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ORIGINAL RESEARCH

Association of Metabolic Dysfunction-Associated Fatty Liver Disease With Risk of HF and AF

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ABSTRACT

BACKGROUND Metabolic dysfunction-associated fatty liver disease (MAFLD) is a novel concept of hepatic disease. Although the prevalences of heart failure (HF) and atrial fibrillation (AF) are increasing worldwide, limited data have assessed the extent to which MAFLD is associated with incident HF and AF.

OBJECTIVES The authors sought to examine the association of MAFLD with incident HF and AF.

METHODS Analyses were conducted using a nationwide epidemiologic database including 3,279,918 individuals (median age 45 years; 57.6% men). Metabolic dysfunction was defined as 1 or more of the following: overweight (body mass index ≥23 kg/m^2), metabolic syndrome, or diabetes mellitus. FLD was defined as fatty liver index of >30. MAFLD was defined as the coexistence of metabolic dysfunction and FLD. We categorized study participants into 4 groups: non-FLD/nonmetabolic dysfunction (n = 1,709,116), metabolic dysfunction (n = 584,483), FLD (n = 89,497), and MAFLD (n = 896,822). The primary outcomes were HF and AF.

RESULTS Over a mean follow-up period of 1,160 ± 905 days, 62,746 incident HF events and 15,408 incident AF events were recorded. Compared with the non-FLD/non-metabolic dysfunction group, HRs for HF and AF, respectively, were 1.20 (95% CI: 1.18-1.23) and 1.13 (95% CI: 1.08-1.19) for metabolic dysfunction, 1.24 (95% CI: 1.19-1.30) and 1.13 (95% CI: 1.04-1.23) for FLD, and 1.73 (95% CI: 1.69-1.76) and 1.51 (95% CI: 1.46-1.57) for MAFLD. MAFLD was also associated with a higher risk of developing myocardial infarction, angina pectoris, and stroke. A risk of developing cardiovascular events differed between MAFLD subtypes (Wald test $P < 0.001$).

CONCLUSIONS MAFLD was associated with a greater risk of developing HF and AF, suggesting the clinical importance of this novel hepatic disease concept. (JACC: Asia 2023;3:908-921) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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A novel concept of metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged, and its clinical significance has attracted interest. The prevalence of fatty liver disease (FLD) is increasing and is a growing public health issue. In addition to the hepatic and oncologic consequences, cardiovascular disease (CVD) is a major concern in people with FLD. The former definition of nonalcoholic fatty liver disease (NAFLD) lacked a unified set of "positive" criteria accounting for key metabolic features, which resulted in heterogeneous disease characterization. The novel concept of MAFLD, which replaces the term "NAFLD," was suggested by a group of experts worldwide in 2020.[1] MAFLD has its own inclusion criteria based on a variety of metabolic abnormalities regardless of alcohol consumption. This transition enables the identification of metabolically complicated fatty liver superimposed on chronic liver disease or alcoholism while distinguishing fatty liver associated with metabolic dysfunction. Previous studies have reported a relationship between MAFLD and a higher incidence of atherosclerotic CVD, such as myocardial infarction (MI), angina pectoris (AP), and stroke.[2,3] However, the association between MAFLD and the subsequent risk of heart failure (HF) and atrial fibrillation (AF) has not yet been established. The number of patients with HF and AF is increasing in developed countries,[4-6] and the clinical and public health importance of both are increasing among various CVDs. Thus, robust epidemiologic data on the relationship between MAFLD and the incidence of HF and AF are required. Furthermore, in most previous studies, CVD risk comparisons were made between MAFLD and non-MAFLD. However, because FLD and metabolic dysfunction are each associated with an increased risk of developing CVD, it is difficult to clarify the clinical importance of the concept of MAFLD by comparing MAFLD and non-MAFLD simply. To this end, it is necessary to validate whether there is an additional increased risk in individuals with MAFLD (coexisting FLD and metabolic dysfunction) compared to those with FLD or metabolic dysfunction alone. Additionally, MAFLD is classified into subtypes according to concomitant metabolic abnormalities; however, the association of MAFLD subtypes with future risks of HF and AF is unclear. Here, we sought to clarify the relationship between MAFLD and incident HF and AF based on each MAFLD subtype using a nationwide population-based dataset.

METHODS

Anonymized data are publicly available for purchase from JMDC Inc.

STUDY POPULATION. We conducted this retrospective observational study using the JMDC Claims Database, a large-scale administrative claims dataset, collected between 2005 and 2021.[7-9] The JMDC Claims Database consists of workplace employees' annual health check-up data, including demographics, medical history, medications, and insurance claims records with International Classification of Diseases-10th Revision (ICD-10) coding as well as death information collected from more than 60 insurers. Diagnosis of CVD includes not only inpatient but also outpatient settings.

We extracted 4,205,391 records with available data on the assessment of MAFLD and excluded the following individuals: aged <20 years (n = 4,940); with a history of CVD, defined as MI, AP, stroke, HF, and AF (n = 194,416); with a history of liver disease defined as liver cancer (ICD-10 code: C22), fibrosis and cirrhosis of liver (ICD-10 code: K74), hepatitis B (ICD-10 code: B16), hepatitis C (ICD-10 code: B182), autoimmune hepatitis (ICD-10 code: K754), and cholangitis (ICD-10 code: K830) (n = 27,117); with a history of renal replacement therapy, defined as dialysis and renal transplantation (n = 977); and with missing data on cigarette smoking (n = 184,085), alcohol consumption (n = 329,418), and physical activity (n = 184,520). Finally, 3,279,918 participants were included in the analysis (Supplemental Figure 1).

ETHICS. This study was conducted in accordance with the ethical guidelines of our institution (approval by the Ethical Committee of the University of Tokyo: 2018-10862) and the principles of the Declaration of Helsinki. Informed consent was not necessary because all data in the JMDC Claims Database were anonymized and deidentified.

DEFINITION OF MAFLD. FLD was defined as a fatty liver index (FLI) of >30. We calculated the FLI using the following formula:

$$\mathrm{FLI} = 1\Big/\Big\{1+e^{-[0.953\times\ln(\text{triglycerides})+0.139\times(\text{body mass index})+0.718\times\ln(\gamma\text{–glutamyl transpeptidase})+0.053\times(\text{waist circumference})-15.745]}\Big\}\times 100$$

Metabolic dysfunction was defined any of the following conditions: diabetes mellitus (DM),

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AP = angina pectoris

CVD = cardiovascular disease

DM = diabetes mellitus

eGFR = estimated glomerular filtration rate

FLD = fatty liver disease

FLI = fatty liver index

HF = heart failure

ICD-10 = International Classification of Diseases-10th Revision

MAFLD = metabolic dysfunction-associated fatty liver disease

MI = myocardial infarction

NAFLD = nonalcoholic fatty liver disease

overweight (body mass index: ≥23 kg/m^2), or metabolic syndrome. The presence of DM was defined as fasting plasma glucose of ≥126 mg/dL or the use of glucose-lowering medications. We defined MAFLD as having both FLD and metabolic dysfunction. Metabolic syndrome is defined in Japan as follows: waist circumference of ≥85 cm for men and ≥90 cm for women and more than 1 of the following criteria: 1) dyslipidemia (triglycerides of ≥150 mg/dL, or high-density lipoprotein cholesterol of <40 mg/dL, or the use of lipid-lowering medications); 2) high blood pressure (systolic blood pressure of ≥130 mm Hg, or diastolic blood pressure of ≥85 mm Hg, or the use of blood pressure-lowering medications); and 3) high plasma glucose (fasting plasma glucose of ≥110 mg/dL or the use of glucose-lowering medications).[10,11] We collected information on smoking (current or noncurrent/never) and alcohol consumption (every day or not every day) from a self-report questionnaire during the health checkup. We defined physical inactivity as not performing 30 minutes of exercise ≥2 times a week or not walking for more than 1 hour per day.

