



Associations between metabolic dysfunction-associated fatty liver disease and extrahepatic cancers: a cohort in China

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Background: To evaluate the associations between a new definition of metabolic dysfunction-associated fatty liver disease (MAFLD) and extrahepatic cancers and compare with nonalcoholic fatty liver disease (NAFLD).

Methods: We enrolled 151,391 Chinese participants in the Kailuan cohort. Hepatic steatosis was detected by abdominal ultrasound. Fine and Gray competing risk regression models were used to estimate hazard ratios (HRs) and 95% confidence interval (CI) between MAFLD and extrahepatic cancers.

Results: MAFLD was associated with increased risk of prostate (HR =1.49, 95% CI: 1.07–2.08) and obesity-related cancers, including thyroid (HR =1.47, 95% CI: 1.01–2.12), kidney (HR =1.54, 95% CI: 1.18–2.00), colorectal (HR =1.15, 95% CI: 0.98–1.34) and breast cancer (HR =1.31, 95% CI: 1.04–1.66). The results were consistent in NAFLD *vs.* non-NAFLD and MAFLD-NAFLD *vs.* neither FLD. Compared with the neither FLD group, the NAFLD-only group had a higher risk of extrahepatic cancers (HR =1.57, 95% CI: 1.18–2.09), esophageal (HR =5.11, 95% CI: 2.25–11.62), and bladder cancer (HR =3.36, 95% CI: 1.23–9.17). The additional risk of extrahepatic cancers (HR =1.42, 95% CI: 1.17–1.73), esophageal (HR =4.37, 95% CI: 2.55–7.49), and breast cancer (HR =1.99, 95% CI: 1.01–3.92) was observed in MAFLD with metabolic dysregulation, and kidney (HR =1.83, 95% CI: 1.38–2.43), prostate (HR =1.46, 95% CI: 1.00–2.14) and breast cancer (HR =1.33, 95% CI: 1.02–1.74) was observed in MAFLD with overweight and metabolic dysregulation, as well as colorectal (HR =1.45, 95% CI: 1.07–1.96) and prostate cancer (HR =2.44, 95% CI: 1.42–4.21) in MAFLD with three risk factors. Additionally, MAFLD with excessive alcohol consumption would increase extrahepatic cancers (HR =1.14, 95% CI: 1.01–1.29) and breast cancer (HR =7.27, 95% CI: 2.33–22.69) risk.

Conclusions: MAFLD and NAFLD shared similar excessive risks of obesity-related cancers, suggesting a driving role of FLD in these cancers. Metabolic dysregulation beyond obesity may play additional kidney, colorectal, and prostate cancer risks in MAFLD patients. It may be helpful in the clinic to relieve symptoms by treating metabolic disorders and preventing adverse outcomes of extrahepatic cancers.

Keywords: Metabolic dysfunction-associated fatty liver disease (MAFLD); nonalcoholic fatty liver disease (NAFLD); extrahepatic cancers; metabolic risk; dual etiology

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Introduction

Nonalcoholic fatty liver disease (NAFLD), characterized by hepatic steatosis after excluding competing liver disease etiologies, is a rapidly increasing common chronic liver disease affecting 25.2% of the global adult population (1) and 20.1% of the adults in China (2). NAFLD has been reported as a risk factor for some extrahepatic cancers, i.e., colorectal, cholangiocarcinoma, breast, gastric, pancreatic, prostate, and esophageal cancer (3,4).

However, NAFLD's heterogeneous pathogenesis and inaccuracies terminology has posed significant challenges to accurate diagnosis and treatment regimens development. Therefore, a panel of international experts from 22 countries proposed a new definition that is both comprehensive yet simple for the diagnosis of metabolic dysfunction-associated fatty liver disease (MAFLD) (5,6). Several studies have reported that this new definition could replace NAFLD, representing the real relationship with adverse outcomes, such as cardiovascular disease (7-9), chronic kidney disease (9-11), and death (9,12). Also, some studies demonstrated a positive association between MAFLD and hepatocellular cancer and extrahepatic cancers (9,13,14). Although some studies showed that the MAFLD definition might better identify significant fibrosis (15) and cardiovascular disease (CVD) risk (16,17) compared to NAFLD, it remains unclear the difference of the association between MAFLD, NAFLD, and extrahepatic cancers.

Therefore, this study aimed to examine the association between MAFLD and extrahepatic cancers in the general population and compare with NAFLD's findings based on the same cohort. We present this article in accordance with the STROBE reporting checklist (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-546/rc>).

Methods

Study design and participants

The Kailuan cohort was established in the Kailuan community in 2006 in Tangshan, Hebei Province, China, where each participant underwent a comprehensive check-up every 2 years (18). In our study, 159,018 participants aged 12–109 years who underwent a check-up between June 2006 and April 2014 were recruited. After excluding those who lack abdominal “real-time” ultrasonography (n=6,864), with self-reported or diagnosed cancer (n=504) or liver cirrhosis (n=250) at baseline, and those younger than 18 years old (n=9), 151,391 participants were finally included (Figure S1).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Ethics Committees of the Kailuan General Hospital approved this study. All participants provided informed consent forms.

Ascertainment of MAFLD and NAFLD

According to the criteria for the diagnosis of MAFLD proposed in 2020 (5), MAFLD was diagnosed as evidence of hepatic steatosis, with one of the following three criteria, (I) overweight/obesity [body mass index (BMI) ≥ 23.00 kg/m² for Asians], (II) type 2 diabetes mellitus, or (III) metabolic dysregulation. In this study, experienced clinicians defined hepatic steatosis by abdominal ultrasound according to Asia-Pacific region definition (19). Type 2 diabetes mellitus was defined according to fasting blood glucose (FBG) level ≥ 7.0 mmol/L, oral hypoglycemic agent or insulin use, or a self-reported physician diagnosis. Metabolic dysregulation was determined by the presence of at least two metabolic risk abnormalities of the followings: (I) waist circumference $\geq 90/80$ cm in men and women, (II) blood pressure $\geq 130/85$ mmHg or specific drug treatment, (III) plasma triglycerides (TG) ≥ 1.70 mmol/L or specific drug treatment, (IV) plasma high-density lipoprotein-cholesterol (HDL-C) < 1.0 mmol/L for men and < 1.3 mmol/L for women or specific drug treatment, (V) prediabetes as FBG levels 5.6 to 6.9 mmol/L, (VI) plasma high-sensitivity C-reactive protein (hs-CRP) level > 2 mg/L (5). Non-MAFLD was defined as the subjects who did not meet the diagnosis criteria of MAFLD, which included those without fatty liver disease or those with fatty liver disease but did not meet one of the three criteria described above.

We further divided MAFLD patients into seven subgroups according to their metabolic conditions: (I) overweight (BMI ≥ 23 kg/m²) only; (II) diabetes only (DB-only); (III) metabolic dysregulation only (MD-only, only with at least two metabolic risk abnormalities); (IV) overweight and DB; (V) overweight and MD; (VI) DB and MD; (VII) overweight, DB, and MD.

NAFLD was diagnosed as having fatty liver in the participants without excessive alcohol intake (≥ 30 g/day for men and ≥ 20 g/day for women) or positive hepatitis B surface antigen (HBsAg) (19,20).

Cancer assessment and follow-up

Incident cancer cases were collected by self-report, linked with the local vital statistics data, the Tangshan

medical insurance system, and the Kailuan Social Security Information System. Then, all the cases were validated by checking medical and discharge records by clinical experts as in the previous study (21). Extrahepatic cancers were selected, and 12 of the most common extrahepatic cancers were identified. The follow-up started from the baseline and ended at the date of cancer diagnosis, death, or study termination (12-31-2019).

Covariates at baseline

Demographic characteristics (age, sex, education level), lifestyle factors (smoking status, alcohol intake, and physical activity), medical history, related medication, and laboratory tests were collected as in the previous study (21). Excessive alcohol consumption was defined as alcohol intake ≥ 30 g/day for men or ≥ 20 g/day for women. Physical activity level was categorized as inactive, moderately active, and active according to the frequency of physical activity (≥ 20 min/time) during leisure time. Weight, height, and blood pressure were measured, and BMI was calculated as weight in kilograms divided by height in square meters. In addition, the total cholesterol (TC), TG, HDL-C, alanine aminotransferase (ALT), hs-CRP, FBG, and HBsAg were tested in the central laboratory of the Kailuan General Hospital.

Statistical analyses

The covariates between MAFLD status were compared using *t*-test, analysis of variance test, or Wilcoxon signed-rank test for continuous variables and chi-square test for categorical variables. Cumulative incidence was estimated using the Kaplan-Meier methods. The incidence between MAFLD and non-MAFLD was compared by log-rank test. Considering the competing risk of death, we used three Fine and Gray competing risk regression models (22) to analyze the associations between MAFLD and extrahepatic cancers: unadjusted, age-, sex-adjusted, and multivariable-adjusted model (adjusting sex, age, education level, smoking, alcohol consumption, physical activity, and family history of cancer). Stratified analyses were conducted by sex and age (<50 vs. ≥ 50 years, the median age of our cohort).

Due to the partial overlap between MAFLD and NAFLD, we used the generalized estimating equation (GEE) model to compare the direct incidence difference between MAFLD and NAFLD as the previous studies described (16). Then we separated all participants into four mutually exclusive groups (neither-FLD, NAFLD-

only, MAFLD-only, and MAFLD-NAFLD) to compare the different associations of NAFLD and MAFLD on cancer (12). We also investigated the association of subgroup of MAFLD by dividing MAFLD into different subgroups according to BMI, diabetes and metabolic dysregulation, or HBsAg and drinking status. Finally, we conducted sensitivity analyses by excluding the participants who developed incident cancers within the three years of follow-up and with the original dataset without imputation to test the robustness of our results.

All analyses were performed with Statistical Analysis System (SAS) (version 9.4, SAS Institute Inc. Cary, NC, USA). Missing data were imputed using Multivariate Imputation by Chained Equations (MICE) by R (version 3.5.2., <https://www.rproject.org/>) (23). Details of missing data were presented in [Table S1](#). All tests were two-sided, with statistical significance set at $P < 0.05$.

