

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

1. This study was initiated by the Kailuan Group, a large enterprise involved in various fields such as coal, healthcare, finance, and manufacturing. Since 2006, employees of this enterprise have been continuously invited to undergo physical examinations at the Kailuan General Hospital and its 11 affiliated hospitals. We collected their physical examination data, questionnaire interview data, dietary information, laboratory test results, etc. biennially, and conducted annual follow-ups. Trained doctors or nurses conducted all surveys, and all participants signed informed consent. Due to the fact that this study is based on the largest tertiary hospital in Tangshan City, our database also connects provincial vital statistics data, Tangshan Medical Insurance System, and Kailuan Social Security Information System.

2. The diagnosis of NAFLD is based on B-ultrasound. In imaging diagnosis of China, patients' ultrasonography need to meet at least two of the following three conditions: (i) increased echogenicity of the liver near field region with deep attenuation of the ultrasound signal; (ii) hyperechogenicity of liver tissue ("bright liver"), as often compared to hypoechogenicity of the kidney cortex; and (iii) vascular blurring [1,2].

The severity of steatosis was differentiated by ultrasonography: mild (diffuse increase in fine echoes in liver parenchyma), moderate (diffuse increase in fine echoes with impaired visualization of the intrahepatic vessel borders and diaphragm), and severe (diffuse increase in fine echoes with nonvisualization of the intrahepatic vessel borders and diaphragm)[3].

Abdominal ultrasonography was routinely performed by experienced radiologists using a high-resolution B-mode topographical ultrasound system with a 3.5 MHz probe (ACUSON X300, Siemens, Germany) in the Kailuan study.

3. The diagnosis of MAFLD first needs to confirm liver steatosis based on imaging diagnosis, and then it is accompanied by any of the following three conditions, overweight/obesity, diabetes or the risk of metabolic abnormalities [4,5]. The metabolic risk abnormalities were defined as the presence of two or more of the following conditions: (1) Waist circumference ≥ 90 in men and 80 cm in women. (2) Blood pressure $\geq 130/85$ mmHg or specific drug treatment. (3) TG ≥ 1.70 mmol/l or specific drug treatment. (4) HDL-C < 1.0 mmol/L for men and < 1.3 mmol/L for women. (5) Prediabetes (i.e., fasting glucose levels 5.6 to 6.9 mmol/L, or 2-hour post-load glucose levels 7.8 to 11.0 mmol/L or HbA1c 5.7% to 6.4%). (6) Homeostasis model assessment-insulin resistance score ≥ 2.5 . (7) C-reactive protein (CRP) level > 2 mg/L.

4. The Kailuan cohort was followed up by using face-to-face questionnaires and electronic medical record systems and reviewing death certificates from the Provincial Vital Statistics Offices, Tangshan medical insurance system, and Kailuan Social Security Information System [6].

5. The cancer types included were as follows: digestive system cancers [esophageal cancer (C15), gastric cancer (C16), small intestine cancer (C17), colorectal cancer (CRC; C18–C21), liver cancer (C22.0), pancreatic cancer (C25), gallbladder and extrahepatic bile duct cancer (C23–C24)], lung cancer (C34), urinary system tumors [kidney cancer (C64–C65), bladder cancer (C67)], lymphoma (C81–C89) and leukemia (C90–C96), gender-specific tumors [breast cancer (C50), cervix cancer (C53), uterus cancer (C54–C55), ovarian cancer (C56), prostate cancer (C61)], and other cancers.

6. Among them, regular physical activity was defined as ≥ 30 min/time, ≥ 3 times/week. A current smoker was defined as one who smokes at least one cigarette a day and has been smoking for at least 6 months. Sedentary was categorized based on self-reported time as < 4 hours, 4–8 hours, and > 8 hours. High-fat diet refers to a dietary pattern characterized by a higher intake of fatty acids but low in fiber, vitamins, and minerals, such as excessive consumption of fried foods, high-fat dairy products, pastries, and desserts. Salt consumption was self-reported and classified into three categories: low (< 6 g/day), medium (6–9 g/day) or high (≥ 10 g/day). All laboratory indicators were measured after analysis with the automatic analyzer (Hitachi 747; Hitachi, Tokyo, Japan) in the central laboratory of Kailuan General Hospital.

