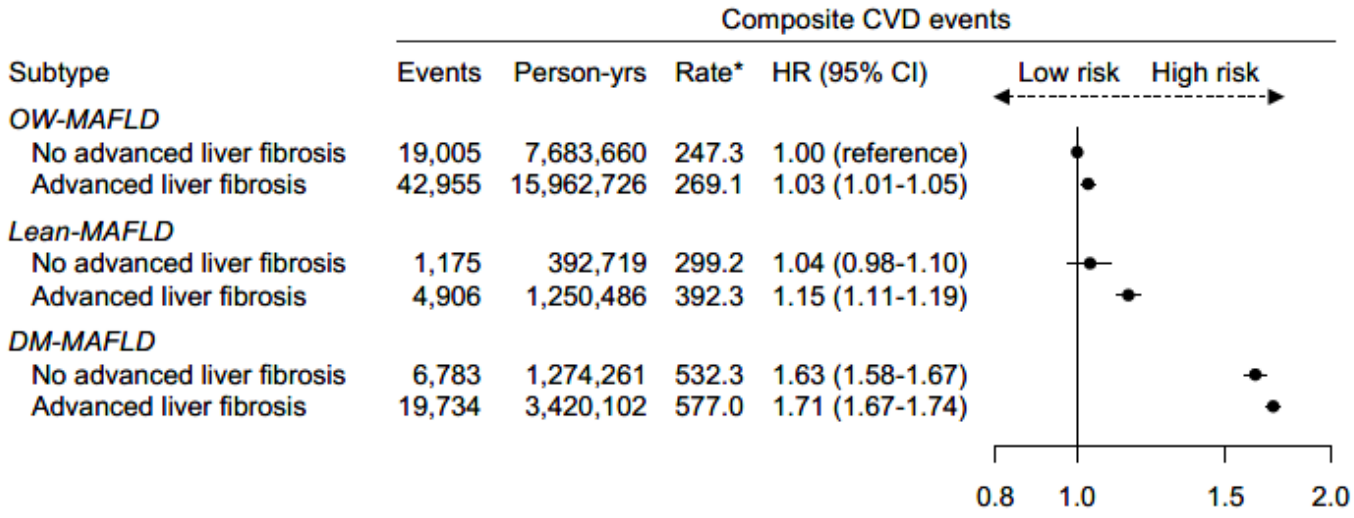

Figure 3

Cardiovascular disease risk according to MAFLD subtypes and advanced liver fibrosis

*Rate per 100,000 person-years. HRs adjusted for age, sex, household income quartile, residential area, Charlson Comorbidity Index, aspirin use, non-steroidal anti-inflammatory drug use, concomitant liver disease, alcohol consumption, tobacco use, exercise frequency, hypertension, and dyslipidemia.

CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; OW, overweight/obese.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfiles.docx