Results

Population characteristics

Among 151,391 participants, the prevalence of MAFLD was 31.4% (32.6% in men and 26.5% in women). Participants with MAFLD showed higher levels of age, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, TG, TC, low-density lipoprotein-cholesterol (LDL-C), hs-CRP, and ALT, as well as a lower level of HDL-C. In addition, higher proportions of males, lower education level, unhealthy lifestyle factors like smoking, excessive alcohol consumption, and lower prevalence of positive HBsAg than those without MAFLD were also seen ([Table 1](#)).

MAFLD and extrahepatic cancers

After a median follow-up of 12.64 years, 5,405 incident extrahepatic cancers were identified. After adjusting the competing risk of death, the cumulative incidence of extrahepatic cancers and site-specific cancers with and without MAFLD was presented in [Figure 1](#) and [Figures S2,S3](#). Log-rank tests showed that extrahepatic cancers ($P=0.003$), colorectal ($P=0.037$), kidney ($P<0.001$), breast cancers ($P<0.001$) were significantly different.

[Table 2](#) showed the associations between MAFLD and extrahepatic cancers under different models. The significantly increased risk of all extrahepatic cancers was only observed in the unadjusted model [hazard ratio (HR) = 1.09, 95% confidence interval (CI): 1.03–1.15]. For the

Table 1 Baseline characteristics in the participants with and without MAFLD

Characteristics	Non-MAFLD	MAFLD	P
n	103,854	47,537	
Age, years	48.8±14.5	51.0±12.6	<0.001
Male	82,808 (79.7)	39,957 (84.1)	<0.001
Education level			<0.001
Junior high school or below	76,700 (73.9)	36,422 (76.6)	
Senior high school or higher	27,154 (26.1)	11,115 (23.4)	
Past/current smoking	41,288 (39.8)	20,591 (43.3)	<0.001
Excessive alcohol consumption	13,752 (13.2)	8,373 (17.6)	<0.001
Physical activity			0.384
Inactive	15,050 (14.5)	6,879 (14.5)	
Moderately active	73,350 (70.6)	33,455 (70.4)	
Active	15,454 (14.9)	7,203 (15.2)	
Family history of cancers			<0.001
Yes	4,369 (4.2)	2,508 (5.3)	
No	64,348 (62.0)	28,618 (60.2)	
Unknown	35,137 (33.8)	16,411 (34.5)	
BMI, kg/m ²	23.8±3.1	27.4±3.2	<0.001
WC, cm	84.0±9.5	92.5±9.2	<0.001
SBP, mmHg	126.6±20.1	135.8±20.5	<0.001
DBP, mmHg	81.4±11.2	87.2±11.6	<0.001
FBG, mmol/L	5.3±1.4	5.9±2.0	<0.001
TG, mmol/L	1.4±1.0	2.2±1.5	<0.001
TC, mmol/L	4.8±1.1	5.1±1.2	<0.001
LDL-C, mmol/L	2.4±0.9	2.5±0.9	<0.001
HDL-C, mmol/L	1.5±0.3	1.4±0.4	<0.001
hs-CRP, mg/dL	0.8 (0.3, 2.0)	1.4 (0.6, 3.2)	<0.001
ALT, U/L	17.0 (12.0, 23.0)	22.7 (16.1, 32.0)	<0.001
HBsAg positive	2,986 (2.9)	1,061 (2.2)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) of participants with a condition. MAFLD, metabolic associated fatty liver disease; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen.

site-specific cancers, MAFLD was associated with kidney and breast cancer in the unadjusted, age-, sex-adjusted, and multivariable-adjusted model. The HRs (95% CI) in multivariate model were 1.54 (1.18–2.00) and 1.31 (1.04–1.66), respectively. For thyroid and prostate cancer, an increased risk was observed in age-, sex-adjusted and multivariate-adjusted models, with HRs (95% CI) of 1.47 (1.01–2.12) and 1.49 (1.07–2.08) in the multivariate-adjusted model, respectively. For colorectal cancer, an increased risk was observed in unadjusted and marginally significant in age-, sex-adjusted, and multivariate model, with HRs (95% CI) of 1.15 (0.98–1.34) in the multivariate-adjusted model.

There was no interaction between age, sex, and MAFLD in cancer occurrence after stratified by sex and age (details in [Tables S2,S3](#)).

Comparison between MAFLD, NAFLD, and extrahepatic cancers

The proportion of NAFLD was lower than that of MAFLD in our population (26.0% vs. 31.4%). [Table S4](#) showed the characteristics of the participants with NAFLD and non-NAFLD. Compared with non-NAFLD, the HR (95% CI) of NAFLD was 1.58 (1.09–2.30), 1.21 (1.02–1.43), 1.55 (1.17–2.05), 1.44 (1.01–2.06) and 1.28 (1.01–1.62) for developing thyroid, colorectal, kidney, prostate, and breast cancer in the multivariate-adjusted model ([Table S5](#)).

Considering the overlap between MAFLD and NAFLD, we used the GEE model to compare the incidence of extrahepatic cancers ([Table S6](#)). We only observed a significantly lower risk of esophageal [adjusted odds ratio (OR) =0.19, 95% CI: 0.08–0.45] and bladder cancer (adjusted OR =0.33, 95% CI: 0.12–0.95) in patients with MAFLD than in patients with NAFLD.

When considering the combination of MAFLD and NAFLD, the neither FLD, NAFLD-only, MAFLD-only, and MAFLD-NAFLD group accounted for 67.9%, 0.6%, 6.2%, and 25.3%, respectively. MAFLD-only group had the highest proportion of past/current smokers, excessive alcohol consumption, positive HBsAg, and ALT levels. In comparison, the NAFLD-only group had the lowest BMI, WC, FBG, SBP, and DBP ([Table S7](#)). [Table 3](#) showed the extrahepatic cancers risks by the combination of MAFLD and NAFLD status. Compared with the neither FLD group, MAFLD-NAFLD participants showed higher risks of the thyroid (HR =1.62, 95% CI: 1.11–2.35), colorectal (HR =1.19, 95% CI: 1.00–1.41), kidney (HR =1.58, 95% CI: 1.19–2.09), prostate (HR =1.48, 95% CI: 1.04–2.11), and

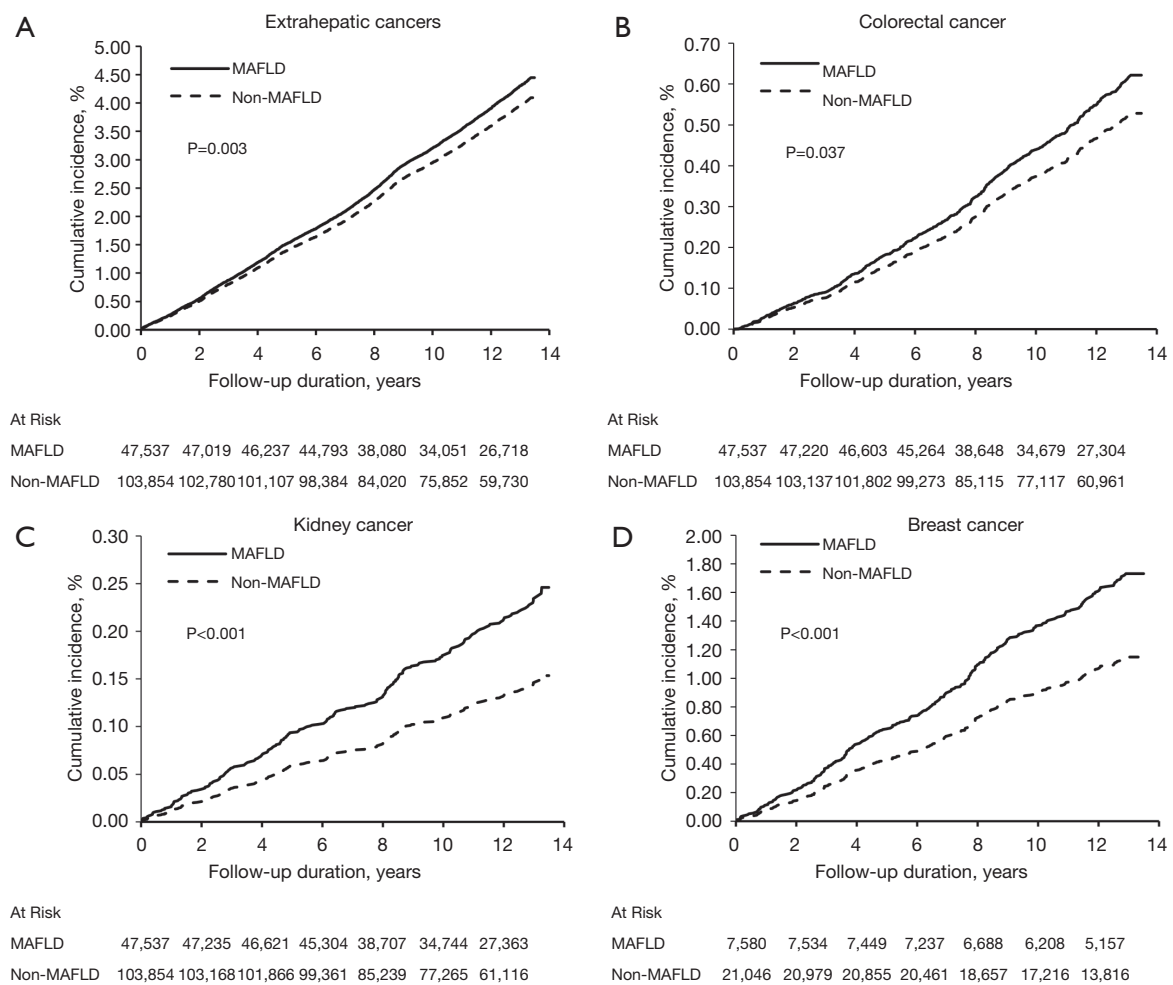


Figure 1 Cumulative incidence of extrahepatic (A), colorectal (B), kidney (C) and breast cancer (D) after adjusting competing risk of death. MAFLD, metabolic associated fatty liver disease.

breast cancer (HR =1.29, 95% CI: 1.02–1.64). In addition, a significantly higher risk of extrahepatic cancers (HR =1.57, 95% CI: 1.18–2.09), esophageal (HR =5.11, 95% CI: 2.25–11.62), and bladder cancer (HR =3.36, 95% CI: 1.23–9.17) was observed in the NAFLD-only group (Table 3).