OUTCOMES. This study was conducted between January 2005 and April 2021. The primary outcomes were HF (ICD-10: I500, I501, I509, and I110) and AF (ICD-10: I480, I481, I482, I483, I484, and I489). We set the secondary outcomes as MI (ICD-10: I210, I211, I212, I213, I214, and I219), AP (ICD-10: I200, I201, I208, and I209), and stroke (ICD-10: I630, I631, I632, I633, I634, I635, I636, I638, I639, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I613, I614, I615, I616, I619, and I629). We analyzed each outcome separately; therefore, if one participant experienced ≥2 outcomes, all these outcomes were recorded. We set composite CVD incidents using HF, AF, MI, AP, and stroke. If a participant experienced more than 1 event, the first event was recorded as the outcome.

STATISTICAL ANALYSIS. The median (IQR) for skewed variables and number (percentage), if appropriate, were used to report descriptive statistics. To calculate the *P* value, the Kruskal-Wallis test or chi-square test was used for continuous or categorical variables. The Kaplan-Meier method and log-rank test were adopted for the cumulative incidence of each CVD event and to compare the cumulative incidence of CVD events among the 4 groups (non-FLD/nonmetabolic dysfunction, FLD, metabolic dysfunction, and MAFLD). Cox regression analyses were conducted to clarify the relationships among the 4 groups (non-FLD/nonmetabolic dysfunction, FLD, metabolic dysfunction, and MAFLD) and the subsequent risk of CVD. HRs were obtained in both unadjusted and adjusted models for potential confounders, including age, sex, low-density lipoprotein cholesterol level, cigarette smoking, alcohol consumption, and physical inactivity. Covariates were selected from previous studies that showed an association with CVD events.[12,13] We performed 6 sensitivity analyses. First, we conducted subtype analyses stratified by age (≥50 and <50 years), sex, alcohol consumption status, and systolic blood pressure (≥118 [median] and <118 mm Hg). Second, we conducted a competing risk analysis to consider the impact of death as a competing risk factor for CVD. Third, we set an induction period of 2 years to exclude individuals with latent CVD. Fourth, multiple imputations for missing covariate data were performed. A chained equation method with 20 iterations was used. We adopted Rubin's rule to calculate HRs and standard errors. Fifth, we added estimated glomerular filtration rate (eGFR) as another covariate for the adjusted model of Cox regression analyses. Sixth, we defined metabolic syndrome as having any 3 or more following criteria using the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria: 1) waist circumference of ≥102 cm for men and ≥88 cm for women; 2) dyslipidemia (triglycerides of ≥150 mg/dL, or high-density lipoprotein cholesterol of <40 mg/dL for men or <50 mg/dL for women, or the use of lipid-lowering medications); 3) high blood pressure (systolic blood pressure of ≥130 mm Hg, or diastolic blood pressure of ≥85 mm Hg, or the use of blood pressure-lowering medications); and 4) high plasma glucose (fasting plasma glucose of ≥100 mg/dL or the use of glucose-lowering medications).

Participants with MAFLD were classified into 7 subtypes based on the combination of comorbid metabolic dysfunction (overweight, metabolic syndrome, and DM), and we compared the risk of CVD events among the 7 groups using Cox regression analyses. We set participants having overweight alone as the reference. We conducted the Wald test to compare the HRs between individual MAFLD subgroups. Statistical significance was set at *P* value of <0.05. Statistical analyses were conducted using STATA version 17 (StataCorp LLC).

RESULTS

CLINICAL CHARACTERISTICS. The baseline clinical characteristics of the patients are summarized in Table 1. The median age was 45 years (IQR: 38-53 years), and 1,888,132 (57.6%) were men. Study participants were divided into 4 groups: non-FLD/nonmetabolic dysfunction (n = 1,709,116), metabolic

TABLE 1 Clinical Characteristics

	Non-FLD/Nonmetabolic Dysfunction (n = 1,709,116)	Metabolic Dysfunction (n = 584,483)	FLD (n = 89,497)	MAFLD (n = 896,822)	*P* Value
Age, y	43 (36-51)	46 (39-54)	49 (42-55)	47 (41-54)	<0.001
Men	743,798 (43.5)	341,289 (58.4)	78,111 (87.3)	724,934 (80.8)	<0.001
Body mass index, kg/m^2	20.4 (19.1-21.6)	24.1 (23.4-25)	22.1 (21.3-22.6)	26.6 (24.9-28.9)	<0.001
Systolic blood pressure, mm Hg	112 (103-122)	119 (110-129)	123 (113-132)	126 (118-136)	<0.001
Diastolic blood pressure, mm Hg	69 (62-76)	73 (66-81)	78 (71-85)	80 (73-87)	<0.001
Fasting plasma glucose, mg/dL	89 (84-95)	92 (87-99)	95 (89-101)	97 (90-106)	<0.001
Diabetes mellitus	0 (0.0)	43,585 (7.5)	0 (0.0)	99,104 (11.1)	<0.001
Low-density lipoprotein cholesterol, mg/dL	111 (93-132)	121 (102-141)	125 (102-148)	133 (113-154)	<0.001
High-density lipoprotein cholesterol, mg/dL	69 (58-80)	61 (52-71)	57 (48-68)	51 (44-60)	<0.001
Triglycerides, mg/dL	65 (49-88)	73 (56-96)	173 (128-244)	139 (102-193)	<0.001
Cigarette smoking	362,403 (21.2)	133,430 (22.8)	39,124 (43.7)	301,073 (33.6)	<0.001
Alcohol consumption	341,277 (20.0)	112,364 (19.2)	49,531 (55.3)	255,845 (28.5)	<0.001
Physically inactive	875,927 (51.3)	294,365 (50.4)	52,760 (59.0)	519,212 (57.9)	<0.001

Values are median (IQR) or n (%). *P* values were calculated using a chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.
FLD = fatty liver disease; MAFLD = metabolic dysfunction-associated fatty liver disease.

