Comparison of cardiovascular mortality between MAFLD and NAFLD: a cohort study

Short running title: MAFLD and cardiovascular mortality

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Abstract

Background and Aims

A new diagnostic criterion of metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed. However, only a few studies have shown that MAFLD predicts cardiovascular disease (CVD) mortality better than non-alcoholic fatty liver disease (NAFLD). Therefore, a cohort study was conducted to assess this relationship.

Methods and Results

Health examination data from health care centers in South Korea were assessed after excluding participants with missing covariates and cancer history (n = 701,664). Liver ultrasonography reports, laboratory and anthropometric data were extracted. Diagnoses of NAFLD and MAFLD were performed according to standard definitions. Participants were categorized based on the presence of NAFLD and MAFLD. In addition, participants were classified into five categories: no fatty liver disease (no FLD), NAFLD-only, MAFLD-only, both FLDs, and alcoholic FLD (AFLD) and non-MAFLD. Multivariable regression modeling was performed.

The median follow-up duration was 8.77 years, and 52.56% of participants were men. After stratifying the cohort into no-MAFLD and MAFLD groups, MAFLD was associated with increased CVD mortality (adjusted HR 1.14, 95% CI 1.02-1.28). When participants were divided into no-NAFLD and NAFLD groups, there was a non-significant trend towards an increase in CVD mortality in NAFLD group (adjusted HR 1.07, 95% CI 0.95-1.21). When participants were divided into five categories, MAFLD-only group showed increased CVD mortality (adjusted HR 1.35, 95% CI 1.07-1.70) while NAFLD-only group showed no significant association with CVD mortality (adjusted HR 0.67, 95% CI 0.38-1.19).

Conclusions

In conclusion, MAFLD is associated with increased CVD mortality in a relatively young Korean population.

Keywords: MAFLD, NAFLD, cardiovascular disease mortality

1. INTRODUCTION

The prevalence of fatty liver disease (FLD) is increasing worldwide owing to the widespread western lifestyle, increased prevalence of obesity and type 2 diabetes, and related metabolic derangements[1-4]. Traditionally, two major categories existed in FLD: non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD)[5, 6]. Although this classification of FLD has been used for nearly 35 years, it has a blind spot because NAFLD does not include FLD with other coexisting liver diseases or moderate alcohol intake[7]. This problem led to the development of a new class of FLD, known as metabolic dysfunction-associated fatty liver disease (MAFLD)[7, 8] to include these patient populations that were previously challenging to classify.

The newly proposed definition of MAFLD consists of hepatic fat and metabolic abnormalities regardless of alcohol consumption or secondary causes of liver diseases and steatosis[7, 9]. This new definition is expected to facilitate the identification of patients with FLD with chronic liver diseases or alcoholism, which were previously excluded by the traditional NAFLD definition[9]. However, this change has also provoked new concerns. Younossi et al. suggested that this change is premature because the new terminology was created without evidence of the pathogenesis of MAFLD or the effect of MAFLD on long-term complications[10].

Many researchers have investigated the association between FLD and cardiovascular disease (CVD) mortality[11-14]. Growing evidence suggests that patients with NAFLD are at increased risk of developing type 2 diabetes, coronary artery disease, cardiomyopathy, and cardiac arrhythmias, which may lead to increased CVD mortality[7, 15-17]. These findings suggest that NAFLD is a predictor of CVD events, independent of traditional risk factors [14, 18].

Considering the new definition of MAFLD, one could speculate that MAFLD is associated with higher CVD mortality, as it incorporates a wider range of patients with FLD with metabolic derangements[7]. However, data on CVD mortality in the MAFLD population are limited[7]. There is debate over whether the MAFLD definition predicts CVD mortality better than the NAFLD classification[7]. To clarify this ambiguity, we conducted a large-scale cohort study to assess the

relationship between FLD and CVD mortality.

2. MATERIALS AND METHODS

2.1 Study population

The Kanbguk Samsung Health Study (KSHS) data were used for our analysis. The cohort and methods have been described in a previous study by our team[19]. In brief, the KSHS cohort was created using data from regular comprehensive health examinations among employers in Korea's public or private sectors. All examinations were conducted at two health examination centers in South Korea. Extensive information was collected using a standardized questionnaire during the health examination, including sociodemographic data, results of laboratory tests including homeostatic model assessment for insulin resistance (HOMA-IR) score and plasma high-sensitivity C-reactive protein (hs-CRP) levels, anthropometric data, and information on health-related behaviors. All examinations were performed in a standardized manner by trained medical personnel. The study was conducted from January 3, 2002, to December 31, 2019. Initially, participants who underwent liver ultrasound examinations were screened (n = 722,449). Participants with a past history of cancer (n = 13,384) and missing covariates (n = 7,483) were excluded from the analysis.