Associations between subgroup of MAFLD and extrahepatic cancers

MAFLD individuals were divided into seven subgroups according to BMI, diabetes, and metabolic dysregulation. The baseline characteristics of subgroups were presented in Table S8, and the association results were observed in Table 4. Compared with non-MAFLD, MAFLD with MD-only group showed an increased risk of extrahepatic cancers

(HR =1.42, 95% CI: 1.17–1.73), esophageal (adjusted HR =4.37, 95% CI: 2.55–7.49), and breast cancer (HR =1.99, 95% CI: 1.01–3.92) after adjusting covariates. Also, increased risk of the kidney (HR =1.83, 95% CI: 1.38–2.43), prostate (HR =1.46, 95% CI: 1.00–2.14), and breast cancer (HR =1.33, 95% CI: 1.02–1.74) were found in MAFLD with both overweight/obesity and MD. In addition, MAFLD with three metabolic disorders had an increased risk of colorectal (HR =1.45, 95% CI: 1.07–1.96) and prostate cancer (HR =2.44, 95% CI: 1.42–4.21).

Associations between MAFLD with other risk factors and extrahepatic cancers

Table S9 and Table 5 showed the baseline characteristics

Table 2 Associations between MAFLD and extrahepatic cancers in all participants

Cancer types	MAFLD		Non-MAFLD		Unadjusted		Age-, sex-adjusted		Multivariate adjusted [†]	
	No. of events	Incidence rate (/10 ⁵ PYs)	No. of events	Incidence rate (/10 ⁵ PYs)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Extrahepatic	1,790	344.90	3,615	316.31	1.09 (1.03–1.15)	0.003	1.05 (0.99–1.11)	0.123	1.05 (0.99–1.11)	0.114
Thyroid	46	8.75	85	7.36	1.19 (0.83–1.70)	0.343	1.44 (1.00–2.08)	0.049	1.47 (1.01–2.12)	0.042
Lung	495	94.39	1138	98.71	0.95 (0.85–1.05)	0.330	0.92 (0.83–1.02)	0.126	0.92 (0.83–1.02)	0.130
Esophageal	68	12.94	158	13.67	0.95 (0.71–1.26)	0.698	0.91 (0.69–1.21)	0.522	0.89 (0.67–1.15)	0.421
Gastric	132	25.13	278	24.07	1.04 (0.85–1.28)	0.699	1.01 (0.82–1.24)	0.924	1.02 (0.83–1.25)	0.863
Biliary	29	5.52	72	6.23	0.88 (0.57–1.36)	0.575	0.87 (0.57–1.34)	0.530	0.89 (0.58–1.37)	0.595
Pancreatic	44	8.37	100	8.65	0.97 (0.68–1.38)	0.845	0.94 (0.66–1.34)	0.729	0.97 (0.68–1.38)	0.849
Small intestine	16	3.04	23	1.99	1.53 (0.81–2.89)	0.193	1.47 (0.78–2.78)	0.236	1.52 (0.80–2.87)	0.199
Colorectal	250	47.65	466	40.38	1.18 (1.01–1.38)	0.035	1.14 (0.98–1.33)	0.090	1.15 (0.98–1.34)	0.078
Kidney	98	18.66	134	11.60	1.59 (1.22–2.06)	0.001	1.53 (1.18–1.99)	0.002	1.54 (1.18–2.00)	0.001
Bladder	66	12.56	147	12.72	0.99 (0.74–1.32)	0.921	0.99 (0.74–1.32)	0.941	0.98 (0.73–1.32)	0.903
Prostate [§]	59	3.28	94	10.28	1.29 (0.93–1.80)	0.122	1.44 (1.04–2.01)	0.030	1.49 (1.07–2.08)	0.018
Breast [¶]	120	136.63	217	89.42	1.51 (1.21–1.89)	<0.001	1.30 (1.03–1.65)	0.028	1.31 (1.04–1.66)	0.024

[†], adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers; [§], only for men; [¶], only for women. MAFLD, metabolic associated fatty liver disease; PYs, person-years; HR, hazard ratio; CI, confidence interval.

Table 3 Extrahepatic cancers risks in participants by the combination of MAFLD and NAFLD status

Cancer types	Incidence rate (/10 ⁵ PYs)				HR (95% CI)			
	Neither FLD [†]	NAFLD-only	MAFLD-only	MAFLD-NAFLD [‡]	Neither FLD	NAFLD-only	MAFLD-only	MAFLD-NAFLD
Extrahepatic	315.01	451.24	350.07	343.70	1	1.57 (1.18–2.09)	1.01 (0.89–1.15)	1.06 (0.99–1.13)
Thyroid	7.43	0.00	2.01	10.33	1	–	0.41 (0.09–1.82)	1.62 (1.11–2.35)
Lung	98.70	99.73	114.02	89.82	1	1.10 (0.61–2.00)	0.90 (0.72–1.13)	0.93 (0.83–1.05)
Esophageal	13.28	54.27	24.17	10.32	1	5.11 (2.25–11.62)	0.86 (0.53–1.41)	0.95 (0.67–1.35)
Gastric	23.95	36.18	34.26	23.00	1	1.60 (0.59–4.30)	1.51 (0.96–2.36)	0.93 (0.73–1.17)
Biliary	6.20	9.04	4.03	5.86	1	1.60 (0.22–11.56)	0.79 (0.27–2.38)	0.91 (0.57–1.45)
Pancreatic	8.65	9.04	6.04	8.92	1	1.13 (0.16–8.08)	0.70 (0.29–1.72)	1.02 (0.70–1.50)
Small intestine	2.01	0.00	3.02	3.05	1	–	2.85 (0.85–9.55)	1.36 (0.69–2.72)
Colorectal	39.98	81.78	50.44	47.00	1	2.32 (1.19–4.49)	1.06 (0.74–1.50)	1.19 (1.00–1.41)
Kidney	11.62	9.05	16.12	19.25	1	0.76 (0.11–5.45)	1.42 (0.74–2.72)	1.58 (1.19–2.09)
Bladder	12.50	36.23	14.10	12.20	1	3.36 (1.23–9.17)	0.79 (0.43–1.46)	1.07 (0.77–1.49)
Prostate [§]	10.42	0.00	8.23	14.72	1	–	1.45 (0.59–3.54)	1.48 (1.04–2.11)
Breast [¶]	89.27	109.60	241.97	134.09	1	1.19 (0.30–4.79)	2.01 (0.90–4.48)	1.29 (1.02–1.64)

The model was adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [†], neither FLD: participants without MAFLD or NAFLD; [‡], MAFLD-NAFLD: participants with MAFLD and NAFLD; [§], only for men; [¶], only for women; –, no cancer was observed in this group. MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; PYs, person-years; FLD, fatty liver disease; HR, hazard ratio; CI, confidence interval.

Table 4 HRs of extrahepatic cancers in participants by MAFLD risk factors

Cancer types	One			Two			Three
	Overweight-only	DB-only	MD-only	Overweight and DB	Overweight and MD	DB and MD	
Extrahepatic	0.91 (0.78–1.07)	0.52 (0.17–1.60)	1.42 (1.17–1.73)	1.23 (0.89–1.71)	1.04 (0.97–1.11)	1.36 (0.89–2.07)	1.05 (0.93–1.19)
Thyroid	1.97 (0.95–4.06)	–	0.78 (0.11–5.62)	2.26 (0.31–16.42)	1.45 (0.95–2.20)	–	1.25 (0.50–3.11)
Lung	0.92 (0.70–1.20)	1.00 (0.25–4.04)	1.26 (0.87–1.82)	1.45 (0.85–2.45)	0.93 (0.82–1.05)	0.59 (0.19–1.84)	0.78 (0.60–1.01)
Esophageal	0.53 (0.22–1.30)	–	4.37 (2.55–7.49)	–	0.75 (0.53–1.07)	1.46 (0.20–10.50)	0.86 (0.44–1.68)
Gastric	0.89 (0.51–1.55)	–	1.28 (0.60–2.70)	0.84 (0.21–3.38)	1.05 (0.83–1.33)	0.84 (0.12–6.05)	0.95 (0.59–1.53)
Biliary	1.51 (0.61–3.74)	–	0.70 (0.10–5.00)	1.72 (0.24–12.38)	0.69 (0.40–1.21)	–	1.37 (0.63–2.97)
Pancreatic	1.19 (0.52–2.73)	–	2.11 (0.78–5.73)	–	0.89 (0.58–1.36)	–	1.02 (0.48–2.21)
Small intestine	0.81 (0.11–5.91)	–	–	–	1.71 (0.85–3.43)	–	1.95 (0.58–6.51)
Colorectal	0.91 (0.59–1.40)	–	1.60 (0.96–2.68)	1.80 (0.85–3.80)	1.07 (0.89–1.29)	1.44 (0.46–4.46)	1.45 (1.07–1.96)
Kidney	1.16 (0.59–2.28)	–	0.79 (0.20–3.20)	0.87 (0.12–6.19)	1.83 (1.38–2.43)	–	1.02 (0.52–2.00)
Bladder	0.98 (0.46–2.09)	–	0.64 (0.16–2.61)	2.39 (0.76–7.51)	0.90 (0.63–1.28)	1.45 (0.20–10.40)	1.27 (0.72–2.23)
Prostate [§]	0.51 (0.13–2.09)	–	1.22 (0.30–4.98)	1.37 (0.19–9.86)	1.46 (1.00–2.14)	–	2.44 (1.42–4.21)
Breast [¶]	0.83 (0.37–1.87)	–	1.99 (1.01–3.92)	1.46 (0.20–10.58)	1.33 (1.02–1.74)	2.65 (0.84–8.33)	1.17 (0.71–1.93)

Data were presented as HR (95% confidence interval). The model was adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [§], only for men; [¶], only for women; –, no cancer was observed in this group. HR, hazards ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; DB, diabetes; MD, metabolic dysregulation.