7. PAFs indicate the proportion of disease-induced morbidity (or death) owing to certain exposure in the total morbidity (or death) of the population. Calculation method of PAF: In this study, we use the Miettinen formula: $PAF = pc(1 - 1/RR)$. RR represents the relative risk, and pc represents the prevalence of case exposure. This calculation method is well-suited for cohort studies and can compute PAFs that account for multiple exposure levels or confounding factors [7]. "AF" package (R 4.2.0) is used to calculate PAF.

8. The participants were divided into the high inflammation group (hs-CRP ≥ 3 mg/L) and the low inflammation group (hs-CRP < 3 mg/L). Because of the limited sample size, the number of patients with abnormal liver function (>40 U/L) was too small, and we, therefore, divided the participants into the high ALT group (≥ 19 U/L) and low ALT group (< 19 U/L) based on median of ALT.

Reference

- [1] Wang Z, Zhao X, Chen S, Wang Y, Cao L, Liao W, Sun Y, Wang X, Zheng Y, Wu S, Wang L. Associations Between Nonalcoholic Fatty Liver Disease and Cancers in a Large Cohort in China. *Clin Gastroenterol Hepatol*. 2021 Apr;19(4):788-796.e4. doi: 10.1016/j.cgh.2020.05.009.
- [2] Gao X, Fan JG; Study Group of Liver and Metabolism, Chinese Society of Endocrinology. Diagnosis and management of non-alcoholic fatty liver disease and related metabolic disorders: consensus statement from the Study Group of Liver and Metabolism, Chinese Society of Endocrinology. *J Diabetes*. 2013 Dec;5(4):406-15. doi: 10.1111/1753-0407.12056. Epub 2013 Jun 4.
- [3] Xu J, Dai L, Zhang Y, Wang A, Li H, Wang Y, Meng X, Wu S, Wang Y. Severity of Nonalcoholic Fatty Liver Disease and Risk of Future Ischemic Stroke Events. *Stroke*. 2021 Jan;52(1):103-110. doi: 10.1161/STROKEAHA.120.030433.
- [4] Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hepatol Int*. 2020 Dec;14(6):889-919. doi: 10.1007/s12072-020-10094-2.
- [5] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol*. 2020 Jul;73(1):202-209. doi: 10.1016/j.jhep.2020.03.039.
- [6] Liu T, Zhang Q, Song C et al. C-reactive protein trajectories and the risk of all cancer types: A prospective cohort study. *Int J Cancer* 2022; 151: 297-307.
- [7] Hanley JA. A heuristic approach to the formulas for population attributable fraction. *J Epidemiol Community Health*. 2001 Jul;55(7):508-14. doi: 10.1136/jech.55.7.508.

eTable 1 Determination of new-onset NAFLD

2006-07	2008-09	2010-11	2012-13	2014-15	2006-07	2008-09	2010-11	2012-13	2014-15	2016-17
0	1				NA	NA	NA	NA	0	1
NA	0	1			NA	NA	NA	0	NA	1
0	NA	1			NA	NA	NA	0	0	1
0	0	1			NA	NA	0	NA	NA	1
NA	NA	0	1		NA	NA	0	NA	0	1
NA	0	NA	1		NA	NA	0	0	NA	1
NA	0	0	1		NA	NA	0	0	0	1
0	NA	NA	1		NA	0	NA	NA	NA	1
0	NA	0	1		NA	0	NA	NA	0	1
0	0	NA	1		NA	0	NA	0	NA	1
0	0	0	1		NA	0	NA	0	0	1
0	0	0	0	1	NA	0	0	NA	NA	1
0	0	0	NA	1	NA	0	0	NA	0	1
0	0	NA	0	1	NA	0	0	0	NA	1
0	0	NA	0	1	NA	0	0	0	0	1
0	NA	0	0	1	0	NA	NA	NA	NA	1
0	NA	0	NA	1	0	NA	NA	NA	0	1
0	NA	NA	0	1	0	NA	NA	0	NA	1
0	NA	NA	NA	1	0	NA	NA	0	0	1
NA	0	0	0	1	0	NA	0	NA	NA	1
NA	0	0	NA	1	0	NA	0	NA	0	1
NA	0	NA	0	1	0	NA	0	0	NA	1
NA	0	NA	NA	1	0	0	0	0	0	1
NA	NA	0	0	1	0	0	NA	NA	NA	1
NA	NA	NA	0	1	0	0	NA	NA	0	1
NA	NA	0	NA	1	0	0	NA	0	NA	1
					0	0	NA	0	0	1
					0	0	0	NA	NA	1
					0	0	0	NA	0	1
					0	0	0	0	NA	1
					0	0	0	0	0	1