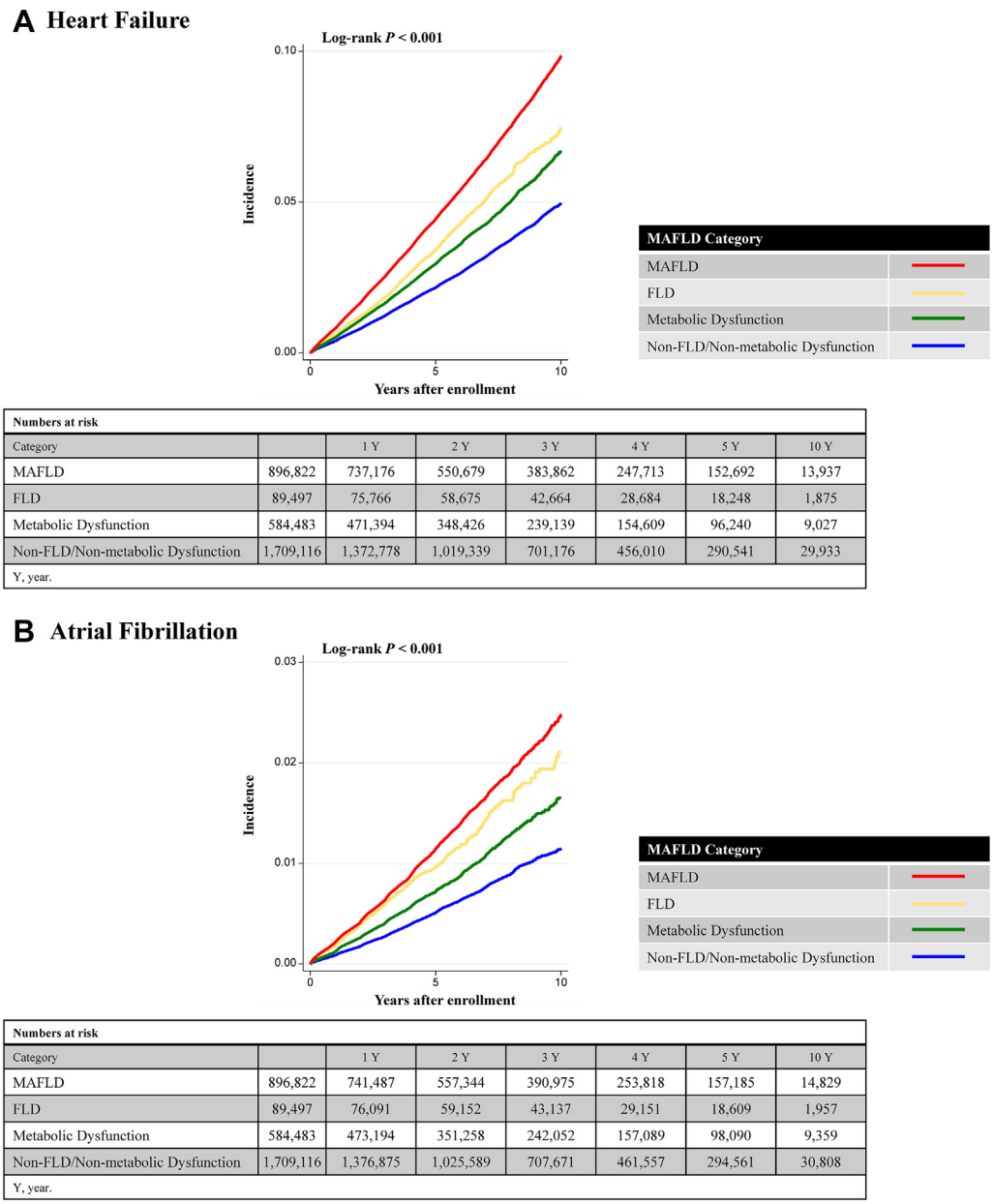
dysfunction (n = 584,483), FLD (n = 89,497), and MAFLD (n = 896,822). Compared with individuals with non-FLD/nonmetabolic dysfunction, those with MAFLD were older and more likely to be men. As expected, cardiovascular risk status was generally better in people without MAFLD. The clinical characteristics of the patients by sex in the age quintile are shown in Supplemental Table 1.

MAFLD AND THE RISK OF HF AND AF. During a mean follow-up period of 1,160 ± 905 days, 62,746 HF and 15,408 AF events occurred. The Kaplan-Meier curves showed that the cumulative incidence of HF and AF events was lowest in the non-FLD/nonmetabolic dysfunction group, followed by the metabolic dysfunction, FLD, and MAFLD groups (Figure 1). The event rates for HF events were lowest in the non-FLD/non-metabolic dysfunction group (44.5 [95% CI: 43.9-45.1] per 10,000 person-years), followed by the metabolic dysfunction group (60.1 [95% CI: 59.0-61.2] per 10,000 person-years), the FLD group (69.9 [95% CI: 67.0-72.9] per 10,000 person-years), and the MAFLD group (91.6 [95% CI: 90.5-92.7] per 10,000 person-years). The event rates for AF events were also lowest in the non-FLD/nonmetabolic dysfunction group (10.2 [95% CI: 9.9-10.5] per 10,000 person-years), followed by the metabolic dysfunction group (14.7 [95% CI: 14.1-15.2] per 10,000 person-years), FLD group (20.2 [95% CI: 18.7-21.8] per 10,000 person-years), and MAFLD group (23.0 [95% CI: 22.5-23.6] per 10,000 person-years). After multivariable adjustment, the HRs for HF were 1.20 (95% CI: 1.18-1.23) for the metabolic dysfunction group, 1.24 (95% CI: 1.19-1.30) for the FLD group, and 1.73 (95% CI: 1.69-1.76) for the MAFLD group compared with the non-FLD/non-metabolic dysfunction group. After multivariable adjustment, the HRs for AF were 1.13 (95% CI: 1.08-1.19) for the metabolic dysfunction group, 1.13 (95% CI: 1.04-1.23) for the FLD group, and 1.51 (95% CI: 1.46-1.57) for the MAFLD group compared with the non-FLD/nonmetabolic dysfunction group (Figure 2).

MAFLD AND THE RISK OF MI, AP, AND STROKE. During the follow-up period, 6,909 MI; 59,317 AP; and 29,546 stroke events were recorded. The cumulative incidence of MI, AP, stroke, and composite CVD events was the highest in the MAFLD group, followed by the FLD, metabolic dysfunction, and non-FLD/nonmetabolic dysfunction groups (Figure 1). In adjusted models, the HRs for MI, AP, stroke, and composite CVD events, respectively, were 1.35 (95% CI: 1.25-1.45), 1.17 (95% CI: 1.14-1.20), 1.15 (95% CI: 1.11-1.18), and 1.17 (95% CI: 1.15-1.18) for the metabolic dysfunction group; 1.17 (95% CI: 1.02-1.35), 1.19 (95% CI: 1.14-1.25), 1.24 (95% CI: 1.17-1.32), and 1.21 (95% CI: 1.18-1.25) for the FLD group; and 1.95 (95% CI: 1.84-2.07), 1.54 (95% CI: 1.51-1.57), 1.42 (95% CI: 1.38-1.46), and 1.57 (95% CI: 1.55-1.59) for the MAFLD group compared with the non-FLD/non-metabolic dysfunction group (Figure 2).

SENSITIVITY ANALYSES. First, we found a consistent association between MAFLD and risks of developing HF and AF across subgroups stratified by age, sex, alcohol consumption status, and systolic blood pressure (Supplemental Figure 2). However, the relationships between MAFLD and the incidence of HF and AF were more pronounced in individuals aged <50 years. Second, the association of MAFLD (including the metabolic dysfunction and FLD group)

FIGURE 1 Kaplan-Meier Curves



Numbers at risk

Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
MAFLD	896,822	737,176	550,679	383,862	247,713	152,692	13,937
FLD	89,497	75,766	58,675	42,664	28,684	18,248	1,875
Metabolic Dysfunction	584,483	471,394	348,426	239,139	154,609	96,240	9,027
Non-FLD/Non-metabolic Dysfunction	1,709,116	1,372,778	1,019,339	701,176	456,010	290,541	29,933

Y, year.