Table 5 HRs of extrahepatic cancers in participants stratified by dual etiology of MAFLD

Cancer types	MAFLD without positive HBsAg and excessive alcohol consumption	MAFLD with positive HBsAg only	MAFLD with excessive alcohol consumption only	MAFLD with excessive alcohol consumption and positive HBsAg
Extrahepatic	1.03 (0.97–1.10)	1.17 (0.83–1.65)	1.14 (1.01–1.29)	1.48 (0.74–2.95)
Thyroid	1.57 (1.08–2.27)	–	0.74 (0.18–3.05)	–
Lung	0.90 (0.80–1.01)	1.31 (0.73–2.37)	1.00 (0.81–1.24)	2.03 (0.76–5.42)
Esophageal	0.76 (0.55–1.07)	1.66 (0.41–6.71)	1.41 (0.88–2.25)	3.29 (0.46–23.38)
Gastric	0.93 (0.74–1.17)	1.90 (0.71–5.11)	1.36 (0.92–2.02)	2.35 (0.33–16.84)
Biliary	0.91 (0.58–1.43)	–	0.87 (0.32–2.40)	–
Pancreatic	1.02 (0.70–1.49)	–	0.78 (0.34–1.78)	–
Small intestine	1.47 (0.74–2.89)	–	1.95 (0.51–7.41)	–
Colorectal	1.12 (0.95–1.33)	1.71 (0.76–3.83)	1.29 (0.93–1.78)	–
Kidney	1.60 (1.22–2.11)	1.84 (0.46–7.43)	1.28 (0.72–2.26)	–
Bladder	0.97 (0.70–1.34)	–	1.20 (0.69–2.11)	–
Prostate [§]	1.54 (1.09–2.18)	1.81 (0.25–12.91)	1.17 (0.53–2.55)	–
Breast [¶]	1.29 (1.02–1.64)	1.23 (0.30–5.00)	7.27 (2.33–22.69)	*

Data were presented as HR (95% confidence interval). The model was adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [§], only for men; [¶], only for women; *, no participants in this group; –, no cancer was observed in this group. HR, hazards ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; HBsAg, hepatitis B surface antigen.

and associations between the MAFLD with or without positive HBsAg, excessive alcohol consumption, and the risk of extrahepatic cancers among MAFLD individuals. MAFLD without positive HBsAg and excessive alcohol consumption accounted for 93.9% of all MAFLD patients. Compared with non-MAFLD, MAFLD without positive HBsAg and excessive alcohol consumption had a higher chance of thyroid (HR =1.57, 95% CI: 1.08–2.27), kidney (HR =1.60, 95% CI: 1.22–2.11), prostate (HR =1.54, 95% CI: 1.09–2.18), and breast cancer (HR =1.29, 95% CI: 1.02–1.64). In addition, an increased risk of extrahepatic cancers (HR =1.14, 95% CI: 1.01–1.29) and breast cancer (HR =7.27, 95% CI: 2.33–22.69) was observed in MAFLD with excessive alcohol consumption only, which accounted for 5.4% of the MAFLD patients. However, MAFLD with HBsAg (+) (with or without excessive alcohol consumption) only made up 0.12% and 0.58% of the MAFLD patients. We did not observe any significant difference in extrahepatic cancers between them and non-MAFLD.

Sensitivity analysis

After excluding the participants who had developed incident cancers within the first 3 years of follow-up (Table S10), and the original dataset without imputation (Table S11), the association between MAFLD and thyroid, kidney, prostate, and breast cancer remained constant.

Discussion

This prospective cohort study provides vital results to the knowledge of MAFLD, NAFLD, and their associations with extrahepatic cancers. Firstly, MAFLD was observed to have a higher risk of developing overweight & obesity-related cancers (thyroid, kidney, breast, and colorectal cancer) and prostate cancer. Similar associations were observed in NAFLD *vs.* non-NAFLD, MAFLD-NAFLD *vs.* neither FLD. However, a higher probability of extrahepatic, esophageal, and bladder cancer was only observed in NAFLD-only *vs.* neither FLD group. Secondly, our results showed different site-specific cancer risks in populations with various metabolic components. A higher probability of extrahepatic, esophageal, and breast cancer was demonstrated in MAFLD with MD; kidney, prostate, and breast cancer in MAFLD with overweight and MD; and colorectal and prostate cancer in MAFLD with three risk factors. Lastly, when considering other etiological factors, we observed that MAFLD with excessive alcohol

consumption showed the highest risk of extrahepatic and breast cancer than the other groups.

In our population, increased risk with similar HRs of overweight & obesity-related cancers, including thyroid, kidney, breast, and colorectal cancer, were observed in MAFLD *vs.* non-MAFLD, NAFLD *vs.* non-NAFLD, and MAFLD-NAFLD *vs.* neither FLD. Our results are consistent with a meta-analysis and a Danish cohort study, which showed a positive association between NAFLD and colorectal, prostate, breast, and kidney cancer (3,24). The association between obesity and cancers could be explained by insulin-like growth factor-1, adipokines, chronic inflammation, and sex steroid hormones (25). However, no significant association of overweight & obesity-related cancers was observed in MAFLD with overweight-only *vs.* non-MAFLD, suggesting a driver role of FLD in the occurrence of overweight & obesity-related cancers. Our hypothesis could be demonstrated by a cohort study in a US population that reported a higher risk of extrahepatic cancers in NAFLD than obesity-only (26).

Our study also observed an increased risk of the kidney (HR =1.83, 95% CI: 1.38–2.43) in MAFLD with overweight and metabolic dysregulation, as well as colorectal (HR =1.45, 95% CI: 1.07–1.96) and prostate cancer (HR =2.44, 95% CI: 1.42–4.21) in MAFLD with three risk factors but not in MAFLD with overweight. A close relationship between insulin resistance and prostate (27), kidney (28), and colorectal cancers (29) could partially explain it. Furthermore, our results were consistent with a study from Fukunaga *et al.* (30), which also observed that MAFLD, particularly non-obese MAFLD, could better predict the presence of colorectal adenoma rather than NAFLD. All above results indicate roles of metabolic dysregulation beyond obesity in these three cancers development in MAFLD participants.

Also, our study found a consistent relationship between NAFLD, MAFLD, and prostate cancer. Although meta-analysis reported an inverse association between DB and prostate cancer (31), MAFLD with overweight-MD, MAFLD with overweight-MD-DB groups displayed elevated prostate cancer risk in our cohort. This phenomenon highlights the importance of MD as a comprehensive indicator involved in central obesity, elevated blood pressure, abnormal blood lipids, and systemic inflammatory response, with or without overweight/obesity, in developing prostate cancer (32).

Compared with the neither FLD group, the NAFLD-only group had a higher risk of esophageal (HR =5.11,

95% CI: 2.25–11.62) and bladder cancer (HR =3.36, 95% CI: 1.23–9.17). This relationship may be false-positive because only six esophageal and four bladder cancer cases occurred in the NAFLD-only group. However, another two studies reported a positive relationship between NAFLD and esophageal cancer (a pooled HR =1.77, 95% CI: 1.19–2.62) (3) and one study of NAFLD and bladder cancer (OR =2.61, 95% CI: 1.30–5.22) (33). So, we called for further research with larger populations to validate the results. Once confirmed, it would suggest a unique mechanism between NAFLD and these two cancers.

Clinically meaningful interactions between MAFLD and hepatitis B virus (HBV)/hepatitis C virus (HCV) infection on hepatocellular carcinoma and all cancers were reported by other studies (34). However, the increased risk of all extrahepatic cancers did not reach statistically significant in MAFLD patients with HBsAg (+) (with or without excessive alcohol consumption) in our study. False negativity by the small sample size of the MAFLD-only group in our study population may partially explain it because of only 877 MAFLD with HBsAg (+) only and 184 MAFLD with HBsAg (+) and excessive alcohol consumption. A Finland reported that 30–49 g/day alcohol intake could increase the risk of all cancers in patients with FLD (35). And a Japan cohort reported that ≥ 40 g/day was associated with increased risk for Hepatocarcinogenesis in FLD (36). Our study also found that the risk of breast cancer significantly increased with excessive alcohol consumption, with HR reaching 7.27 (95% CI: 2.33–22.69). Alcohol intake is closely related to breast cancer risk in a positive dose-response relationship (37). Thus result underlines the importance of decreasing alcohol consumption to prevent breast cancer in MAFLD patients.

Several studies have shown better identification of clinical outcomes of MAFLD than NAFLD (38), especially for the Asia-Pacific region where fatty liver disease is frequently observed in lean/normal-weight individuals and patients with concomitant viral hepatitis (34). The consistent relationship between NAFLD, MAFLD, and most cancers in our study also suggests that this definition may be proper in a clinic where more patients in need of treatment can be easily diagnosed. In addition, treatment of metabolic disorders and dual etiology may reduce the incidence of cancers in these high-risk populations.

Before making any recommendations, it is essential to discuss the limitations involved. Firstly, we used abdominal ultrasound to identify fatty liver, which could not detect hepatic steatosis when fat content is <20% (39).

Therefore, misclassification of MAFLD with mild steatosis would underestimate the relationships of MAFLD with cancers. Secondly, 2-hour-post-load glucose, HbA1c, and serum insulin for homeostasis model assessment-insulin resistance scores were unavailable in our cohort, which might misclassify MAFLD to be non-MAFLD and cause underestimating the association between MAFLD and cancers. Thirdly, we did not have data on other potential confounders to be further adjusted for each site-specific cancer. For instance, we were not considering menopause status when estimating the association between MAFLD and breast cancer which would bring about residual confounding. Thus, more comprehensive and detailed studies are needed to verify the results.

Conclusions

This study demonstrated increased risks with similar HRs of prostate cancer and obesity-related cancers, including thyroid, kidney, breast, and colorectal cancer in MAFLD and NAFLD. MAFLD with more metabolic disorders beyond obesity, especially MD, leads to other risks of kidney, colorectal, and prostate cancer. Additionally, MAFLD with excessive alcohol consumption would dramatically increase extrahepatic and breast cancer risk. Though the MAFLD definition still leaves a great deal of ambiguity, it may be helpful in the clinic to relieve symptoms by treating metabolic disorders and preventing adverse outcomes like extrahepatic cancers.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-546/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-546/cif>)

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was based on The Kailuan Study (trial identification: ChiCTR-TNC-11001489), approved by ethics committee of Kailuan General Hospital, and Institute of Basic Medical Sciences Chinese Academy of Medical Sciences Informed consent was taken from all individual participants.