Participants were excluded from the NAFLD assessment if they met one of the following criteria: alcohol intake $\geq$ 30/20 g/day (male/female), hepatitis C antibody titer $\geq$ 0.5, or hepatitis B surface antigen titer $\geq$ 0.5 (weakly positive or positive) (n = 33,390). Thus, 701,664 participants were included in the analysis for MAFLD and 668,274 participants in the analysis for NAFLD (**Figure 1**). The Institutional Review Board of Kangbuk Samsung Hospital (IRB No.:2022- 05- 024) approved the current study. Informed consent was waived because we used only non-identifiable data obtained during the health-screening examinations.

2.2 Definition of liver disease and categorization of participants

NAFLD was defined as follows: participants with evidence of hepatic steatosis confirmed by liver ultrasonography without a history of excessive alcohol consumption (>30 g/day for men and >20 g/day for women) and other coexisting liver diseases[20-22]. MAFLD was defined when the participants had hepatic steatosis confirmed by ultrasonography with one or more of the following criteria: overweight or obesity (body mass index [BMI] ≥ 23 kg/m^2), coexisting type 2 diabetes, and at least two of the following seven metabolic abnormalities (waist circumference ≥ 90 cm in men and ≥ 80 cm in women, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or taking antihypertensive medication, serum triglyceride level ≥ 150 mg/dL, serum high-density lipoprotein (HDL) level < 40 mg/dL in men or <50 mg/dL in women, fasting glucose level 100–125 mg/dL or HbA1c level 5.7%–6.4%, HOMA-IR score ≥ 2.5, or hsCRP level ≥ 0.2 mg/dL)[9, 21, 23]. We used BMI ≥ 23 kg/m^2 as a cutoff for overweight, following the World Health Organization and 2018 Korean Society for the Study of Obesity Guidelines[24, 25]. AFLD was defined as the presence of hepatic steatosis confirmed by ultrasonography with self-reported alcohol intake of >30 g/day for men and >20 g/day for women[5, 20].

Participants were categorized into MAFLD and no-MAFLD groups (reference) and NAFLD and no-NAFLD groups (reference). CVD mortality rates for each group were compared. In addition, participants were categorized into five groups to compare CVD mortality: no FLD, NAFLD-only, MAFLD-only, both FLD (participants who met the criteria for both MAFLD and NAFLD), and AFLD and non-MAFLD (**Figure 2**). By grouping the participants into these subgroups, unequal distribution of CVD risk factors between the groups was expected, as all participants with diabetes and other metabolic risk factors were excluded from the NAFLD-only group and were assigned to the MAFLD-only or both FLD group. Even though such categorization is not appropriate, we categorized the particpants into above five groups to compare with previous study results[9, 26, 27].

2.3 Hepatic steatosis examination

During the health examination, liver ultrasonography was performed by experienced radiologists who were blinded to the study's purpose and aim. Sagittal views of the right lobe of the liver and right kidney and the left lateral segment of the liver and spleen and liver transverse view were obtained during the sonographic examination. Hepatic steatosis was diagnosed when a participant had increased echogenicity of the liver compared with the renal cortex, where the intrahepatic vessels and diaphragm appeared normal [5].

2.4 Statistical analysis

Continuous variables are expressed as the median and interquartile range (IQR) or mean ± standard deviation based on the distribution of the variables. Categorical variables are expressed as percentages. One-way analysis of variance (ANOVA) and independent sample t-tests were used to compare the means of the continuous variables between the groups. Pearson's Chi-squared test was used to compare categorical variables. Cox proportional hazard analysis was used to estimate hazard ratios (HRs) with a 95% confidence interval (CI) for the CVD mortality rate (per 10^4 person-year [PY]). Model 1 was adjusted for age, sex, education level, smoking status, and performance of regular exercise in multivariable analysis. Model 2 was further adjusted for serum low-density lipoprotein (LDL) cholesterol levels in addition to the factors of model 1. STATA version 17.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. The significance level was set at $P < 0.05$.

3. RESULTS

3.1 Baseline characteristics

The median follow-up duration was 8.77 years, and the mean follow-up duration was 9.24 ± 5.26 years. The mean age of the participants was 39.81 ± 10.92 years, and 52.56% (n = 368,824) were men (**Supplemntary Table 1**). Among the 701,664 study participants, participants were stratified into no-MAFLD (n = 523,933, 74.67%), and MAFLD (n = 177,731, 25.33%) group. The proportions of men (76.73%), smokers (30.64%), and individuals with high alcohol consumption (16.4%) were higher in the MAFLD group than no MAFLD group (p <0.001). In addition, BMI (26.59±2.92), systolic and diastolic blood pressure (119.00 ± 13.50 mmHg, 76.69 ± 9.90 mmHg), fasting glucose level (102.66 ± 23.22 mg/dL), HbA1c level (5.8 ± 0.8%), HOMA-IR score (2.02, 1.39-2.94), serum gamma-glutamyl transferase (35 U/L, 23-58 U/L), triglyceride level (148 mg/dL, 105-207 mg/dL), and prevalence of diabetes (11.77%), hypertension (27.93%), and dyslipidemia (17.56%) were higher in MAFLD group (p<0.001) (**Table 1**).