Numbers at risk

Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
MAFLD	896,822	741,487	557,344	390,975	253,818	157,185	14,829
FLD	89,497	76,091	59,152	43,137	29,151	18,609	1,957
Metabolic Dysfunction	584,483	473,194	351,258	242,052	157,089	98,090	9,359
Non-FLD/Non-metabolic Dysfunction	1,709,116	1,376,875	1,025,589	707,671	461,557	294,561	30,808

Y, year.

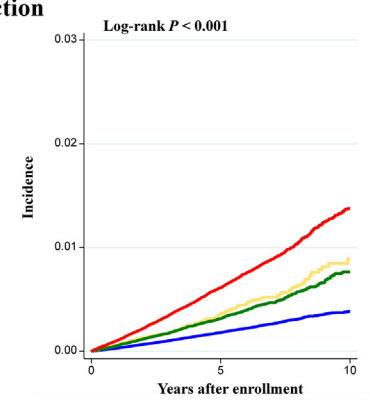
The cumulative probability of (A) heart failure, (B) atrial fibrillation, (C) myocardial infarction, (D) angina pectoris, (E) stroke, and (F) composite endpoint by MAFLD classification were calculated using the Kaplan-Meier method. The log-rank test was used to calculate *P* values, and the values were all <0.001. Participants were categorized as non-FLD/nonmetabolic dysfunction, metabolic dysfunction, FLD, and MAFLD (having both FLD and metabolic dysfunction). FLD = fatty liver disease; MAFLD = metabolic dysfunction-associated fatty liver disease.

Continued on the next page

with incident HF and AF was unchanged in a competing risk model (Supplemental Figure 3). Third, we set an induction period of 2 years and analyzed 1,974,531 individuals in this case scenario (Supplemental Figure 4). Even in this analysis, the relationship between MAFLD and risks of developing HF and AF remained unchanged. Fourth, multiple imputations for missing covariate data were

FIGURE 1 Continued

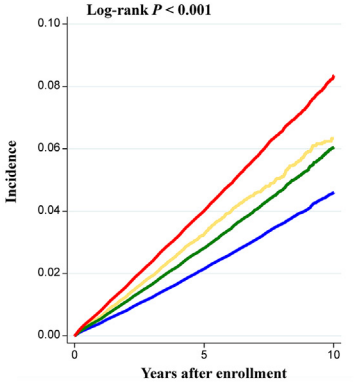
C Myocardial Infarction



Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
MAFLD	896,822	742,325	558,495	392,131	254,781	157,817	14,906
FLD	89,497	76,176	59,296	43,317	29,292	18,698	1,972
Metabolic Dysfunction	584,483	473,534	351,765	242,584	157,559	98,426	9,422
Non-FLD/Non-metabolic Dysfunction	1,709,116	1,377,659	1,026,699	708,855	462,653	295,341	30,952

Y, year.

D Angina Pectoris



Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
MAFLD	896,822	737,137	550,613	383,678	247,426	152,158	13,823
FLD	89,497	75,763	58,616	42,550	28,582	18,157	1,867
Metabolic Dysfunction	584,483	471,230	348,185	238,761	154,220	95,900	8,882
Non-FLD/Non-metabolic Dysfunction	1,709,116	1,372,402	1,018,758	700,379	455,116	289,467	29,699

Y, year.

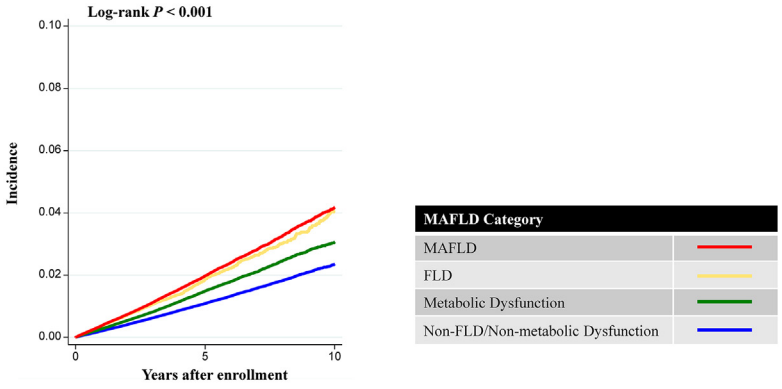
Continued on the next page

conducted, and the results were similar (Supplemental Figure 5). Fifth, we extracted data on 1,654,546 individuals with available data on eGFR. We conducted a multivariable Cox proportional analysis by adding eGFR as another variable. The MAFLD group had a higher risk of developing HF and AF compared with the non-FLD/nonmetabolic dysfunction group even after adjustment for eGFR (Supplemental Figure 6). Sixth, we redefined metabolic syndrome using NCEP-ATP III criteria. The association between MAFLD and risks of developing HF and AF were unchanged from the primary analysis in this case scenario (Supplemental Figure 7).

MAFLD SUBTYPES AND THE RISK OF CVD EVENTS. The incidence of subsequent CVD events was lowest in the subtype with overweight alone. In model 3, the risk of developing CVD events was highest in the subtype with overweight, metabolic syndrome, and

FIGURE 1 Continued

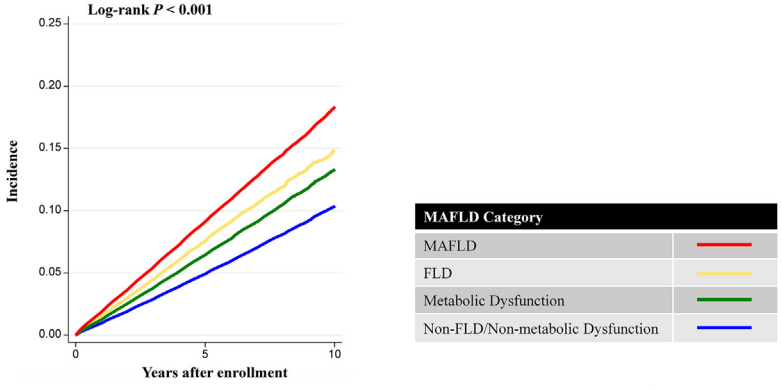
E Stroke



Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
MAFLD	896,822	740,389	555,617	389,082	252,096	155,773	14,565
FLD	89,497	75,964	58,969	42,975	28,987	18,448	1,917
Metabolic Dysfunction	584,483	472,530	350,243	240,964	156,101	97,284	9,229
Non-FLD/Non-metabolic Dysfunction	1,709,116	1,375,335	1,023,167	705,043	459,229	292,718	30,440

Y, year.

F Composite CVD Outcome



Numbers at risk							
Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
MAFLD	896,822	729,360	539,416	372,136	237,751	145,077	12,624
FLD	89,497	75,116	57,631	41,534	27,677	17,456	1,732
Metabolic Dysfunction	584,483	467,887	343,228	233,703	149,887	92,665	8,374
Non-FLD/Non-metabolic Dysfunction	1,709,116	1,364,869	1,007,635	688,957	445,280	282,208	28,332

Y, year.