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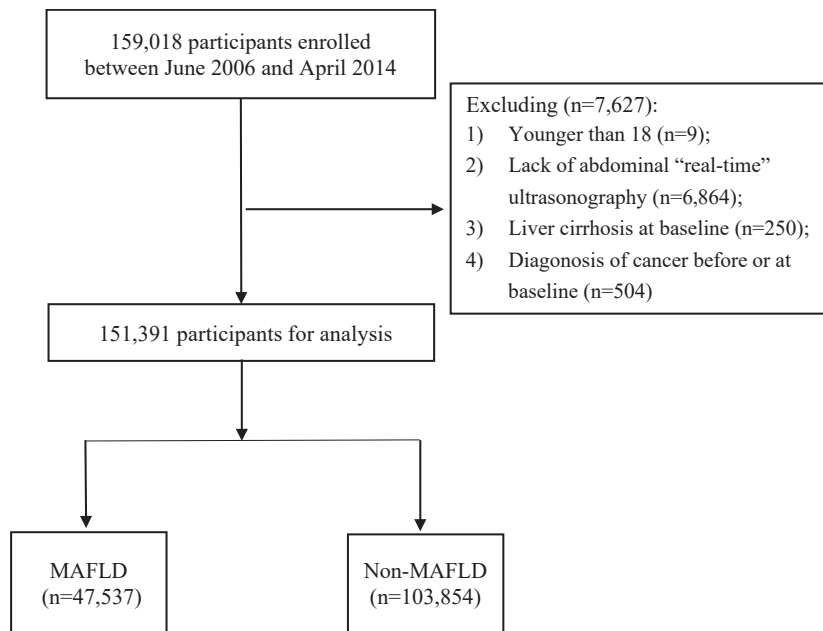


Figure S1 Flow chart. MAFLD, metabolic dysfunction-associated fatty liver disease.

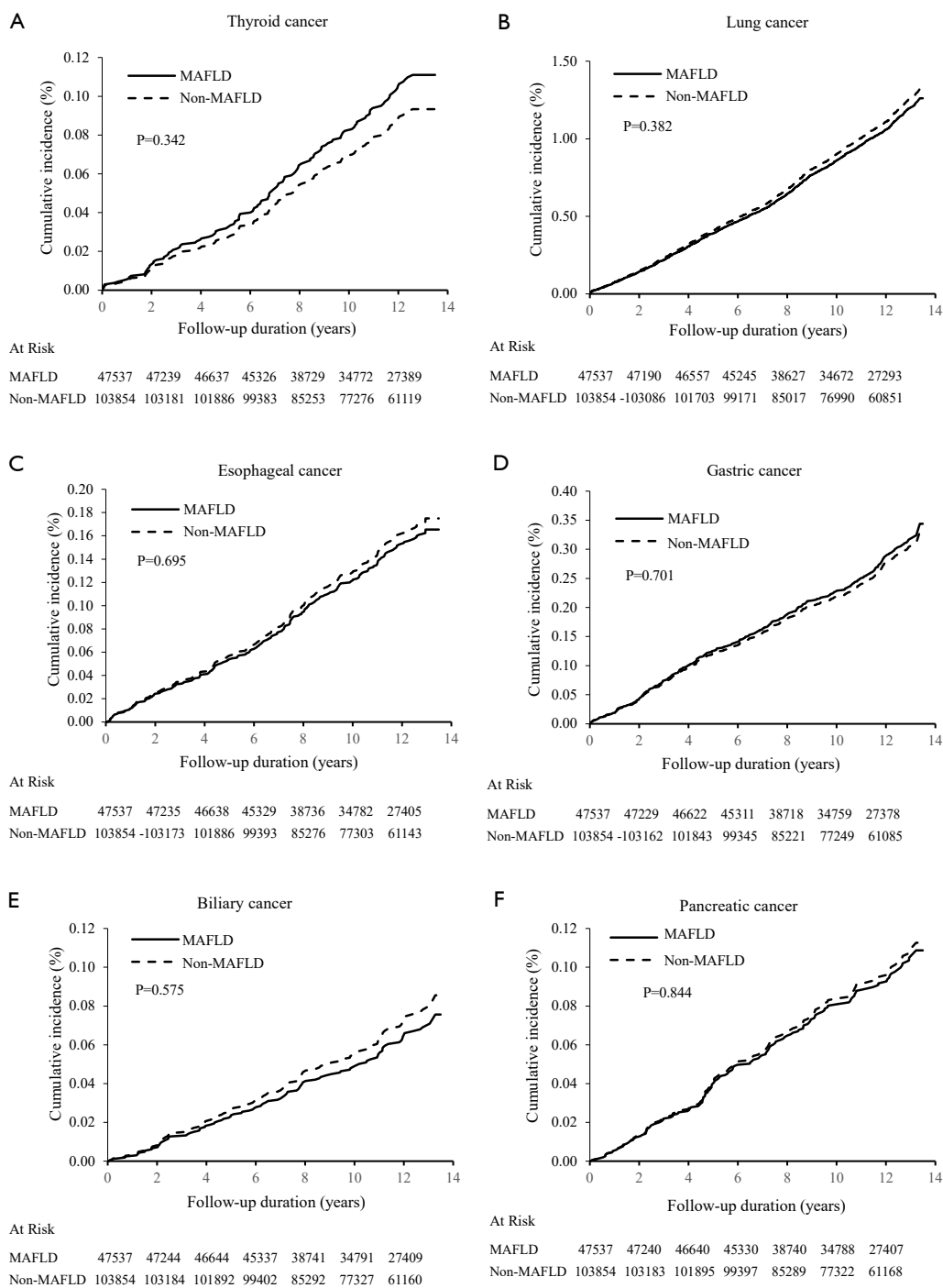


Figure S2 Cumulative incidence of the thyroid (A), lung (B), esophageal (C), gastric (D), biliary (E), and pancreatic cancer (F) after adjusting competing risk of death. MAFLD, metabolic dysfunction-associated fatty liver disease.

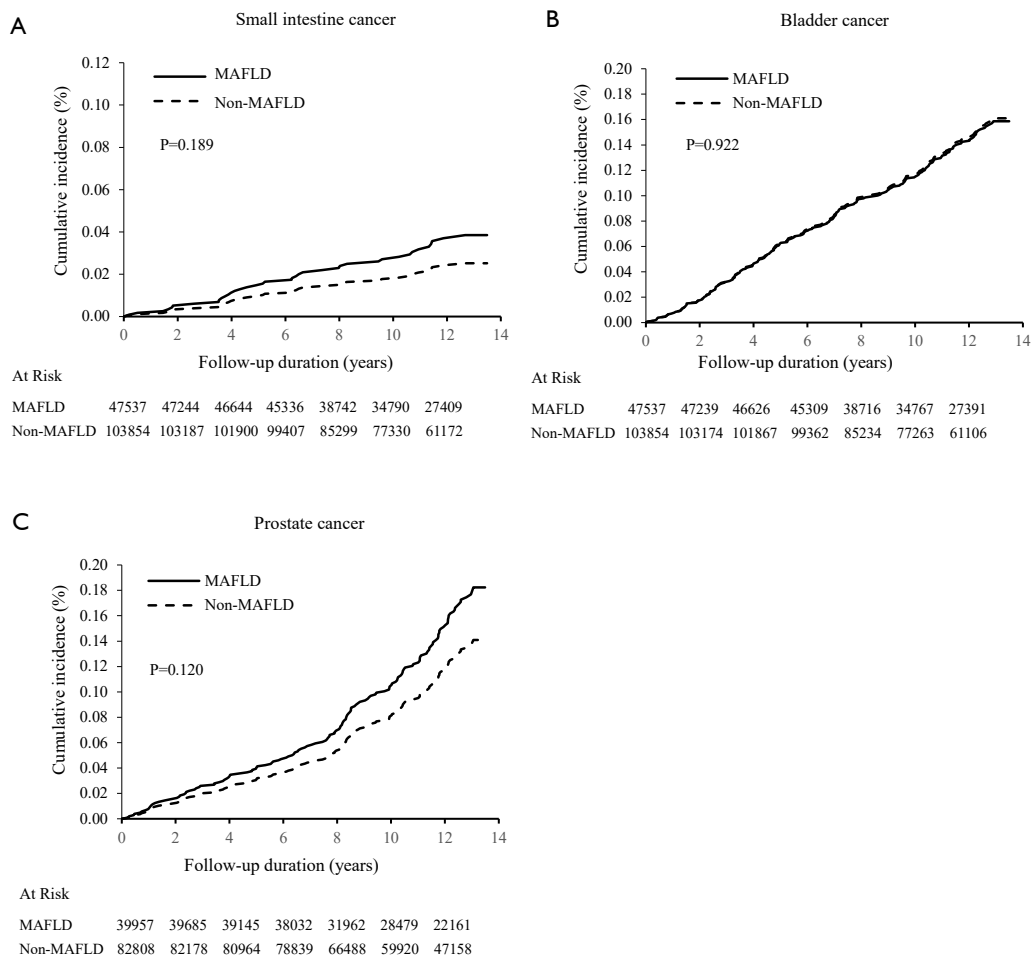


Figure S3 Cumulative incidence of the small intestine (A), bladder (B), and prostate cancer (C) after adjusting competing risk of death. MAFLD, metabolic dysfunction-associated fatty liver disease.