Next, participants were stratified into no-NAFLD (n = 510,726, 76.42%), and NAFLD (n = 157,548, 23.58%) groups. When we compared the baseline characteristics of the participants based on the presence or absence of NAFLD, all baseline data showed significant differences between the groups (p<0.001) (**Table 2**). Lastly, Among the 701,664 study participants, there were five groups according to the presence or absence of fatty liver diseases: no FLD (n = 510,726, 72.79%), NAFLD-only (n = 11,612, 1.65%), MAFLD-only (n = 31,795, 4.53%), both FLDs (n = 145,936, 20.8%), and AFLD and non-MAFLD (n = 1,595, 0.23%). Baseline characteristics of all the five groups were significantly different (p<0.001) (**Supplementary Table 1, Figure 2**).

3.2 Cardiovascular mortality comparison in MAFLD vs. no-MAFLD groups, NAFLD vs. no-NAFLD groups

The participants were divided into the no-MAFLD and MAFLD groups. Before the adjustment, the MAFLD group and the NAFLD group were associated with increased CVD mortality, compared with the no-MAFLD group and the no-NAFLD group, respectively (crude, MAFLD, HR 1.70, 95% CI 1.52-1.91; NAFLD, HR 1.55, 95% CI 1.38-1.75).

After the adjustment, compared with the no-MAFLD group, the MAFLD group was weakly associated with increased CVD mortality (no-MAFLD, reference; model 1, HR 1.13, 95% CI 1.01-1.27; model 2, HR 1.14, 95% CI 1.02-1.28). However, there was no significant increase in CVD mortality between the NAFLD and no-NAFLD groups (no-NAFLD, reference; model 1, HR 1.07, 95% CI 0.95-1.21; model 2, HR 1.07, 95% CI 0.95-1.21) (**Table 3**).

3.3 Cardiovascular mortality according to the fatty liver disease category

Participants were stratified into five groups according to the presence or absence of fatty liver disease (no FLD, reference group; NAFLD-only, MAFLD-only, both FLDs, AFLD and non-MAFLD). Before the adjustment, MAFLD-only, both FLD and AFLD and non-MAFLD group were associated with increased CVD mortality (crude, MAFLD only, HR 2.11, 95% CI 1.69-2.65; both FLD, HR 1.63, 95% CI 1.44-1.84; AFLD and non-MAFLD, HR 3.18, 95% CI 1.42-7.10). After adjustment for age, sex, education level, smoking status, and performance of regular exercise, the MAFLD-only group was associated with increased CVD mortality. In contrast, the NAFLD-only and both FLD groups were not significantly associated with CVD mortality (model 1, NAFLD-only, adjusted HR 0.67, 95% CI 0.38-1.18; MAFLD-only, adjusted HR 1.35, 95% CI 1.07-1.70; both FLDs, adjusted HR 1.09, CI 0.97-1.23; AFLD and non-MAFLD, adjusted HR 1.91, 95% CI 0.85-4.27). This association remained unchanged even after additional adjustment for serum LDL-C level (model 2, NAFLD-only, HR 0.67, 95% CI 0.38-1.19; MAFLD-only, HR 1.35, 95% CI 1.07-1.70; both FLDs, HR 1.10, 95% CI 0.97-1.24; AFLD and non-MAFLD, HR 1.90, 95% CI 0.85-4.24) (**Supplementary**

Table 2).

4. DISCUSSION

To our knowledge, this was one of the major studies to date that showed the association between MAFLD and the risk of CVD mortality in a cohort of individuals who underwent liver ultrasonography to define hepatic steatosis. In our study cohort, the presence of MAFLD was associated with an increased risk of CVD mortality, whereas the presence of NAFLD did not show any such significant association. When we divided the participants into 5 categories, the MAFLD-only group was associated with an increased risk of CVD mortality. The findings of this study are novel as the study incorporated relatively young, low-risk Korean participants (mean age 39.81 ± 10.92 years), with a long-term follow-up duration (median 8.77 years).

Previous studies have stratified participants into at least four categories: NAFLD-only, MAFLD-only, NAFLD and MAFLD (both FLD groups in our study), and neither NAFLD nor MAFLD group to compare CVD events or mortality. Qi-Huang et al. showed that there was no difference in CVD mortality between MAFLD-only and NAFLD-only groups[26]. Another study showed high cumulative incidence rates of CVD-related mortality in MAFLD-only participants, followed by NAFLD and MAFLD, and NAFLD-only participants[27].