NA: The participants did not come to the hospital for medical examination in this cycle.

0: The participants participated in this round of physical examination, but was not diagnosed as NAFLD.

1: The participants participated in this round of physical examination and was diagnosed as NAFLD.

eTable 2 Comparison of baseline characteristics between stayed and excluded participants

Variables	Patients with missing covariate data (Excluded group)	Patients included in the final analysis (Stayed group)	P value (excluding missing data)
N	10240	31848	
Age (year)	51.19(11.67)	51.37(12.43)	0.853
Men (%)	8503(83.2)	26382(82.8)	0.640
Regular Physical activity (%)	1547(15.1)	4874(15.3)	0.630
Current Smoke (%)			0.443 ^a
No	6510(63.6)	25061(78.7)	
Yes	1084(10.6)	6787(21.3)	
Unknown	1928(18.8)	0	
GSD (%)			0.009 ^a
No	8878(86.7)	31122(97.7)	
Yes	251(2.5)	726(2.3)	
Unknown	1111(10.8)	0	
Gallbladder polyps (%)			0.071 ^a
No	8946(87.4)	31300(98.3)	
Yes	183(1.8)	548(1.7)	
Unknown	1111(10.8)	0	
Diabetes (%)			0.075 ^a
No	9150(89.4)	28696(90.1)	
Yes	1074(10.5)	3152(9.9)	
Unknown	16(0.2)	0	
Hypertension (%)	4739(46.3)	14518(45.6)	0.229
BMI			0.111 ^a
<24.0	2352(23.0)	8511(26.7)	
24-27.99	4427(43.2)	16867(53.0)	
≥28	1744(17.0)	6470(20.3)	
Unknown	1717(16.8)	0	
BMI (Kg/m2)	25.81(3.25)	25.78(2.97)	0.233 ^a
WC (cm)	88.35(9.53)	89.22(9.11)	<0.001 ^a
TG (mmol/L)	1.49[1.01,2.51]	1.46[1.02,2.19]	<0.001 ^a
TC (mmol/L)	4.98[4.20,5.72]	5.08[4.49,5.75]	<0.001 ^a
HDL-c (mmol/L)	1.37[1.14,1.66]	1.36[1.14,1.63]	0.377 ^a
hsCRP (mg/L)	1.40[0.60,2.80]	1.40[0.70,2.90]	0.057 ^a
TBil (umol/L)	13.3[10.2,17.2]	13.0[10.2,16.5]	<0.001 ^a
ALT (u/L)	20.0[15.0,27.0]	20.0[15.0,28.0]	<0.001 ^a

^a Participants with missing values will be excluded when performing group comparisons. For example, for Current Smoke, there were 1928 participants with unknown status. When comparing, these 1928 participants would not be included in the chi-square test.