Table S1 Missing covariate rates

Variables	Total	Missing	Percentage
Age, years	151,391	1,003	0.7
Male	151,391	541	0.4
Education level	151,391	4,030	2.7
Smoking	151,391	2,952	1.9
Alcohol	151,391	21,090	13.9
Physical activity	151,391	3,883	2.6
Family history of cancers	151,391	51,548	34.0
BMI, kg/m ²	151,391	2,403	1.6
WC, cm	151,391	4,753	3.1
SBP, mmHg	151,391	1,239	0.8
DBP, mmHg	151,391	1,239	0.8
FBG, mmol/L	151,391	1,416	0.9
TG, mmol/L	151,391	1,767	1.2
TC, mmol/L	151,391	1,383	0.9
LDL-C, mmol/L	151,391	1,621	1.1
HDL-C, mmol/L	151,391	4,168	2.8
hs-CRP, mg/dL	151,391	5,847	3.9
ALT, U/L	151,391	1,748	1.2
HBsAg positive	151,391	3,087	2.0

ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S2 Baseline characteristics in the participants with and without MAFLD by sex

Characteristics	Male subjects			Female subjects		
	Non-MAFLD	MAFLD	P	Non-MAFLD	MAFLD	P
n	82,808	39,957		21,046	7,580	
Age, years	49.8±14.8	50.5±12.9	<0.001	44.6±12.5	53.3±10.6	<0.001
Education level			0.915			<0.001
Junior high school or below	63,793 (77.0)	30,770 (77.0)		12,907 (61.3)	5,652 (74.6)	
Senior high school or higher	19,015 (23.0)	9,187 (23.0)		8,139 (38.7)	1,928 (25.4)	
Past/current smoking	40,928 (49.4)	20,356 (50.9)	<0.001	360 (1.7)	235 (3.1)	<0.001
Excessive alcohol consumption	13,675 (16.5)	8,329 (20.8)	<0.001	77 (0.4)	44 (0.6)	0.014
Physical activity			<0.001			<0.001
Inactive	12,825 (15.5)	6,145 (15.4)		2,225 (10.6)	734 (9.7)	
Moderately active	56,843 (68.6)	27,884 (69.8)		16,507 (78.4)	5,571 (73.5)	
Active	13,140 (15.9)	5,928 (14.8)		2,314 (11.0)	1,275 (16.8)	
Family history of cancers			<0.001			<0.001
Yes	3,508 (4.2)	1,986 (5.0)		861 (4.1)	522 (6.9)	
No	50,734 (61.3)	23,504 (58.8)		13,614 (64.7)	5,114 (64.5)	
Unknown	28,566 (34.5)	14,467 (36.2)		6,571 (31.2)	1,944 (25.7)	
BMI, kg/m ²	23.9±3.0	27.4±3.1	<0.001	23.2±3.2	27.5±3.5	<0.001
WC, cm	85.2±8.9	93.0±9.0	<0.001	79.4±10.0	89.6±9.6	<0.001
SBP, mmHg	128.7±19.9	136.1±20.2	<0.001	118.5±18.9	134.1±21.6	<0.001
DBP, mmHg	82.6±11.1	87.8±11.7	<0.001	76.9±10.3	84.2±11.1	<0.001
FBG, mmol/L	5.3±1.4	5.9±1.9	<0.001	5.1±1.2	5.9±2.2	<0.001
TG, mmol/L	1.4±1.1	2.2±1.5	<0.001	1.2±0.8	2.0±1.3	<0.001
TC, mmol/L	4.8±1.1	5.1±1.2	<0.001	4.8±1.0	5.2±1.2	<0.001
LDL-C, mmol/L	2.4±0.9	2.5±0.9	<0.001	2.3±0.9	2.4±1.0	<0.001
HDL-C, mmol/L	1.5±0.3	1.4±0.4	<0.001	1.6±0.3	1.5±0.4	<0.001
hs-CRP, mg/dL	0.8 (0.3–2.0)	1.3 (0.6–3.0)	<0.001	0.7 (0.3–1.9)	1.8 (0.8–4.2)	<0.001
ALT, U/L	18.0 (13.0–24.0)	23.0 (17.0–33.0)	<0.001	14.0 (10.0–20.0)	19.0 (14.0–27.0)	<0.001
HBsAg positive	2575 (3.1)	925 (2.3)	<0.001	411 (2.0)	136 (1.8)	0.391

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) of participants with a condition. ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic associated fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S3 Associations between MAFLD and extrahepatic cancers by sex and age

Cancer types	Sex		P for interaction	Age		P for interaction
	Male	Female		<50 years	≥50 years	
Extrahepatic cancers	1.04 (0.98–1.11)	1.23 (1.07–1.40)	0.867	1.12 (1.04–1.20)	1.04 (0.95–1.14)	0.095
Thyroid	1.92 (1.13–3.25)	1.25 (0.70–2.22)	0.058	1.39 (0.95–2.02)	2.18 (0.55–8.68)	0.640
Lung	0.91 (0.82–1.02)	1.06 (0.75–1.49)	0.635	0.98 (0.85–1.12)	0.87 (0.73–1.03)	0.306
Esophageal	0.89 (0.66–1.18)	0.94 (0.16–5.51)	0.985	1.08 (0.77–1.52)	0.53 (0.30–0.94)	0.097
Gastric	1.07 (0.86–1.33)	0.70 (0.34–1.46)	0.284	1.12 (0.86–1.47)	0.89 (0.63–1.25)	0.502
Biliary	0.79 (0.49–1.27)	1.53 (0.48–4.89)	0.229	0.91 (0.47–1.76)	0.82 (0.46–1.47)	0.581
Pancreatic	0.89 (0.60–1.31)	1.77 (0.56–5.56)	0.527	0.94 (0.57–1.55)	1.02 (0.61–1.72)	0.664
Small intestine	1.43 (0.71–2.87)	1.74 (0.34–8.78)	0.519	1.23 (0.54–2.82)	2.13 (0.75–6.10)	0.866
Colorectal	1.13 (0.95–1.33)	1.14 (0.76–1.71)	0.490	1.09 (0.89–1.33)	1.27 (0.99–1.61)	0.341
Kidney	1.50 (1.13–1.98)	2.10 (0.89–4.96)	0.408	1.69 (1.23–2.32)	1.39 (0.87–2.22)	0.439
Bladder	0.98 (0.73–1.32)	0.94 (0.22–4.03)	0.416	0.95 (0.60–1.50)	0.97 (0.66–1.42)	0.512
Prostate [§]	1.49 (1.07–2.08)	–	–	1.40 (0.73–2.67)	1.44 (0.98–2.12)	0.627
Breast [¶]	–	1.31 (1.04–1.66)	–	1.51 (1.18–1.95)	1.33 (0.76–2.31)	0.640

Data were presented as hazard ratio (95% confidence interval). The model was adjusted for age, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [§], only for men; [¶], only for women. MAFLD, metabolic dysfunction-associated fatty liver disease.

Table S4 Baseline characteristics in the participants with and without NAFLD

Characteristics	Non-NAFLD	NAFLD	P
n	112082	39309	
Age, years	48.8±14.2	51.2±12.9	<0.001
Male	91,018 (81.2)	31,747 (80.8)	0.053
Education level			<0.001
Junior high school or below	83,013 (74.1)	30,109 (76.6)	
Senior high school or higher	29,069 (25.9)	9,200 (23.4)	
Past/current smoking	48,220 (43.0)	13,659 (34.7)	<0.001
Excessive alcohol consumption	22,125 (19.7)	0 (0.0)	<0.001
Physical activity			<0.001
Inactive	16,978 (15.1)	4,951 (12.6)	
Moderately active	78,116 (69.7)	28,689 (73.0)	
Active	16,988 (15.2)	5,669 (14.4)	
Family history of cancers			<0.001
Yes	4,837 (4.3)	2,040 (5.2)	
No	68,590 (61.2)	24,376 (62.0)	
Unknown	38,655 (34.5)	12,893 (32.8)	
BMI, kg/m ²	24.1±3.2	27.4±3.3	<0.001
WC, cm	84.8±9.7	92.1±9.4	<0.001
SBP, mmHg	127.5±20.3	135.3±20.6	<0.001
DBP, mmHg	82.0±11.4	86.7±11.6	<0.001
FBG, mmol/L	5.3±1.5	5.9±2.0	<0.001
TG, mmol/L	1.4±1.1	2.1±1.5	<0.001
TC, mmol/L	4.9±1.1	5.1±1.2	<0.001
LDL-C, mmol/L	2.4±0.9	2.5±0.9	<0.001
HDL-C, mmol/L	1.5±0.3	1.4±0.4	<0.001
hs-CRP, mg/dL	0.8 (0.3–2.1)	1.4 (0.6–3.2)	<0.001
ALT, U/L	17.0 (12.0–24.0)	22.0 (16.0–31.0)	<0.001
HBsAg positive	4,047 (3.6)	0(0.0)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) of participants with a condition. ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S5 Associations between NAFLD and extrahepatic cancers in all participants

Cancer types	NAFLD		Non-NAFLD		Unadjusted		Age-, sex-adjusted		Multivariate-adjusted [†]	
	No. of events	Incidence rate (/10 ⁵ PYs)	No. of events	Incidence rate (/10 ⁵ PYs)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Extrahepatic	1,495	346.40	3910	317.81	1.08 (1.02–1.15)	0.008	1.01 (0.95–1.08)	0.661	1.07 (1.01–1.14)	0.027
Thyroid	44	10.06	87	6.99	1.43 (1.00–2.06)	0.052	1.56 (1.08–2.26)	0.019	1.58 (1.09–2.30)	0.016
Lung	393	90.07	1240	99.92	0.90 (0.80–1.00)	0.057	0.87 (0.77–0.97)	0.014	0.94 (0.84–1.06)	0.304
Esophageal	50	11.43	176	14.15	0.80 (0.59–1.10)	0.173	0.80 (0.58–1.09)	0.158	1.05 (0.75–1.18)	0.765
Gastric	102	23.34	308	24.77	0.94 (0.75–1.17)	0.570	0.91 (0.72–1.13)	0.388	0.94 (0.74–1.18)	0.590
Biliary	26	5.95	75	6.03	0.98 (0.63–1.53)	0.932	0.94 (0.60–1.46)	0.774	0.93 (0.59–1.46)	0.751
Pancreatic	39	8.92	105	8.44	1.05 (0.73–1.52)	0.784	1.02 (0.70–1.47)	0.935	1.03 (0.70–1.50)	0.880
Small intestine	13	2.97	26	2.09	1.42 (0.73–2.76)	0.305	1.35 (0.70–2.62)	0.375	1.31 (0.66–2.60)	0.439
Colorectal	209	47.87	507	40.81	1.17 (0.99–1.37)	0.062	1.11 (0.94–1.30)	0.209	1.21 (1.02–1.43)	0.026
Kidney	83	18.99	149	11.98	1.58 (1.21–2.06)	0.001	1.53 (1.17–2.01)	0.002	1.55 (1.17–2.05)	0.002
Bladder	56	12.81	157	12.62	1.01 (0.74–1.37)	0.947	1.01 (0.74–1.37)	0.973	1.13 (0.82–1.56)	0.459
Prostate [§]	50	14.33	102	10.20	1.40 (1.00–1.96)	0.052	1.44 (1.03–2.02)	0.035	1.44 (1.01–2.06)	0.042
Breast [¶]	117	133.58	220	90.57	1.46 (1.17–1.83)	<0.001	1.26 (0.99–1.59)	0.057	1.28 (1.01–1.62)	0.042

[†], adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers; [§], only for men; [¶], only for women. CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease.