Other studies showed a comparison of the CVD events in each FLD subgroup. Lee et al. showed that both NAFLD-only and MAFLD-only groups were associated with increased incidence of CVD events in a large-scale Korean cohort. The MAFLD-only group showed a stronger association than the NAFLD-only group [9]. Moon et al. showed that MAFLD was associated with CVD events but not CVD mortality [28]. However, the results of these studies require careful analysis, as the fatty liver index (FLI) was used to diagnose hepatic steatosis, and only a few studies have validated the use of FLI for the diagnosis of MAFLD [22, 29, 30]. Another study that used ultrasound to define hepatic steatosis showed that the MAFLD-only group showed increased incidence of fatal/non-fatal CVD events. In contrast, the NAFLD-only group showed no increase in the incidence of CVD events[31]. One study

that used liver histology to diagnose hepatic steatosis showed no significant difference in CVD event prevalence between the NAFLD and MAFLD groups. However, this study did not consider the overlapping MAFLD and NAFLD groups[32].

To compare with previous study results, our study stratified the participants into MAFLD-only and NAFLD-only groups. Our results showed that MAFLD-only group was associated with increased CVD mortality, which align with the results of previous studies [27]. However, a difference exists, as our study cohort showed no difference of CVD mortality in both FLD groups and NAFLD only groups compared with no FLD group. This might be due to NAFLD-only and both FLD group's healthier baseline characteristics, which showed lower blood pressure, less smoking rate, less men proportion and better liver function profile in comparison to MAFLD group. Given this difference in baseline characteristic, it is possible that NAFLD-only and both FLD population in our cohort had less severe forms of fatty liver disease.

Although most published studies compared CVD risk in the MAFLD-only and NAFLD-only groups by dividing participants into the four categories mentioned above, this comparison has potential limitations[9, 26, 27]. First, as observed in our study, the MAFLD-only group may incorporate more CVD risk factors, such as hypertension, dyslipidemia, high alcohol intake, and obesity, than the NAFLD-only group. After excluding the MAFLD group, the NAFLD-only group included participants with normal weight without metabolic syndrome who have fatty liver[21, 22]. Naturally, it is unlikely that the NAFLD-only group has the same risk of CVD as patients with MAFLD[21, 33]. Second, all patients with FLD with underlying diabetes were classified into the MAFLD-only group. The coexistence of diabetes in patients with FLD is a known risk factor[34]. Third, it is extremely difficult to define patients as "NAFLD-only" or "MAFLD-only" in a clinical setting. MAFLD is a diagnosis of inclusion, which includes a wide array of metabolic diseases[7, 35]. To define patients with NAFLD-only, rigorous tests including anthropometric and extensive laboratory analyses are mandatory to rule out MAFLD. This could lead to practical concerns, including increased medical expenditures and time-consuming processes.

To address this limitation in categorizing participants into NAFLD-only and MAFLD-only, we conducted an analysis by comparing CVD mortality between MAFLD and no-MAFLD populations and between NAFLD and no-NAFLD populations. Our research suggested that the MAFLD population was associated with increased CVD mortality, while no such association was found between NAFLD and CVD mortality. A previous study on assessing the association between MAFLD and CVD mortality showed no significant association. It is possible that the association was masked in the previous study owing to the relatively small number of participants (n = 3,306 in the control and MAFLD groups, CI 0.97-2.20)[36].

However, the modest numerical association between MAFLD and CVD mortality in our study is another factor that should be considered. This finding suggested that MAFLD may play a role in identifying the previous "blind spot" in diagnosing FLD. However, it might not be a strong indicator for identifying CVD mortality. Using the Framingham risk score or pooled cohort equations could be more practical in estimating CVD mortality in the FLD population[37, 38]. Further studies are required to validate the role of MAFLD as a predictor of incident CVD events and mortality.

Though multiple previous studies have reported the association between NAFLD and CVD mortality, our cohort did not show a significant mortality difference between NAFLD and no-NAFLD groups [14]. This result might be due to our cohort's relatively young study population, which resulted in an overall small number of CVD mortality (1,210 among 668,274 included participants, 6,277,064 person-year). In addition, this result might suggest that MAFLD may predict CVD mortality better than NAFLD in the young Asian population.