eTable 3 The number of onset-cases in four groups

		Onset age of NAFLD			
		<45	45-54	55-64	≥65
Esophageal cancer	Control	2	20	13	8
	NAFLD	5	21	11	10
Stomach cancer	Control	7	21	27	22
	NAFLD	5	28	40	24
Small intestine cancer	Control	1	4	3	1
	NAFLD	0	2	1	4
Colorectal cancer	Control	5	24	56	24
	NAFLD	17	54	59	26
Liver cancer	Control	12	23	24	13
	NAFLD	23	27	25	10
Gallbladder and extrahepatic bile duct cancer	Control	1	2	6	2
	NAFLD	2	2	6	2
Pancreatic cancer	Control	2	7	9	8
	NAFLD	5	6	8	6
Lung cancer	Control	21	89	130	88
	NAFLD	26	120	143	75
Kidney cancer	Control	2	12	10	8
	NAFLD	2	14	9	1
Bladder cancer	Control	2	10	21	17
	NAFLD	3	11	26	17
Lymphoma and Leukemia	Control	5	9	10	6
	NAFLD	4	11	7	7
Breast cancer	Control	13	38	30	11
	NAFLD	8	37	25	5
Female reproductive system cancers ^a	Control	5	21	10	2
	NAFLD	7	13	10	0
Prostate cancer	Control	0	1	5	13
	NAFLD	0	3	13	13

^a Female reproductive system tumors included cervical cancer, endometrial cancer, ovarian cancer, etc.

Other tumors (including head and neck tumors, skin tumors, bone tumors and some special tumors) were not listed in the table.

eTable 4 Subgroup analysis (based on hs-CRP) of the Average Hazard Ratios (95% CI) of cancers among participants with new-onset NAFLD versus controls across age groups.

Age of new-onset NAFLD	hs-CRP<3mg/L (n=49170)		hs-CRP≥3mg/L (n=14526)	
	Average HR (95%CI)	P value	Average HR (95%CI)	P value
All cancer types				
<45	1.528(0.991, 2.357)	0.054	1.376(0.789,2.401)	0.261
45-54	1.448(1.166,1.800)	0.001	1.837(1.077,3.135)	0.026
55-64	1.021(0.772,1.352)	0.882	1.239(1.016,1.512)	0.034
≥65	1.026(0.555,1.896)	0.936	0.440(0.286,0.676)	0.001
P for interaction ^a	0.058		0.015	
Digestive System Cancers				
<45	1.945(0.870,4.349)	0.105	1.936(0.851,4.406)	0.115
45-54	1.786(1.236,2.578)	0.002	2.102(1.157,3.818)	0.014
55-64	1.231(0.801,1.599)	0.484	1.002(0.607,1.655)	0.992
≥65	1.223(0.798,1.838)	0.335	0.632(0.332,1.203)	0.163
P for interaction ^a	0.121		<0.001	
Liver cancer				
<45	2.482(0.874,7.044)	0.087	2.992(0.627,14.308)	0.170
45-54	1.316(0.387,4.518)	0.662	2.672(1.268,5.628)	0.010
55-64	1.286(0.595,2.781)	0.523	1.010(0.364,3.322)	0.866
≥65	1.519(0.460,5.014)	0.492	0.409(0.060,2.687)	0.452
P for interaction ^a	0.080		<0.001	
Colorectal cancer				
<45	1.534(0.239,9.842)	0.652	5.438(0.431,48.643)	0.191
45-54	2.336(1.158,4.712)	0.018	8.641(1.783,31.888)	0.007
55-64	1.164(0.702,1.932)	0.554	0.871(0.387,1.960)	0.739
≥65	1.244(0.518,2.986)	0.625	1.242(0.431,3.576)	0.688
P for interaction ^a	0.688		0.024	
Lung cancer				
<45	0.731(0.212,2.522)	0.620	2.844(1.202,6.921)	0.017
45-54	1.721(0.893,3.315)	0.104	1.873(1.156,3.035)	0.011
55-64	1.152(0.810,1.636)	0.430	0.986(0.596,1.631)	0.956
≥65	0.605(0.282,1.300)	0.198	0.569(0.283,1.148)	0.116
P for interaction ^a	0.151		0.017	

The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical).

^a The interaction between NAFLD and its age at diagnosis.

eTable 5 Subgroup analysis (based on ALT) of the Average Hazard Ratios (95% CI) of cancers among participants with new-onset NAFLD versus controls across age groups.