Table S6 Difference in extrahepatic cancers of MAFLD vs. NAFLD by generalized estimating equation model

Cancer types	OR (95% CI)*	
	Unadjusted	Multivariate-adjusted**
Extrahepatic	0.78 (0.58–1.04)	0.67 (0.27–1.02)
Thyroid [†]	–	–
Lung	0.97 (0.53–1.76)	0.85 (0.46–1.56)
Esophageal	0.24 (0.10–0.55)	0.19 (0.08–0.45)
Gastric	0.71 (0.226–1.92)	0.60 (0.22–1.64)
Biliary	0.62 (0.08–4.58)	0.57 (0.08–4.27)
Pancreatic	0.95 (0.13–6.87)	0.85 (0.12–6.19)
Small intestine [†]	–	–
Colorectal	0.60 (0.31–1.16)	0.52 (0.27–1.02)
Kidney	2.11 (0.29–15.14)	2.07 (0.29–14.88)
Bladder	0.35 (0.13–0.97)	0.33 (0.12–0.95)
Prostate ^{§†}	–	–
Breast [¶]	1.29 (0.32–5.25)	0.82 (0.22–1.64)

*, ORs were estimated using NAFLD as the reference; **, the model was adjusted for age, sex, education level, smoking status, alcohol consumption, physical activity, and family history of cancers. [§], only for men; [¶], only for women; [†], generalized estimating equation was failed as no cancer of NAFLD in this group. CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease.

Table S7 Baseline characteristics in the participants according to NAFLD and MAFLD

Characteristics	Neither FLD	NAFLD-only	MAFLD-only	MAFLD-NAFLD	P
n	102,832	1,022	9,250	38,287	
Age, years	48.8±14.5	48.9±13.1	49.6±10.9	51.3±12.9	<0.001
Male	81,948 (79.7)	860 (84.1)	9,070 (98.1)	30,887 (80.7)	<0.001
Education level					<0.001
Junior high school or below	75,953 (73.9)	747 (73.1)	7,060 (76.3)	29,362 (76.7)	
Senior high school or higher	26,879 (26.1)	275 (26.9)	2,190 (23.7)	8,925 (23.3)	
Past/current smoking	40,878 (39.8)	410 (40.1)	7,342 (79.4)	13,249 (34.6)	<0.001
Excessive alcohol consumption	13,752 (13.4)	0 (0.0)	8,373 (90.5)	0 (0.0)	<0.001
Physical activity					<0.001
Inactive	14,900 (14.5)	150 (14.7)	2,078 (22.5)	4,801 (12.5)	
Moderately active	72,608 (70.6)	742 (72.6)	5,508 (59.5)	27,947 (73.0)	
Active	15,324 (14.9)	130 (12.7)	1,664 (18.0)	5,539 (14.5)	
Family history of cancers					<0.001
Yes	4,337 (4.2)	32 (3.1)	500 (5.4)	2,008 (5.2)	
No	63,760 (62.0)	588 (57.5)	4,830 (52.2)	23,788 (62.1)	
Unknown	34,735 (33.8)	402 (39.3)	3,920 (42.4)	12,491 (32.6)	
BMI, kg/m ²	23.8±3.1	21.6±1.3	27.0±3.1	27.5±3.2	<0.001
WC, cm	84.1±9.5	80.4±6.9	92.5±9.0	92.5±9.2	<0.001
SBP, mmHg	126.7±20.1	121.7±17.0	136.5±20.2	135.6±20.5	<0.001
DBP, mmHg	81.4±11.2	79.5±9.6	88.6±11.8	86.9±11.6	<0.001
FBG, mmol/L	5.3±1.4	5.0±0.6	5.9±1.8	5.9±2.0	<0.001
TG, mmol/L	1.4±1.0	1.2±0.7	2.2±1.6	2.1±1.5	<0.001
TC, mmol/L	4.8±1.1	4.9±1.0	5.3±1.2	5.1±1.2	<0.001
LDL-C, mmol/L	2.4±0.9	2.4±0.7	2.6±0.9	2.5±0.9	<0.001
HDL-C, mmol/L	1.5±0.3	1.6±0.3	1.5±0.4	1.4±0.4	<0.001
hs-CRP, mg/dL	0.8 (0.3–2.0)	0.6 (0.3–1.2)	1.3 (0.6–2.8)	1.4 (0.6–3.2)	<0.001
ALT, U/L	17.0 (12.0–23.0)	19.0 (14.0–26.0)	24.0 (17.9–35.0)	22.0 (16.0–31.0)	<0.001
HBsAg positive	2986 (2.9)	0 (0.0)	1061 (11.5)	0 (0.0)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) of participants with a condition. ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; FLD, fatty liver disease; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S8 Baseline characteristics in the participants MAFLD subgroup stratified by risk factors

Characteristics	Non-MAFLD	MAFLD subgroups							P
		Overweight-only	DB-only	MD-only	Overweight and DB	Overweight and MD	DB and MD	Three risk factors [†]	
n	103,854	6,492	155	1,940	808	31,773	382	5,987	
Age, years	48.8±14.5	46.3±12.4	54.9±9.9	53.4±12.3	52.7±9.6	50.8±12.7	57.3±10.7	55.6±10.6	<0.001
Male	82,808 (79.7)	5,815 (89.6)	146 (94.2)	1,562 (80.5)	743 (92.0)	26,561 (83.6)	295 (77.2)	4,835 (80.8)	<0.001
Education level									<0.001
Junior high school or below	76,700 (73.9)	4,685 (72.2)	141 (91.0)	1,595 (82.2)	671 (83.0)	24,073 (75.8)	317 (83.0)	4,940 (82.5)	
Senior high school or higher	27,154 (26.1)	1,807 (27.8)	14 (9.0)	345 (17.8)	137 (17.0)	7,700 (24.2)	65 (17.0)	1,047 (17.5)	
Past/current smoking	41,288 (39.8)	2,913 (44.9)	78 (50.3)	852 (43.9)	338 (41.8)	13,805 (43.4)	155 (40.6)	2,450 (40.9)	<0.001
Excessive alcohol consumption	13,752 (13.2)	1,131 (17.4)	40 (25.8)	487 (25.1)	138 (17.1)	5,595 (17.6)	74 (19.4)	908 (15.2)	<0.001
Physical activity									<0.001
Inactive	15,050 (14.5)	972 (15.0)	30 (19.4)	306 (15.8)	98 (12.1)	4,667 (14.7)	52 (13.6)	754 (12.6)	
Moderately active	73,350 (70.6)	4,680 (72.1)	105 (67.7)	1,367 (70.5)	572 (70.8)	22,344 (70.3)	268 (70.2)	4,119 (68.8)	
Active	15,454 (14.9)	840 (12.9)	20 (12.9)	267 (13.8)	138 (17.1)	4,762 (15.0)	62 (16.2)	1,114 (18.6)	
Family history of cancers									<0.001
Yes	4,369 (4.2)	234 (3.6)	3 (1.9)	95 (4.9)	28 (3.5)	1,778 (5.6)	20 (5.2)	350 (5.8)	
No	64,348 (62.0)	3,920 (60.4)	88 (56.8)	1,043 (53.8)	547 (67.7)	19,068 (60.0)	204 (53.4)	3,748 (62.6)	
Unknown	35,137 (33.8)	2,338 (36.0)	64 (41.3)	802 (41.3)	233 (28.8)	10,927 (34.4)	158 (41.4)	1,889 (31.6)	
BMI, kg/m ²	23.8±3.1	26.4±2.4	21.8±1.0	21.7±1.3	26.1±2.1	28.0±2.9	21.8±1.2	28.0±3.1	<0.001
WC, cm	84.0±9.5	86.8±7.0	81.9±5.9	85.1±9.3	86.7±6.8	93.9±8.7	86.4±8.7	95.0±9.5	<0.001
SBP, mmHg	126.6±20.1	122.3±16.3	127.6±19.2	136.6±20.1	128.4±19.8	137.3±19.9	140.2±20.5	143.2±20.8	<0.001
DBP, mmHg	81.4±11.2	80.5±9.5	81.9±9.5	86.5±11.2	82.7±11.6	88.4±11.5	87.3±11.3	89.5±11.8	<0.001
FBG, mmol/L	5.3±1.4	5.0±0.5	10.3±3.5	5.3±0.8	9.4±2.7	5.3±0.7	9.9±3.3	9.3±2.8	<0.001
TG, mmol/L	1.4±1.0	1.3±0.8	1.5±1.2	2.2±1.5	1.5±1.1	2.3±1.5	2.6±1.7	2.6±1.8	<0.001
TC, mmol/L	4.8±1.1	4.9±1.0	5.3±1.5	5.2±1.2	5.2±1.2	5.1±1.2	5.5±1.4	5.3±1.4	<0.001
LDL-C, mmol/L	2.4±0.9	2.5±0.7	2.6±1.0	2.4±1.0	2.7±0.8	2.5±0.9	2.6±1.1	2.6±1.0	<0.001
HDL-C, mmol/L	1.5±0.3	1.5±0.3	1.6±0.4	1.5±0.4	1.5±0.3	1.4±0.4	1.5±0.4	1.4±0.4	<0.001
hs-CRP, mg/dL	0.8 (0.3–2.0)	0.8 (0.4–1.3)	0.7 (0.3–1.4)	1.6 (0.6–3.6)	0.8 (0.4–1.3)	1.6 (0.7–3.5)	2.1 (0.8–4.4)	2.0 (0.9–4.3)	<0.001
ALT, U/L	17.0 (12.0–23.0)	22.0 (16.0–29.8)	20.9 (13.0–26.0)	20.3 (14.1–29.0)	22.0 (16.0–29.0)	23.0 (17.0–32.0)	20.0 (15.0–27.0)	23.0 (16.0–33.0)	<0.001
HBsAg positive	2,986 (2.9)	179 (2.8)	6 (3.9)	36 (1.9)	19 (2.4)	695 (2.2)	10 (2.6)	116 (1.9)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) of participants with a condition. [†], overweight/obesity, DB, and MD. ALT, alanine aminotransferase; BMI, body mass index; DB, diabetes; DBP, diastolic blood pressure; FBG, fasting blood glucose; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; MD, metabolic dysregulation; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S9 Baseline characteristics in the MAFLD participants according to HBsAg and alcohol consumption