Our study is unique because we used liver ultrasonography to define hepatic steatosis, while previous study in Korean population used FLI to diagnose hepatic steatosis [9, 28]. In addition, we extracted all data to diagnose MAFLD from our large-scale cohort database. The prevalence of MAFLD in our study cohort was 25.3%, which was similar to previous reports in South Korea (16.9% to 33.9%), which suggests our study cohort reflects the prevalence of MAFLD in general population [39, 40] However, our study has a few limitations. First, our analysis was performed on a Korean cohort of a

single ethnicity. Second, the study participants were relatively young. However, this young age is also a unique feature of our study, as the mean age in previous studies was higher[9, 31], and the participants of our study could be relatively free from other comorbidities associated with increased age. Third, selection bias also needs to be considered, as our study cohort consisted of individuals who participated in regular health checkups. However, as annual or biannual health checkups are mandatory for employees in South Korea, the authors believe that the effect of selection bias was minimal. Fourth, some variables included in the analysis, including smoking, exercise, BMI, and medication exposure, might have changed during the follow-up period. In addition, reporting bias should be considered. These uncontrolled time-varying factors and reporting bias could have affected our study result. Fifth, our study did not investigate the dietary habits of study participants, which can affect CVD mortality[41]. Lastly, it is possible that the fatty liver of the participants changed from NAFLD to MAFLD, or vice versa, during follow-up. Due to the above limitations, our study result needs cautious interpretation.

Conclusions

In conclusion, our study showed that the presence of MAFLD was associated with increased CVD mortality in a relatively young Korean population. However, the strength of this association was not strong. Therefore, careful application of MAFLD for CVD risk prediction is required.

DECLARATIONS

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CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

TKY: Conceptualization, methodology, writing – original draft, and writing – review and editing. **MYL:** Formal analysis and investigation. **SHK**: Writing – review and editing; **M-HZ:** writing – review and editing; **GT:** writing – review and editing; **CDB:** writing – review and editing; **K-CS**: conceptualization, methodology, writing – review and editing, supervision, and project administration.

ETHICAL STATEMENT

The Institutional Review Board of Kangbuk Samsung Hospital (IRB No.:2022- 05- 024) approved the current study. Informed consent was waived because we used only non-identifiable data obtained during the health-screening examinations.

DATA SHARING STATEMENT

The data that support the findings of this study are available on request from the corresponding author, Ki-Chul Sung, upon reasonable request.

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Table 1. Baseline Characteristics of participants stratified according to presence of MAFLD

	No MAFLD	MAFLD	P-value
Number	523,933	177,731	
Age, years	38.82±10.61	42.72±11.3	<0.001
Men, %	232,454 (44.37)	136,370 (76.73)	<0.001
Current smoker, %	95,515 (18.23)	54,457 (30.64)	<0.001
High alcohol intake, %	56,971 (10.87)	29,139 (16.4)	<0.001
Higher education, %	309,589 (59.09)	101,229 (56.96)	<0.001
BMI, kg/m2	22.31±2.74	26.59±2.92	<0.001
Waist circumference, cm	77.43±8.34	89.95±7.74	<0.001
SBP, mmHg	109.47±13.39	119±13.5	<0.001
DBP, mmHg	70±9.64	76.69±9.9	<0.001
Fasting glucose, mg/dl	92.54±12.28	102.66±23.22	<0.001
HbA1c, %	5.46±0.42	5.8±0.8	<0.001
HbA1c, mmol/L	8.77±0.97	9.44±0.86	<0.001
HOMA-IR	1.1 (0.74 - 1.58)	2.02 (1.39 - 2.94)	<0.001
ALT, U/l	17 (13 - 23)	31 (22 - 47)	<0.001
AST, U/l	20 (17 - 24)	25 (21 - 32)	<0.001
GGT, U/l	16 (11 - 26)	35 (23 - 58)	<0.001
HDL, mg/dL	61.08±14.75	49.35±11.07	<0.001
LDL, mg/dL	112.96±30.24	132.3±33.41	<0.001
hs-CRP, mg/dL	0.04 (0.02 - 0.07)	0.08 (0.05 - 0.16)	<0.001
Triglycerides, mg/dl	82 (61 - 116)	148 (105 - 207)	<0.001
Diabetes, %	11,480 (2.19)	20,919 (11.77)	<0.001
HTN, %	53,282 (10.18)	49,603 (27.93)	<0.001
History of CVD, %	10,979 (2.1)	5,715 (3.22)	<0.001

History of Dyslipidemia%	33,463 (6.39)	31,216 (17.56)	<0.001
Regular exercise, %	77,682 (14.83)	24,524 (13.8)	<0.001
Anti-HCV antibody, %	444 (0.08)	139 (0.08)	0.409
HBV surface antigen, %	100,33 (1.91)	3,045 (1.71)	<0.001
Metabolic risk abnormalities			
1) Waist >90/80 cm	70,072 (16.72)	87,728 (59.46)	<0.001
2) BP >130/85/med	73,245 (13.98)	63,329 (35.63)	<0.001
3) TG >150 mg/dL	66,311 (12.66)	87,039 (48.97)	<0.001
4) HDL >40/50 mg/dL	41,214 (9.83)	37,685 (25.54)	<0.001
5) pre-diabetes	129,776 (29.96)	81,049 (54.31)	<0.001
6) HOMA-IR >2.5	19,464 (5.77)	40,414 (35.1)	<0.001
7) hsCRP >0.2 mg/L	27,152 (8.07)	21,852 (19.92)	<0.001

Values are expressed as means ±standard deviation, medians (interquartile range), or percentages.