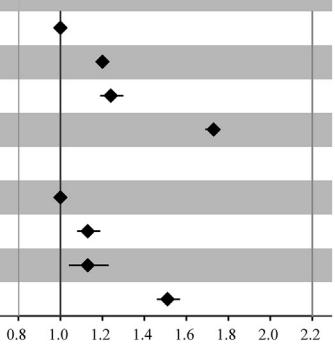
DM. The Wald tests showed that the risk of developing CVD events significantly differed among the 7 MAFLD subtypes (Wald test, all $P < 0.001$) (Figure 3).

DISCUSSION

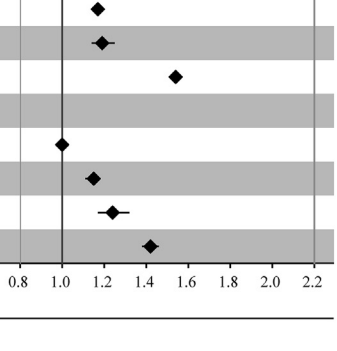
This analysis, using a nationwide population-based database, including more than 3.2 million people without a history of CVD and liver disease, demonstrated that the subsequent risk of developing HF, AF, and other CVD events increased in individuals with FLD or metabolic dysfunction and further increased in those with MAFLD (Central Illustration). A subsequent risk of the development of HF, AF, and other cardiovascular events differed between MAFLD subtypes. Our primary findings were consistent across various sensitivity analyses.

FIGURE 2 **HRs for Cardiovascular Disease Events**

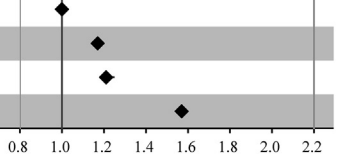
	No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3
Heart Failure						
Non-FLD/Non-metabolic Dysfunction	1,709,116	23,668	44.5 (43.9-45.1)	1 [Reference]	1 [Reference]	1 [Reference]
Metabolic Dysfunction	584,483	10,852	60.1 (59.0-61.2)	1.35 (1.32-1.38)	1.20 (1.17-1.23)	1.20 (1.18-1.23)
FLD	89,497	2,163	69.9 (67.0-72.9)	1.56 (1.49-1.63)	1.24 (1.19-1.30)	1.24 (1.19-1.30)
MAFLD	896,822	26,063	91.6 (90.5-92.7)	2.06 (2.03-2.10)	1.72 (1.69-1.76)	1.73 (1.69-1.76)
Atrial Fibrillation						
Non-FLD/Non-metabolic Dysfunction	1,709,116	5,454	10.2 (9.9-10.5)	1 [Reference]	1 [Reference]	1 [Reference]
Metabolic Dysfunction	584,483	2,673	14.7 (14.1-15.2)	1.44 (1.38-1.51)	1.10 (1.05-1.15)	1.13 (1.08-1.19)
FLD	89,497	631	20.2 (18.7-21.8)	1.97 (1.81-2.14)	1.14 (1.05-1.24)	1.13 (1.04-1.23)
MAFLD	896,822	6,650	23.0 (22.5-23.6)	2.26 (2.18-2.35)	1.43 (1.38-1.49)	1.51 (1.46-1.57)



	No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3
Myocardial Infarction						
Non-FLD/Non-metabolic Dysfunction	1,709,116	1,941	3.6 (3.5-3.8)	1 [Reference]	1 [Reference]	1 [Reference]
Metabolic Dysfunction	584,483	1,184	6.5 (6.1-6.9)	1.79 (1.67-1.93)	1.42 (1.32-1.52)	1.35 (1.25-1.45)
FLD	89,497	226	7.2 (6.3-8.2)	1.98 (1.72-2.27)	1.20 (1.04-1.37)	1.17 (1.02-1.35)
MAFLD	896,822	3,558	12.3 (11.9-12.7)	3.40 (3.22-3.59)	2.23 (2.11-2.36)	1.95 (1.84-2.07)
Angina Pectoris						
Non-FLD/Non-metabolic Dysfunction	1,709,116	23,210	43.7 (43.1-44.3)	1 [Reference]	1 [Reference]	1 [Reference]
Metabolic Dysfunction	584,483	10,452	58.0 (56.9-59.1)	1.33 (1.30-1.36)	1.18 (1.16-1.21)	1.17 (1.14-1.20)
FLD	89,497	2,050	66.4 (63.6-69.3)	1.52 (1.45-1.59)	1.21 (1.15-1.26)	1.19 (1.14-1.25)
MAFLD	896,822	23,605	83.0 (82.0-84.1)	1.90 (1.87-1.94)	1.59 (1.56-1.62)	1.54 (1.51-1.57)
Stroke						
Non-FLD/Non-metabolic Dysfunction	1,709,116	11,707	21.9 (21.5-22.3)	1 [Reference]	1 [Reference]	1 [Reference]
Metabolic Dysfunction	584,483	5,308	29.2 (28.4-30.0)	1.33 (1.29-1.38)	1.14 (1.11-1.18)	1.15 (1.11-1.18)
FLD	89,497	1,165	37.4 (35.3-39.6)	1.70 (1.60-1.80)	1.28 (1.21-1.37)	1.24 (1.17-1.32)
MAFLD	896,822	11,366	39.5 (38.8-40.2)	1.80 (1.76-1.85)	1.45 (1.41-1.49)	1.42 (1.38-1.46)



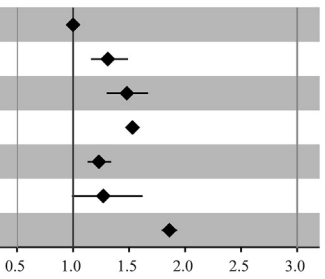
	No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3
Composite Endpoint						
Non-FLD/Non-metabolic Dysfunction	1,709,116	53,475	102.1 (101.2-102.9)	1 [Reference]	1 [Reference]	1 [Reference]
Metabolic Dysfunction	584,483	23,759	134.1 (132.4-135.8)	1.32 (1.30-1.34)	1.17 (1.15-1.19)	1.17 (1.15-1.18)
FLD	89,497	4,763	157.6 (153.2-162.1)	1.54 (1.50-1.59)	1.22 (1.19-1.26)	1.21 (1.18-1.25)
MAFLD	896,822	53,432	192.7 (191.0-194.3)	1.89 (1.87-1.91)	1.58 (1.56-1.60)	1.57 (1.55-1.59)



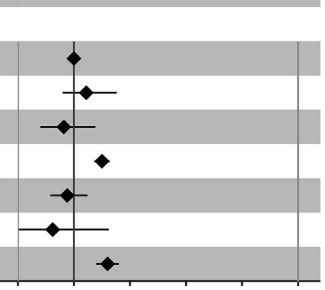
The incidence rate was per 10,000 person-years. Participants were categorized as non-FLD/nonmetabolic dysfunction, metabolic dysfunction, FLD, and MAFLD (having both FLD and metabolic dysfunction). Adjusted models include adjustments for age and sex for model 2 and age, sex, low-density lipoprotein cholesterol, cigarette smoking, alcohol consumption, and physical inactivity for model 3. A forest plot indicates the HRs and 95% CIs. The association between MAFLD classification and the risk of heart failure, atrial fibrillation, myocardial infarction, angina pectoris, stroke, and composite endpoint is shown. Abbreviations as in Figure 1.