Characteristics	MAFLD without positive HBsAg and excessive alcohol consumption	MAFLD with positive HBsAg only	MAFLD with excessive alcohol consumption only	MAFLD with excessive alcohol consumption and positive HBsAg	P
N (%)	142,141 (93.9)	877 (0.58)	8,189 (5.4)	184 (0.12)	
Age, years	49.4±14.1	48.4±11.9	49.7±10.8	47.9±9.6	0.007
Male	113,695 (80.0)	741 (84.5)	8,145 (99.5)	184 (100.0)	<0.001
Education level					<0.001
Junior high school or below	106,062 (74.6)	654 (74.6)	6,275 (76.6)	131 (71.2)	
Senior high school or higher	36,079 (25.4)	223 (25.4)	1,914 (23.4)	53 (28.8)	
Past/current smoking	54,537 (38.4)	314 (35.8)	6,869 (83.9)	159 (86.4)	<0.001
Excessive alcohol consumption	13,752 (9.7)	-	8,189 (100.0)	184 (100.0)	<0.001
Physical activity					<0.001
Inactive	19,851 (14.0)	124 (14.1)	1,911 (23.3)	43 (23.4)	
Moderately active	101,297 (71.3)	636 (72.5)	4,755 (58.1)	117 (63.6)	
Active	20,993 (14.8)	117 (13.3)	1,523 (18.6)	24 (13.0)	
Family history of cancers					<0.001
Yes	2,008 (5.2)	43 (4.9)	444 (5.4)	13 (7.1)	
No	23,788 (62.1)	552 (62.9)	4,184 (51.1)	94 (51.1)	
Unknown	12,491 (32.6)	282 (32.2)	3,561 (43.5)	77 (41.8)	
BMI, kg/m ²	24.8±3.5	27.7±3.3	26.9±3.1	27.5±3.2	<0.001
WC, cm	86.3±10.1	92.7±9.1	92.4±8.9	94.4±13.2	<0.001
SBP, mmHg	129.1±20.6	134.1±19.4	136.7±20.2	137.4±20.4	<0.001
DBP, mmHg	82.9±11.5	86.8±11.6	88.7±11.8	89.9±12.3	<0.001
FBG, mmol/L	5.5±1.6	5.9±2.1	5.9±1.8	5.8±1.7	<0.001
TG, mmol/L	1.6±1.2	1.9±1.4	2.3±1.6	2.0±1.6	<0.001
TC, mmol/L	4.9±1.1	4.9±1.3	5.3±1.2	5.0±1.2	<0.001
LDL-C, mmol/L	2.4±0.9	2.5±0.9	2.7±0.9	2.6±1.0	<0.001
HDL-C, mmol/L	1.5±0.4	1.4±0.4	1.5±0.4	1.5±0.4	<0.001
hs-CRP, mg/dL	0.9 (0.4–2.3)	1.3 (0.6–2.9)	1.3 (0.6–2.8)	1.0 (0.4–2.3)	0.005
ALT, U/L	18.0 (13.0–25.0)	26.0 (18.0–38.0)	24.0 (17.0–34.0)	29.0 (21.0–44.0)	<0.001
HBsAg positive	2,986 (2.1)	877 (100.0)	-	184 (100.0)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%) of participants with a condition. ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; FLD, fatty liver disease; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S10 Associations between MAFLD and extrahepatic cancers after excluding the incident cancers within the first 3 years of follow-up

Cancer types	MAFLD		Non-MAFLD		Univariate model		Age-, sex-adjusted		Multivariate model [†]	
	No. of events	Incidence rate (/10 ⁵ PYs)	No. of events	Incidence rate (/10 ⁵ PYs)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Extrahepatic	1,372	265.09	2,783	244.13	1.09 (1.02–1.16)	0.013	1.04 (0.98–1.11)	0.193	1.04 (0.98–1.11)	0.200
Thyroid	34	6.48	69	5.98	1.09 (0.72–1.64)	0.697	1.39 (0.91–2.11)	0.129	1.39 (0.91–2.13)	0.123
Lung	385	73.57	906	78.73	0.93 (0.83–1.05)	0.256	0.90 (0.80–1.02)	0.095	0.90 (0.80–1.02)	0.086
Esophageal	53	10.10	122	10.57	0.96 (0.69–1.32)	0.783	0.92 (0.67–1.27)	0.613	0.90 (0.65–1.24)	0.507
Gastric	97	18.50	204	17.69	1.05 (0.82–1.33)	0.720	1.01 (0.79–1.29)	0.935	1.01 (0.80–1.29)	0.906
Biliary	2	4.38	57	4.94	0.89 (0.55–1.44)	0.627	0.88 (0.54–1.42)	0.596	0.89 (0.55–1.45)	0.651
Pancreatic	32	6.10	78	6.76	0.90 (0.60–1.36)	0.620	0.88 (0.58–1.32)	0.527	0.90 (0.60–1.36)	0.611
Small intestine	14	2.67	18	1.56	1.71 (0.85–3.44)	0.132	1.65 (0.82–3.31)	0.162	1.69 (0.85–3.40)	0.137
Colorectal	207	39.53	387	33.59	1.18 (0.99–1.39)	0.060	1.14 (0.96–1.35)	0.137	1.14 (0.96–1.35)	0.131
Kidney	78	14.88	91	7.89	1.88 (1.39–2.55)	<0.001	1.82 (1.34–2.46)	<0.001	1.85 (1.36–2.50)	<0.001
Bladder	49	9.34	115	9.97	0.94 (0.67–1.31)	0.702	0.93 (0.67–1.30)	0.680	0.92 (0.66–1.29)	0.621
Prostate [§]	48	11.01	77	8.46	1.31 (0.91–1.88)	0.142	1.44 (1.00–2.08)	0.049	1.49 (1.03–2.15)	0.033
Breast [¶]	86	98.10	171	70.53	1.37 (1.06–1.78)	0.017	1.23 (0.94–1.62)	0.136	1.24 (0.95–1.63)	0.120

[†], adjusted for age, sex, education level, smoking status, alcohol consumption, and physical activity. [§], only for men; [¶], only for women. CI, confidence interval; HR, hazard ratio; MAFLD, metabolic associated fatty liver disease; PYs, person-years.

Table S11 Associations between MAFLD and extrahepatic cancers in all participants before imputation

Cancer types	MAFLD		Non-MAFLD		Univariate model		Age-, sex-adjusted model		Multivariate model [†]	
	No. of events	Incidence rate (/10 ⁵ PYs)	No. of events	Incidence rate (/10 ⁵ PYs)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Extrahepatic	1,372	265.08	2,783	244.13	1.09 (1.02–1.17)	0.011	1.06 (1.00–1.14)	0.069	1.06 (0.99–1.13)	0.096
Thyroid	46	8.80	85	7.34	1.28 (0.88–1.87)	0.199	1.58 (1.07–2.34)	0.021	1.60 (1.08–2.36)	0.019
Lung	494	94.73	1,139	98.56	0.94 (0.83–1.05)	0.260	0.90 (0.80–1.01)	0.082	0.90 (0.80–1.01)	0.077
Esophageal	68	13.01	158	13.64	0.87 (0.64–1.19)	0.389	0.84 (0.61–1.14)	0.264	0.81 (0.59–1.11)	0.199
Gastric	130	24.89	280	24.18	1.08 (0.86–1.35)	0.502	1.04 (0.83–1.30)	0.726	1.04 (0.83–1.30)	0.708
Biliary	28	5.36	73	6.30	0.92 (0.58–1.45)	0.714	0.90 (0.57–1.41)	0.639	0.91 (0.58–1.43)	0.679
Pancreatic	44	8.42	100	8.63	0.96 (0.65–1.41)	0.823	0.92 (0.63–1.36)	0.682	0.94 (0.64–1.39)	0.774
Small intestine	16	3.06	23	1.99	1.76 (0.89–3.46)	0.102	1.68 (0.85–3.31)	0.133	1.72 (0.88–3.37)	0.116
Colorectal	249	47.72	467	40.37	1.18 (1.00–1.40)	0.049	1.14 (0.97–1.35)	0.122	1.14 (0.96–1.35)	0.128
Kidney	96	18.38	136	11.74	1.49 (1.13–1.98)	0.005	1.43 (1.08–1.90)	0.012	1.44 (1.09–1.91)	0.011
Bladder	66	12.63	147	12.69	0.97 (0.71–1.33)	0.858	0.97 (0.71–1.34)	0.874	0.97 (0.70–1.33)	0.841
Prostate [§]	57	13.15	95	10.42	1.38 (0.96–1.98)	0.078	1.54 (1.07–2.21)	0.021	1.59 (1.11–2.30)	0.013
Breast [¶]	119	136.80	217	89.45	1.54 (1.23–1.94)	<0.001	1.32 (1.03–1.68)	0.028	1.32 (1.04–1.69)	0.024

[†], adjusted for age, sex, education level, smoking status, alcohol consumption, and physical activity; [§], only for men; [¶], only for women. CI, confidence interval; HR, hazard ratio; MAFLD, metabolic associated fatty liver disease; PYs, person-years.