High alcohol intake was defined as >20 g/day for women, >30g/day for men. Higher education was defined as education higher than college or university graduate.

Abbreviations: FLD, fatty liver disease; NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL, high density lipoprotein cholesterol; Hs-CRP, highly sensitive C-reactive protein; HTN, hypertension; CVD, cardiovascular disease; HCV, hepatitis C virus; HBV, hepatitis B virus; BP, blood pressure; TG, triglycerides.

Table 2. Baseline Characteristics of participants stratified according to presence of NAFLD

	No-NAFLD	NAFLD	P-value
Number	510,726	157,548	
Age, years	38.79±10.62	42.64±11.47	<0.001
Men, %	223,528 (43.77)	114,705 (72.81)	<0.001
Current smoker, %	92,144 (18.04)	42,186 (26.78)	<0.001
High alcohol intake, %	55,597 (10.89)	0 (0)	<0.001
Higher education, %	301,299 (58.99)	89,422 (56.76)	<0.001
BMI, kg/m2	22.32±2.77	26.16±3.07	<0.001
Waist circumference, cm	77.4±8.41	88.69±8.09	<0.001
SBP, mmHg	109.46±13.44	117.89±13.6	<0.001
DBP, mmHg	69.98±9.67	75.82±9.84	<0.001
Fasting glucose, mg/dl	92.54±12.37	101.24±21.91	<0.001
HbA1c, %	5.46±0.42	5.77±0.77	<0.001
HbA1c, mmol/L	8.76±0.97	9.36±0.88	<0.001
HOMA-IR	1.1 (0.74 - 1.57)	1.93 (1.32 - 2.84)	<0.001
ALT, U/l	17 (12 - 23)	30 (21 - 45)	<0.001
AST, U/l	20 (17 - 24)	25 (20 - 31)	<0.001
GGT, U/l	16 (11 - 25)	31 (21 - 50)	<0.001
HDL, mg/dL	61.18±14.78	49.61±11.13	<0.001
LDL, mg/dL	112.66±30.12	131.86±33.25	<0.001
hs-CRP, mg/dL	0.04 (0.02 - 0.07)	0.08 (0.04 - 0.15)	<0.001
Triglycerides, mg/dl	82 (60 - 115)	140 (101 - 197)	<0.001
Diabetes, %	11,480 (2.25)	16,618 (10.55)	<0.001
HTN, %	52,546 (10.3)	39,702 (25.22)	<0.001
History of CVD, %	10,688 (2.09)	5,206 (3.3)	<0.001

History of Dyslipidemia%	32,269 (6.32)	25,630 (16.27)	<0.001
Regular exercise, %	76,211 (14.92)	21,305 (13.52)	<0.001
Metabolic risk abnormalities			
1) Waist 90/80	69,708 (17.07)	70,672 (54.92)	<0.001
2) BP 130/85/med	72,306 (14.16)	50,748 (32.21)	<0.001
3) TG 150	64,302 (12.59)	70,844 (44.97)	<0.001
4) HDL 40/50	40,667 (9.96)	33,099 (25.72)	<0.001
5) pre-diabetes	126,896 (30.06)	67,543 (51.8)	<0.001
6) HOMA-IR 2.5	19,307 (5.87)	31,796 (32.48)	<0.001
7) hsCRP 0.2	26,814 (8.16)	18,216 (18.91)	<0.001

Values are expressed as means ±standard deviation, medians (interquartile range), or percentages.

Abbreviations: FLD, fatty liver disease; NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL, high density lipoprotein cholesterol; Hs-CRP, highly sensitive C-reactive protein; HTN, hypertension; CVD, cardiovascular disease; BP, blood pressure; TG, triglycerides.