FIGURE 3 Comparing Cardiovascular Disease Risk Among MAFLD Subtypes

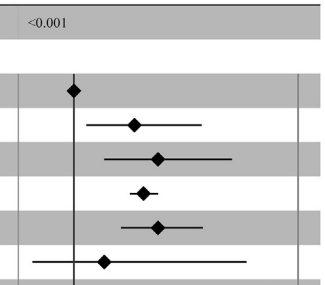
OW	MetS	DM	No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3	P value
Heart Failure									<0.001
Present	Absent	Absent	583,201	13,083	70.0 (68.9-71.3)	1 [Reference]	1 [Reference]	1 [Reference]	
Absent	Present	Absent	6,439	263	124.1 (110.0-140.1)	1.76 (1.56-1.99)	1.29 (1.14-1.46)	1.31 (1.16-1.49)	
Absent	Absent	Present	5,240	248	147.5 (130.2-167.0)	2.11 (1.86-2.39)	1.46 (1.29-1.65)	1.48 (1.30-1.67)	
Present	Present	Absent	208,078	8,090	123.4 (120.8-126.2)	1.77 (1.72-1.82)	1.53 (1.49-1.57)	1.53 (1.49-1.57)	
Present	Absent	Present	16,696	570	109.8 (101.2-119.2)	1.58 (1.45-1.71)	1.24 (1.14-1.35)	1.23 (1.13-1.34)	
Absent	Present	Present	1,586	64	137.2 (107.4-175.3)	1.98 (1.55-2.53)	1.26 (0.98-1.61)	1.27 (0.99-1.62)	
Present	Present	Present	75,582	3,745	164.6 (159.4-169.9)	2.37 (2.29-2.46)	1.86 (1.80-1.94)	1.86 (1.79-1.93)	



OW	MetS	DM	No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3	P value
Atrial Fibrillation									<0.001
Present	Absent	Absent	583,201	3,462	18.3 (17.7-18.9)	1 [Reference]	1 [Reference]	1 [Reference]	
Absent	Present	Absent	6,439	85	39.4 (31.8-48.7)	2.14 (1.73-2.66)	1.18 (0.95-1.47)	1.11 (0.90-1.38)	
Absent	Absent	Present	5,240	58	33.7 (26.0-43.6)	1.84 (1.42-2.39)	0.98 (0.76-1.27)	0.91 (0.70-1.19)	
Present	Present	Absent	208,078	2,048	30.6 (29.3-32.0)	1.67 (1.59-1.77)	1.26 (1.19-1.33)	1.25 (1.18-1.32)	
Present	Absent	Present	16,696	127	24.0 (20.2-28.5)	1.31 (1.10-1.57)	0.94 (0.79-1.12)	0.94 (0.79-1.12)	
Absent	Present	Present	1,586	17	35.7 (22.2-57.4)	1.96 (1.21-3.15)	0.86 (0.54-1.39)	0.81 (0.50-1.31)	
Present	Present	Present	75,582	853	36.5 (34.1-39.0)	2.00 (1.86-2.16)	1.31 (1.21-1.41)	1.30 (1.20-1.40)	



OW	MetS	DM	No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3	P value
Myocardial Infarction									<0.001
Present	Absent	Absent	583,201	1,591	8.4 (8.0-8.8)	1 [Reference]	1 [Reference]	1 [Reference]	
Absent	Present	Absent	6,439	37	17.0 (12.3-23.5)	2.02 (1.46-2.80)	1.35 (0.98-1.88)	1.54 (1.11-2.14)	
Absent	Absent	Present	5,240	40	23.2 (17.0-31.6)	2.76 (2.02-3.78)	1.84 (1.34-2.52)	1.75 (1.27-2.41)	
Present	Present	Absent	208,078	1,101	16.4 (15.5-17.4)	1.96 (1.81-2.11)	1.61 (1.49-1.74)	1.62 (1.50-1.75)	
Present	Absent	Present	16,696	95	17.9 (14.7-21.9)	2.14 (1.74-2.63)	1.80 (1.46-2.22)	1.75 (1.42-2.15)	
Absent	Present	Present	1,586	8	16.7 (8.4-33.4)	2.01 (1.00-4.02)	1.17 (0.58-2.35)	1.27 (0.63-2.54)	
Present	Present	Present	75,582	686	29.3 (27.2-31.6)	3.52 (3.22-3.85)	2.67 (2.44-2.93)	2.67 (2.43-2.93)	

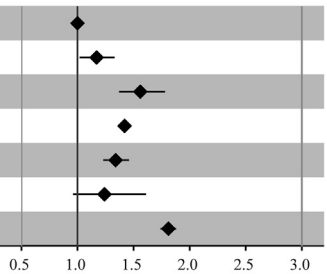


The incidence rate was per 10,000 person-years. Participants with MAFLD were classified into 7 subtypes based on the combination of comorbid metabolic dysfunction (overweight [OW], metabolic syndrome [MetS], and diabetes mellitus [DM]). We performed Cox regression analyses to compare the subsequent risk of cardiovascular disease events among the 7 groups. We set participants having OW alone as the reference. We conducted the Wald test to compare the HRs between individual MAFLD subgroups. Adjusted models include adjustments for age and sex for model 2 and age, sex, low-density lipoprotein cholesterol, cigarette smoking, alcohol consumption, and physical inactivity for model 3. A forest plot indicates the HRs and 95% CIs. The association between MAFLD subtypes and the risk of heart failure, atrial fibrillation, myocardial infarction, angina pectoris, stroke, and composite endpoint is shown. Abbreviations as in Figure 1.

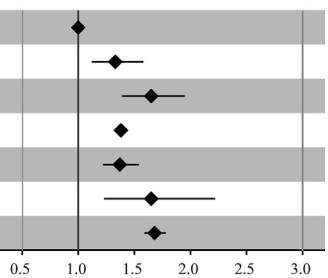
Continued on the next page

FIGURE 3 Continued

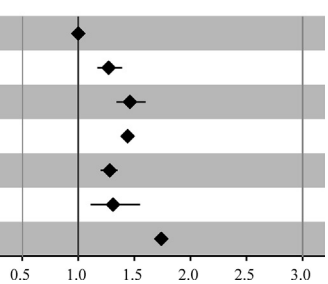
			No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3	P value
Angina Pectoris									<0.001
OW	MetS	DM							
Present	Absent	Absent	583,201	12,173	65.3 (64.1-66.4)	1 [Reference]	1 [Reference]	1 [Reference]	
Absent	Present	Absent	6,439	215	101.3 (88.6-115.8)	1.55 (1.35-1.77)	1.14 (0.99-1.30)	1.17 (1.02-1.33)	
Absent	Absent	Present	5,240	237	141.6 (124.7-160.8)	2.17 (1.91-2.47)	1.52 (1.33-1.72)	1.56 (1.37-1.78)	
Present	Present	Absent	208,078	7,006	106.9 (104.4-109.4)	1.64 (1.59-1.69)	1.42 (1.38-1.46)	1.42 (1.38-1.46)	
Present	Absent	Present	16,696	565	109.3 (100.6-118.7)	1.68 (1.54-1.83)	1.34 (1.23-1.46)	1.34 (1.23-1.46)	
Absent	Present	Present	1,586	58	123.6 (95.6-159.9)	1.90 (1.47-2.46)	1.22 (0.94-1.57)	1.24 (0.96-1.61)	
Present	Present	Present	75,582	3,351	147.4 (142.5-152.4)	2.27 (2.18-2.36)	1.79 (1.72-1.86)	1.81 (1.74-1.88)	