	ALT<19 U/L (n=31838)		ALT≥19 U/L (n=31858)	
Age of new-onset NAFLD	Average HR (95%CI)	P value	Average HR (95%CI)	P value
All cancer types				
<45	1.088(0.685,1.73)	0.720	1.912(1.174,3.113)	0.009
45-54	1.557(1.228,1.1975)	<0.001	1.375(1.038,2.176)	0.029
55-64	1.144(0.886,1.477)	0.304	1.259(0.998,1.588)	0.052
≥65	1.199(0.907,1.585)	0.203	0.558(0.345,0.905)	0.018
P for interaction ^a	0.104		0.005	
Digestive System Cancers				
<45	1.519(0.692,3.513)	0.284	2.792(1.816,4.294)	<0.001
45-54	2.302(1.110,4.774)	0.025	1.559(0.693,3.507)	0.283
55-64	0.923(0.634,1.343)	0.675	1.322(0.874,1.997)	0.186
≥65	1.221(0.760,1.960)	0.409	0.765(0.476,1.232)	0.271
P for interaction ^a	0.028		0.009	
Liver cancer				
<45	8.664(1.700,44.163)	0.009	1.322(0.406,4.301)	0.642
45-54	6.471(2.020,20.724)	0.001	1.149(0.530,2.492)	0.724
55-64	1.674(0.552,5.049)	0.360	1.086(0.515,2.289)	0.829
≥65	0.971(0.242,3.904)	0.967	0.740(0.340,1.607)	0.446
P for interaction ^a	<0.001		<0.001	
Colorectal cancer				
<45	0.676(0.19,2.404)	0.545	3.021(3.630,25.144)	0.002
45-54	4.701(2.153,10.266)	<0.001	2.092(0.914,4.790)	0.081
55-64	0.900(0.524,1.548)	0.704	1.332(0.721,2.492)	0.369
≥65	1.455(0.685,3.091)	0.330	0.958(0.277,3.308)	0.946
P for interaction ^a	0.989		<0.001	
Lung cancer				
<45	1.412(0.445,4.482)	0.558	2.488(0.935,6.622)	0.068
45-54	1.350(0.789,2.310)	0.273	2.112(1.081,4.128)	0.028
55-64	0.968(0.654,1.431)	0.869	1.327(0.858,2.052)	0.204
≥65	0.939(0.598,1.476)	0.786	0.478(0.197,1.159)	0.102
P for interaction ^a	0.123		0.016	

The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical).

^a The interaction between NAFLD and its age at diagnosis.

eTable 6 The association of new-onset NAFLD with the risk of cancers in competing risk analysis

Age of new-onset NAFLD	SD	P value	CS	P value
	HR (95%CI)		HR (95%CI)	
All cancer types				
<45	1.356(1.306,1.776)	0.026	1.359(1.034,1.787)	0.028
45-54	1.069(0.875,1.306)	0.516	1.231(1.068,1.418)	0.004
55-64	1.121(0.981,1.280)	0.092	1.122(0.982,1.282)	0.091
≥65	0.933(0.784,1.110)	0.438	0.933(0.785,1.111)	0.433
Digestive System Cancers				
<45	1.813(1.159,2.835)	0.009	1.815(1.152,2.859)	0.010
45-54	1.436(1.105,1.865)	0.007	1.440(1.110,1.869)	0.006
55-64	1.179(0.931,1.492)	0.171	1.179(0.935,1.486)	0.164
≥65	1.041(0.760,1.426)	0.802	1.046(0.761,1.438)	0.783
Liver cancer				
<45	1.632(0.810,3.286)	0.171	1.635(0.805,3.320)	0.174
45-54	1.172(0.664,2.066)	0.584	1.178(0.675,2.056)	0.565
55-64	1.086(0.615,1.919)	0.775	1.089(0.614,1.930)	0.771
≥65	0.723(0.304,1.722)	0.464	0.724(0.314,1.668)	0.447
Colorectal cancer				
<45	3.333(1.210,9.184)	0.020	3.333(1.211,9.176)	0.020
45-54	2.242(1.375,3.656)	0.001	2.250(1.379,3.671)	0.001
55-64	1.241(0.864,1.783)	0.242	1.243(0.868,1.779)	0.235
≥65	1.074(0.613,1.879)	0.804	1.087(0.614,1.923)	0.775
Lung cancer				
<45	1.538(0.834,2.836)	0.168	1.546(0.846,2.823)	0.156
45-54	1.335(1.023,1.128)	0.043	1.342(1.010,1.784)	0.040
55-64	1.127(0.884,1.437)	0.333	1.128(0.885,1.436)	0.330
≥65	0.932(0.684,1.271)	0.657	0.936(0.685,1.280)	0.679