Table 3. Incident cardiovascular mortality according to presence of MAFLD or NAFLD (n=701,664)

	number	PY	event	Mortality Rate (95% CI)	Crude (HR)	Model 1 (HR)	Model 2 (HR)
MAFLD		6,543,785.1	1,299	1.99 (1.88 - 2.1)			
No MAFLD	523,933 (74.67)	4,925,296.2	836	1.7 (1.59 - 1.82)	1 (reference)	1 (reference)	1 (reference)
MAFLD	177,731 (25.33)	1,618,488.9	463	2.86 (2.61 - 3.13)	1.70 (1.52-1.91)	1.13 (1.01-1.27)	1.14 (1.02 - 1.28)
NAFLD		6,277,064	1,210	1.93 (1.82 - 2.04)			
No-NAFLD	510,726 (76.42)	4,803,746.1	818	1.7 (1.59 - 1.82)	1 (reference)	1 (reference)	1 (reference)
NAFLD	157,548 (23.58)	1,473,317.9	392	2.66 (2.41 - 2.94)	1.55 (1.38-1.75)	1.07 (0.95 – 1.21)	1.07 (0.95 - 1.21)

Model 1 : Adjusted for age, sex, education, smoking, regular exercise (3 times/week)

Model 2 : Adjusted for age, sex, education, smoking, regular exercise (3 times/week), and plasma LDL-cholesterol

Abbreviations: PY, person-year; CI, confidence interval; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; FLD, fatty liver disease; AFLD, alcoholic fatty liver disease.

Figure legends

Figure 1. Flow diagram of study participants.

Figure 2. Classification of study participants.

Abbreviations: FLD, fatty liver disease; CVD, cardiovascular disease HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; FLD, fatty liver disease; AFLD, alcoholic fatty liver disease.

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Supplemental Materials

Supplementary Table 1. Baseline characteristics of participants stratified according to fatty liver disease category

	Overall	no FLD	NAFLD-only	MAFLD-only	Both FLD (NAFLD & MAFLD)	AFLD & non-MAFLD	P value
Number	701,664	510,726 (72.79)	11,612 (1.65)	31,795 (4.53)	145,936 (20.8)	1,595 (0.23)	
Age, years	39.81±10.92	38.79±10.62	39.84±9.93	42.09±10.02	42.86±11.55	40.49±9.72	<0.001
Men, %	368,824 (52.56)	223,528 (43.77)	7,622 (65.64)	29,287 (92.11)	107,083 (73.38)	1,304 (81.76)	<0.001
Current smoker, %	149,972 (21.37)	92,144 (18.04)	2,635 (22.69)	14,906 (46.88)	39,551 (27.1)	736 (46.14)	<0.001
High alcohol intake, %	86,110 (12.27)	55,597 (10.89)	0 (0)	29,139 (91.65)	0 (0)	1,374 (86.14)	<0.001
Higher education, %	410,818 (58.55)	301,299 (58.99)	7,315 (63)	19,122 (60.14)	82,107 (56.26)	975 (61.13)	<0.001
BMI, kg/m^2	23.39±3.35	22.32±2.77	21.76±1.05	26.93±2.98	26.51±2.9	21.74±1.18	<0.001
Waist circumference, cm	80.69±9.86	77.4±8.41	78.3±4.92	91.83±7.57	89.5±7.72	79.39±4.92	<0.001

SBP, mmHg	111.88±14.04	109.46±13.44	109.31±11	120.98±13.09	118.57±13.55	111.33±11.34	<0.001
DBP, mmHg	71.69±10.14	69.98±9.67	70.5±8.39	78.75±9.98	76.24±9.82	72.71±8.54	<0.001
Fasting glucose, mg/dl	95.1±16.38	92.54±12.37	92.45±7.81	105.93±25.96	101.94±22.51	93.52±8.38	<0.001
HbA1c, %	5.55±0.56	5.46±0.42	5.45±0.27	5.8±0.83	5.8±0.79	5.4±0.26	<0.001
HbA1c mmol/L	8.94±0.99	8.76±0.97	9.15±0.95	9.7±0.74	9.38±0.87	9.41±0.88	<0.001
HOMA-IR	1.27 (0.83-1.9)	1.1 (0.74-1.57)	1.18 (0.83-1.62)	2.04 (1.39-2.96)	2.01 (1.39-2.94)	1.12 (0.77-1.55)	<0.001
ALT, U/l	19 (14-29)	17 (12-23)	22 (16-31)	34 (24-49)	31 (22-46)	25 (18-35)	<0.001
AST, U/l	21 (17-26)	20 (17-24)	22 (18-26)	27 (22-36)	25 (20-32)	23 (19-31)	<0.001
GGT, U/l	19 (13-34)	16 (11-25)	21 (15-32)	55 (35-91)	32 (22-51)	35 (23-61)	<0.001
HDL, mg/dL	58.11±14.82	61.18±14.78	56.48±12.5	50.71±11.99	49.06±10.83	61.08±15.69	<0.001
hs-CRP, mg/dL	0.04 (0.02 – 0.09)	0.04 (0.02 - 0.07)	0.04 (0.03 - 0.08)	0.08 (0.05 - 0.16)	0.08 (0.05 - 0.16)	0.05 (0.03 - 0.08)	<0.001
Triglycerides, mg/dl	94 (66-140)	82 (60-115)	100 (74-132)	162 (114-233)	145 (104-202)	106 (78-139)	<0.001
LDL, mg/dL	117.86±32.19	112.66±30.12	125.15±32.17	131.88±34	132.39±33.27	121.5±33.69	<0.001
Diabetes, %	32,399 (4.62)	11,480 (2.25)	0 (0)	4,301 (13.53)	16,618 (11.39)	0 (0)	<0.001