			No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3	P value
Stroke									<0.001
OW	MetS	DM							
Present	Absent	Absent	583,201	5,719	30.4 (29.6-31.2)	1 [Reference]	1 [Reference]	1 [Reference]	
Absent	Present	Absent	6,439	133	61.9 (52.2-73.4)	2.03 (1.71-2.42)	1.33 (1.12-1.58)	1.33 (1.12-1.58)	
Absent	Absent	Present	5,240	140	82.3 (69.7-97.1)	2.71 (2.29-3.21)	1.66 (1.40-1.96)	1.65 (1.39-1.95)	
Present	Present	Absent	208,078	3,404	51.1 (49.5-52.9)	1.69 (1.62-1.76)	1.38 (1.32-1.44)	1.38 (1.32-1.44)	
Present	Absent	Present	16,696	302	57.6 (51.4-64.4)	1.90 (1.69-2.13)	1.38 (1.22-1.54)	1.37 (1.22-1.54)	
Absent	Present	Present	1,586	44	93.3 (69.4-125.4)	3.09 (2.30-4.15)	1.67 (1.24-2.25)	1.65 (1.23-2.22)	
Present	Present	Present	75,582	1,624	70.0 (66.6-73.4)	2.31 (2.19-2.45)	1.67 (1.58-1.77)	1.68 (1.59-1.78)	

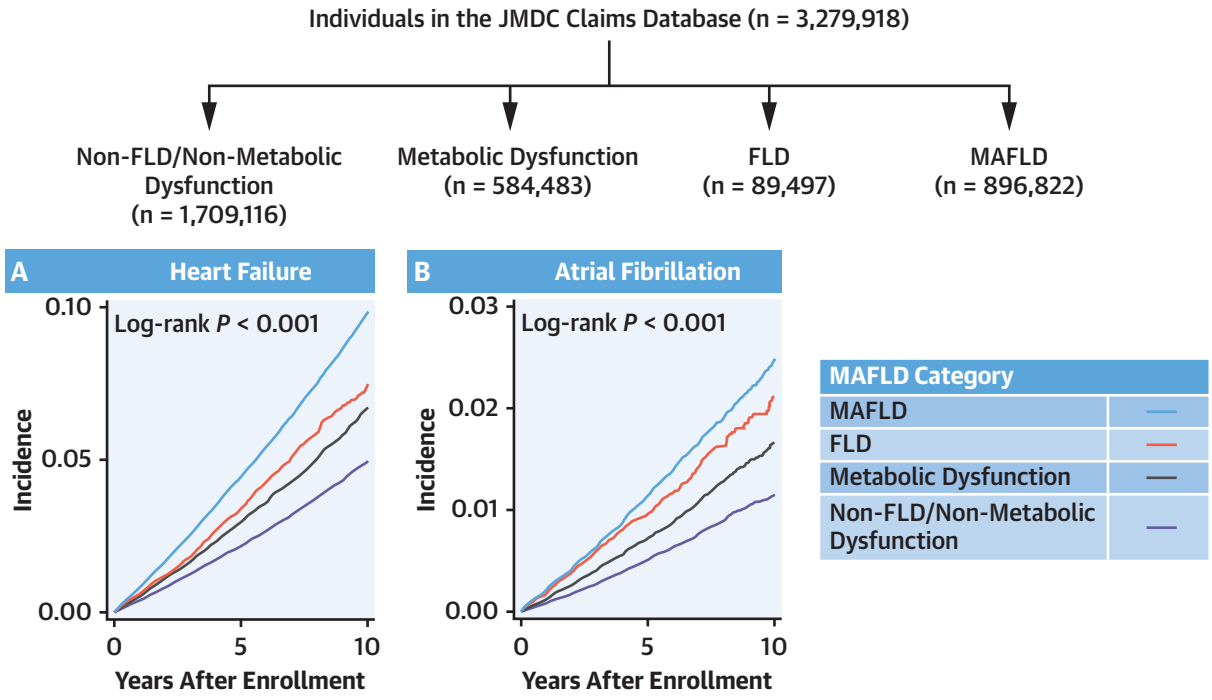


			No.	No. of Events	Incidence Per 10000 person-years (95% CI)	Model 1	Model 2	Model 3	P value
Composite Endpoint									<0.001
OW	MetS	DM							
Present	Absent	Absent	583,201	27,541	150.6 (148.8-152.4)	1 [Reference]	1 [Reference]	1 [Reference]	
Absent	Present	Absent	6,439	542	264.8 (243.4-288.1)	1.76 (1.61-1.91)	1.26 (1.16-1.38)	1.27 (1.17-1.39)	
Absent	Absent	Present	5,240	519	322.2 (295.6-351.1)	2.14 (1.96-2.34)	1.45 (1.33-1.58)	1.46 (1.34-1.60)	
Present	Present	Absent	208,078	16,088	253.6 (249.7-257.5)	1.69 (1.65-1.72)	1.44 (1.42-1.47)	1.44 (1.42-1.47)	
Present	Absent	Present	16,696	1,239	246.8 (233.5-261.0)	1.64 (1.55-1.74)	1.28 (1.20-1.35)	1.28 (1.20-1.35)	
Absent	Present	Present	1,586	142	315.7 (267.8-372.1)	2.10 (1.78-2.48)	1.31 (1.11-1.54)	1.31 (1.11-1.55)	
Present	Present	Present	75,582	7,361	336.9 (329.3-344.6)	2.25 (2.19-2.30)	1.74 (1.70-1.79)	1.74 (1.70-1.79)	



HF and AF are both increasing in prevalence and are recognized as being among the most clinically relevant CVDs, alongside atherosclerotic CVD, such as MI, AP, and stroke. In the United States, approximately 6.0 million persons aged ≥20 years had HF from 2015 to 2018, according to the National Health and Nutrition Examination Survey. The prevalence of HF is expected to increase by 46% in 2030 compared to 2012, and it is expected to affect more than 8 million people in the United States. Moreover, the number of patients with AF in the United States was assumed to be 5.2 million in 2010 and is expected to increase by 2030. Risk stratification is an initial step in overcoming this epidemiologic issue from the perspective of public health and preventive medicine. Although there are various established risk factors for

CENTRAL ILLUSTRATION Summary of Primary Findings



Ohno R, et al. JACC: Asia. 2023;3(6):908-921.

We categorized study participants as non-fatty liver disease (FLD)/nonmetabolic dysfunction, metabolic dysfunction, FLD, and metabolic dysfunction-associated fatty liver disease (MAFLD) (having both FLD and metabolic dysfunction). The cumulative probability of (A) heart failure and (B) atrial fibrillation by MAFLD classification were calculated using the Kaplan-Meier method. The log-rank test was used to calculate *P* values, and the values were all <0.001.