The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical).

eTable 7 The Average Hazard Ratios (95% CI) of overall cancers among participants with new-onset NAFLD versus controls across age groups. (Excluding participants with follow-up less than 1 year, n=63176)

Age of new-onset NAFLD	Average HR (95%CI)	P value
All cancer types		
<45	1.570(1.191,2.070)	<0.001
45-54	1.532(1.084,2.165)	0.016
55-64	1.161(0.979,1.376)	0.086
≥65	0.782(0.445,1.375)	0.393
P for interaction ^a	0.002	
Digestive System Cancers		
<45	1.970(1.422,2.730)	<0.001
45-54	1.942(1.422,2.270)	0.030
55-64	1.084(0.809,1.453)	0.590
≥65	0.720(0.498,1.042)	0.082
P for interaction ^a	0.002	
Liver cancer		
<45	2.896(1.252,6.698)	0.013
45-54	2.226(1.174,4.220)	0.014
55-64	1.343(0.706,2.554)	0.368
≥65	0.506(0.221,1.158)	0.107
P for interaction ^a	<0.001	
Colorectal cancer		
<45	2.054(0.475,8.871)	0.335
45-54	3.042(1.636,5.658)	<0.001
55-64	1.054(0.684,1.625)	0.811
≥65	1.075(0.517,2.236)	0.847
P for interaction ^a	0.242	
Lung cancer		
<45	2.270(1.085,4.747)	0.029
45-54	1.968(1.084,3.572)	0.026
55-64	1.121(0.839,1.520)	0.439
≥65	0.653(0.353,1.207)	0.173
P for interaction ^a	0.006	

The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical).

^a The interaction between NAFLD and its age at diagnosis.

eTable 8 The Average Hazard Ratios (95% CI) of overall cancers among participants with new-onset NAFLD versus controls across age groups. (Excluding participants who take regular physical activity , n=56651, excluding participants who regularly take lipid-lowering drugs, n=52536, and exclude participants who with a late diagnosis of NAFLD, n=62595)

Age of new-onset NAFLD	Excluding participants who take regular physical activity ^a	P value	Excluding participants who regularly take lipid-lowering drugs ^a	P value	Exclude participants who with a late diagnosis of NAFLD ^b	P value	Additional adjusting for stages of steatosis and lifestyle factors ^c	P value
	Average HR (95%CI)		Average HR (95%CI)		Average HR (95%CI)		Average HR (95%CI)	
All cancer types								
<45	1.382(0.974,1.963)	0.069	1.512(1.070,2.102)	0.019	1.453 (1.035,2.040)	0.031	1.515 (1.081,2.123)	0.016
45-54	1.344(1.105,1.635)	0.003	1.552(1.177,2.047)	0.002	1.564 (1.180,2.072)	0.002	1.506 (1.144,1.981)	0.004
55-64	1.241(1.036,1.486)	0.018	1.189(1.006,1.406)	0.042	1.189 (1.007,1.404)	0.042	1.168 (0.990,1.378)	0.066
≥65	1.06(0.838,1.340)	0.626	0.734(0.428,1.260)	0.263	0.724 (0.421,1.245)	0.243	0.763 (0.456,1.278)	0.304
Digestive System Cancers								
<45	1.781(0.986,3.219)	0.055	2.023(1.135,3.607)	0.017	1.907 (1.079,3.372)	0.026	2.077 (1.169,3.691)	0.013
45-54	1.874(1.334,2.631)	<0.001	2.008(1.413,2.855)	<0.001	1.954 (1.419,2.693)	<0.001	1.837 (1.348,2.502)	<0.001
55-64	1.216(0.898,1.645)	0.207	1.204(0.871,1.664)	0.262	1.080 (0.812,1.437)	0.595	1.075 (0.804,1.437)	0.625
≥65	1.520(0.999,2.312)	0.050	0.682(0.445,1.045)	0.078	0.652 (0.455,1.037)	0.075	0.719 (0.503,1.028)	0.071
Liver cancer								
<45	2.327(1.022,5.297)	0.044	3.087(1.306,7.301)	0.010	2.675 (1.216,5.882)	0.014	2.831 (1.302,6.156)	0.009
45-54	2.232(1.054,4.722)	0.036	2.005(1.047,3.840)	0.036	2.475 (1.294,4.731)	0.006	2.132 (1.128,4.029)	0.020
55-64	1.474(0.753,2.881)	0.257	1.529(0.744,3.141)	0.248	1.249 (0.682,2.289)	0.471	1.318 (0.712,2.441)	0.379
≥65	2.061(0.725,5.858)	0.174	0.427(0.177,1.036)	0.059	0.510 (0.251,1.042)	0.065	0.645 (0.281,1.483)	0.302
Colorectal cancer								
<45	2.002(0.483,8.301)	0.339	1.991(0.482,8.227)	0.341	1.818 (0.576,6.934)	0.382	1.974 (0.491,7.943)	0.338
45-54	3.080(1.597,5.893)	0.001	4.307(2.297,8.076)	<0.001	2.933 (1.591,5.406)	<0.001	2.938 (1.601,5.392)	0.001
55-64	1.204(0.770,1.772)	0.416	1.166(0.721,1.885)	0.531	1.012 (0.659,1.554)	0.956	1.026 (0.663,1.588)	0.907