HTN, %	102,885 (14.68)	52,546 (10.3)	619 (5.33)	10,520 (33.12)	39,083 (26.81)	117 (7.34)	<0.001
History of CVD, %	16,694 (2.38)	10,688 (2.09)	265 (2.28)	774 (2.43)	4,941 (3.39)	26 (1.63)	<0.001
History of Dyslipidemia%	64,679 (9.22)	32,269 (6.32)	1,023 (8.81)	6,609 (20.79)	24,607 (16.86)	171 (10.72)	<0.001
Anti-HCV antibody, %	583 (0.08)	436 (0.09)	0 (0)	139 (0.44)	0 (0)	8 (0.5)	<0.001
HBV surface antigen, %	13,078 (1.86)	9,793 (1.92)	0 (0)	3,045 (9.58)	0 (0)	240 (15.05)	<0.001
Regular exercise, %	102,206 (14.57)	76,211 (14.92)	1,270 (10.94)	4,489 (14.12)	20,035 (13.73)	201 (12.6)	<0.001
Metabolic risk abnormalities							
1) Waist >90/80 cm	157,800 (27.85)	69,708 (17.07)	332 (3.54)	17,388 (61.57)	70,340 (58.96)	32 (2.25)	<0.001
2) BP >130/85/med	136,574 (19.46)	72,306 (14.16)	785 (6.76)	13,366 (42.04)	49,963 (34.24)	154 (9.66)	<0.001
3) TG >150 mg/dL	153,350 (21.86)	64,302 (12.59)	1,724 (14.85)	17,919 (56.36)	69,120 (47.36)	285 (17.87)	<0.001

4) HDL 40/50 mg/dL	78,899 (13.92)	40,667 (9.96)	515 (5.48)	5,101 (18.06)	32,584 (27.31)	32 (2.25)	<0.001
5) pre-diabetes	210,825 (36.2)	126,896 (30.06)	2,518 (26.33)	16,024 (56.39)	65,025 (53.82)	362 (25.37)	<0.001
6) HOMA-IR >2.5	59,878 (13.23)	19,307 (5.87)	137 (1.86)	8,755 (35.57)	31,659 (34.97)	20 (1.58)	<0.001
7) hsCRP >0.2 mg/L	49,004 (10.98)	26,814 (8.16)	293 (4.2)	3,929 (19.32)	17,923 (20.06)	45 (4.39)	<0.001

Values are expressed as means ±standard deviation, medians (interquartile range), or percentages.*Abbreviations* : FLD, fatty liver disease; NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic associated fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL, high density lipoprotein cholesterol; hs-CRP, highly sensitive C-reactive protein; HTN, hypertension; CVD, cardiovascular disease; HCV, hepatitis C virus; HBV, hepatitis B virus; BP, blood pressure; TG, triglycerides.

Supplementary Table 2. Incident cardiovascular mortality according to fatty liver disease category (n=701,664)

	number	PY	event	Mortality Rate (95% CI)	Crude (HR)	Model 1 (HR)	Model 2 (HR)
Total		6,543,785.1	1,299	1.99 (1.88 - 2.1)			
no FLD	510,726 (72.79)	4,803,746.1	818	1.7 (1.59 - 1.82)	1 (reference)	1 (reference)	1 (reference)
NAFLD-only	11,612 (1.65)	109,053.86	12	1.1 (0.62 - 1.94)	0.65 (0.36-1.14)	0.67 (0.38-1.18)	0.67 (0.38-1.19)
MAFLD-only	31,795 (4.53)	254,224.79	83	3.26 (2.63 - 4.05)	2.11 (1.69-2.65)	1.35 (1.07-1.70)	1.35 (1.07-1.70)
Both FLD (NAFLD & MAFLD)	145,936 (20.8)	1,364,264.1	380	2.79 (2.52 - 3.08)	1.63 (1.44-1.84)	1.09 (0.97-1.23)	1.10 (0.97-1.24)
AFLD & non-MAFLD	1,595 (0.23)	12,496.24	6	4.8 (2.16 - 10.69)	3.18 (1.42-7.10)	1.91 (0.85-4.27)	1.90 (0.85-4.24)

Model 1 : Adjusted for age, sex, education, smoking, regular exercise (3 times/week)

Model 2 : Adjusted for age, sex, education, smoking, regular exercise (3 times/week), and plasma LDL-cholesterol

Abbreviations: PY, person-year; CI, confidence interval; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; FLD, fatty liver disease; AFLD, alcoholic fatty liver disease.