CVD, including HF and AF, various revisions have been made to existing risk factors for the refinement of CVD risk stratification. For example, hypertension is one of the leading risk factors for CVD, and the 2017 American College of Cardiology/American Heart Association blood pressure guidelines lowered the threshold of blood pressure values for diagnosing hypertension from 140/90 mm Hg to 130/80 mm Hg.[14] In the latest guidelines, blood pressure of 130 to 139/80 to 89 mm Hg was defined as stage 1 hypertension, and blood pressure of ≥140/90 mm Hg was defined as stage 2 hypertension. Accordingly, we reported that both stage 2 and stage 1 hypertension were associated with greater risks of developing HF and AF,[7] which supports the validity of this novel blood pressure classification. Thus, new findings are constantly emerging, even for known risk factors. MAFLD is a novel concept of FLD-related metabolic abnormalities that developed from NAFLD to reflect the knowledge gathered over decades.

Currently, FLD is thought to be prevalent in approximately 20% to 30% of the adults in developed countries.[15,16] Because of the unhealthy lifestyle habits (eg, physical inactivity, sedentary lifestyle, and excess calorie intake) of modern people, FLD accompanied by unhealthy metabolic status (MAFLD) is expected to increase further. As the definition suggests, the presence of various metabolic abnormalities in individuals diagnosed with MAFLD is expected to be associated with an increased risk of CVD events, and the risk assessment of CVD events using MAFLD may provide a new perspective in terms of CVD risk stratification. Indeed, a large body of evidence has been established regarding the association between MAFLD and atherosclerotic CVD. For example, an analysis of 2 community-based cohorts including 8,919 participants in South Korea showed that the presence of MAFLD was associated with a higher risk of developing atherosclerotic CVD, including acute MI, coronary artery disease, and cerebrovascular disease, after adjustment for age, sex, and body mass index (HR: 1.35; 95% CI: 1.13-1.62).[3] Nevertheless, there are insufficient epidemiologic data on the association between MAFLD and the risk

of developing HF and AF. Although there are studies that include HF as a composite endpoint and analyze its association with MAFLD,[17,18] there are no studies that analyze HF as an individual outcome. To the best of our knowledge, there have been no investigations on a relationship of MAFLD with incident AF.

Our study had clinical implications and was distinguishable from previous studies in the following ways. Compared to individuals with neither FLD nor metabolic dysfunction, the risk of CVD events (including HF and AF) was increased in those with either FLD or metabolic dysfunction alone. The risk of CVD events was further increased in individuals with MAFLD (combined with FLD and metabolic dysfunction). These results demonstrate that the MAFLD concept of "FLD and metabolic dysfunction coexistence" is useful for the risk stratification of CVD, including HF and AF. Using a dataset including a large sample size of a general population, we confirmed the robustness of our primary findings through a variety of sensitivity analyses. In particular, our primary results were unchanged when corrected for eGFR in participants for whom eGFR could be calculated. Subgroup analyses showed an association between MAFLD and the risks of HF and AF, irrespective of age, sex, alcohol-drinking habits, or baseline blood pressure. Previously, NAFLD included nonhabitual alcohol drinking. However, the results of the present study showed that MAFLD was associated with an elevated risk of both HF and AF regardless of alcohol consumption, suggesting that defining MAFLD without reference to alcohol consumption habits would be appropriate and that defining MAFLD without reference to alcohol drinking habits may clinically be useful for stratifying the CVD risk. In addition, subgroup analysis stratified by age suggested that the association between MAFLD and the risks of developing HF and AF is more pronounced in younger individuals than in older individuals. Prevention of MAFLD may be more important in younger people, who are at a lower risk of CVD with age. Although our study demonstrated a robust relationship between MAFLD and its subtypes with risks of developing CVD, including HF and AF, it should be noted that our study did not prove a causal relationship because of the nature of the study design. We need to clarify whether therapeutic intervention in people with MAFLD could reduce the risks of HF, AF, and other CVD events. Although there are no approved medications for MAFLD, there are several candidate medications (eg, sodium glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists).[19-22] If the efficacy of these agents in MAFLD could be established, they may play a pivotal role in preventing CVD, including HF and AF. MAFLD can be classified into 7 subtypes according to comorbid metabolic dysfunction (overweight, metabolic syndrome, and DM), and the risk of future CVD events (including HF and AF) significantly differed among the 7 subtypes. Therefore, further risk stratification among individuals with MAFLD would be required. Recently, several genetic variants (eg, *TM6SF2*, *MBOAT7*) have been reported to be associated with the development of FLD or thromboembolism.[23,24] Further investigations using genetic information would be needed to develop "precision medicine" in this field.

STUDY LIMITATIONS. Our study had several limitations, as previously discussed in studies using this dataset.[7-9] Although previous investigations showed the validity (especially specificity) of diagnoses in Japanese administrative claims databases, including the JMDC Claims Database,[25,26] the reliability of diagnoses registered in administrative claims databases should generally be considered inferior to those of registry-based cohort studies. Because the observational period of our dataset was relatively short, further investigations using other datasets with a longer follow-up are needed to validate our findings. Because the JMDC Claims Database does not include individuals aged >75 years, it is inconclusive whether the results can be applied to older adults. The potential influence of unmeasured confounding factors, such as socioeconomic status, could not be eliminated in our study. Also, the diagnosis of MAFLD was based on data from the initial health check-up; however, it was possible that health status might have changed over time or that new medical treatments might have been introduced during an observational period after the initial health check-up, which could have affected the clinical outcomes. In this study, we used the FLI for assessing hepatosteatosis. Unfortunately, our database does not include data on liver biopsy and abdominal ultrasonography. Because of the nature of claims databases, several pieces of clinical information are lacking. For example, chronic inflammation is supposed to play an important role in the development of CVD in individuals having MAFLD. However, data on chronic inflammation are not available in our dataset. Similarly, MAFLD was associated with a higher risk of developing MI. Recently, MI with nonobstructed coronary arteries has attracted clinical

interest. Unfortunately, data on types of MI were unavailable in our dataset, and therefore, we need further research focusing on the relationship between MAFLD and this type of coronary event. Information on the etiology of HF is also unavailable in our dataset.

CONCLUSIONS

Compared with people with non-FLD/non-metabolic dysfunction, the subsequent risk of the development of HF, AF, and other CVD events was higher in people with FLD alone or metabolic dysfunction alone and further increased in those with MAFLD, suggesting the clinical significance of the novel concept of MAFLD (coexisting FLD and metabolic dysfunction). Furthermore, it would also be important to consider the subtype of MAFLD for CVD risk assessment. Assessment of MAFLD and its subtypes may aid in risk stratification for HF and AF events.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In the general population without a history of CVD, MAFLD was associated with higher risks of developing HF and AF. The incidence of cardiovascular events differed among subtypes of MAFLD.

TRANSLATIONAL OUTLOOK: MAFLD is associated not only with atherosclerotic CVD but also with risks of HF and AF. Assessment of MAFLD and its subtypes may aid in risk stratification for future HF and AF events.

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KEY WORDS atrial fibrillation, epidemiology, heart failure, metabolic dysfunction–associated fatty liver disease

APPENDIX For supplemental figures and a table, please see the online version of this paper.