≥65	1.283(0.587,2.806)	0.532	1.455(0.715,2.963)	0.301	1.137 (0.577,2.240)	0.711	1.139 (0.592,2.192)	0.696
Lung cancer								
<45	2.928(1.410,6.081)	0.004	3.397(1.594,7.241)	0.002	2.953 (1.448,6.019)	0.003	2.913 (1.431,5.932)	0.003
45-54	1.267(0.808,1.986)	0.302	2.087(1.067,4.082)	0.032	2.078 (1.050,4.113)	0.036	2.021 (1.038,3.936)	0.038
55-64	1.129(0.828,1.539)	0.443	1.158(0.831,1.616)	0.386	1.154 (0.867,1.537)	0.325	1.126 (0.852,1.489)	0.405
≥65	1.061(0.671,1.676)	0.801	0.524(0.257,1.068)	0.075	0.618 (0.308,1.242)	0.177	0.612 (0.324,1.160)	0.133

^a The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical).

^b A late diagnosis of NAFLD is considered to be severe NAFLD or cirrhosis.

^c The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical), stages of steatosis (categorical), sedentary (categorical), high-fat diet (categorical), salt intake (categorical).

eTable 9 The Average Hazard Ratios (95% CI) of overall cancers among participants with new-onset NAFLD versus controls across age groups after PSM (n=53778)

Age of new-onset NAFLD	Average HR (95%CI)	P value
All cancer types		
<45	1.514(1.162,1.971)	0.002
45-54	1.511(1.081,2.112)	0.015
55-64	1.175(0.977,1.385)	0.054
≥65	0.754(0.444,1.280)	0.296
P for interaction ^a	0.004	
Digestive System Cancers		
<45	2.086(1.136,3.831)	
45-54	1.878(1.377,2.561)	<0.001
55-64	1.082(0.816,1.434)	0.581
≥65	0.707(0.620,1.003)	0.051
P for interaction ^a	0.019	
Liver cancer		
<45	2.355(1.037,5.347)	0.040
45-54	2.203(1.888,4.085)	0.012
55-64	1.245(0.684,2.268)	0.472
≥65	0.276(NA)	
P for interaction ^a	0.001	
Colorectal cancer		
<45	2.033(0.477,8.667)	0.337
45-54	2.988(1.630,5.477)	<0.001
55-64	1.045(0.686,1.594)	0.836
≥65	1.116(0.571,2.187)	0.748
P for interaction ^a	0.240	
Lung cancer		
<45	2.154(1.052,4.409)	0.035
45-54	1.980(1.103,3.553)	0.022
55-64	1.132(0.851,1.505)	0.396
≥65	0.642(0.344,1.199)	0.164
P for interaction ^a	0.006	

The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical).

^a The interaction between NAFLD and its age at diagnosis.

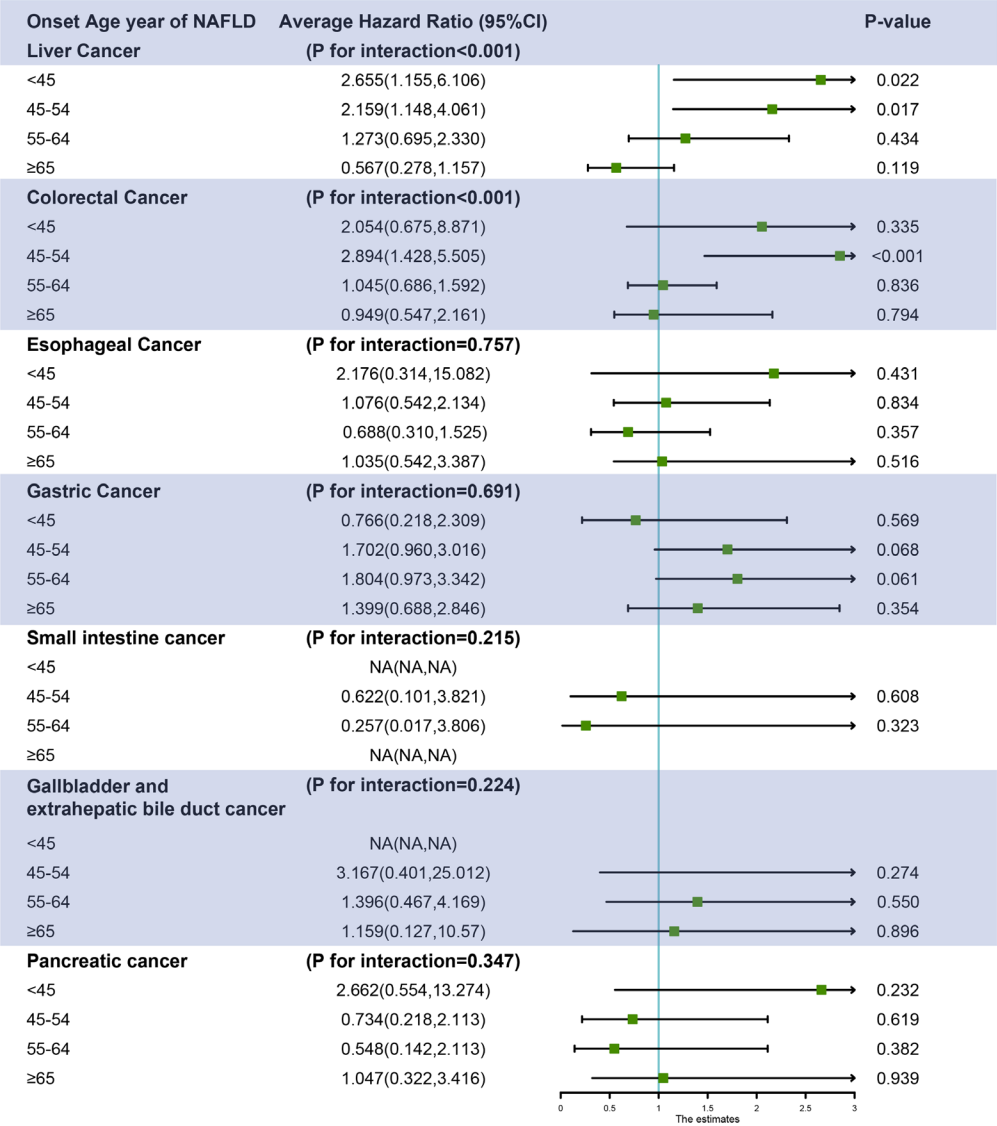
eTable 10 The Average Hazard Ratios (95% CI) of overall cancers among participants with new-onset MAFLD versus controls across age groups. (n=61712)

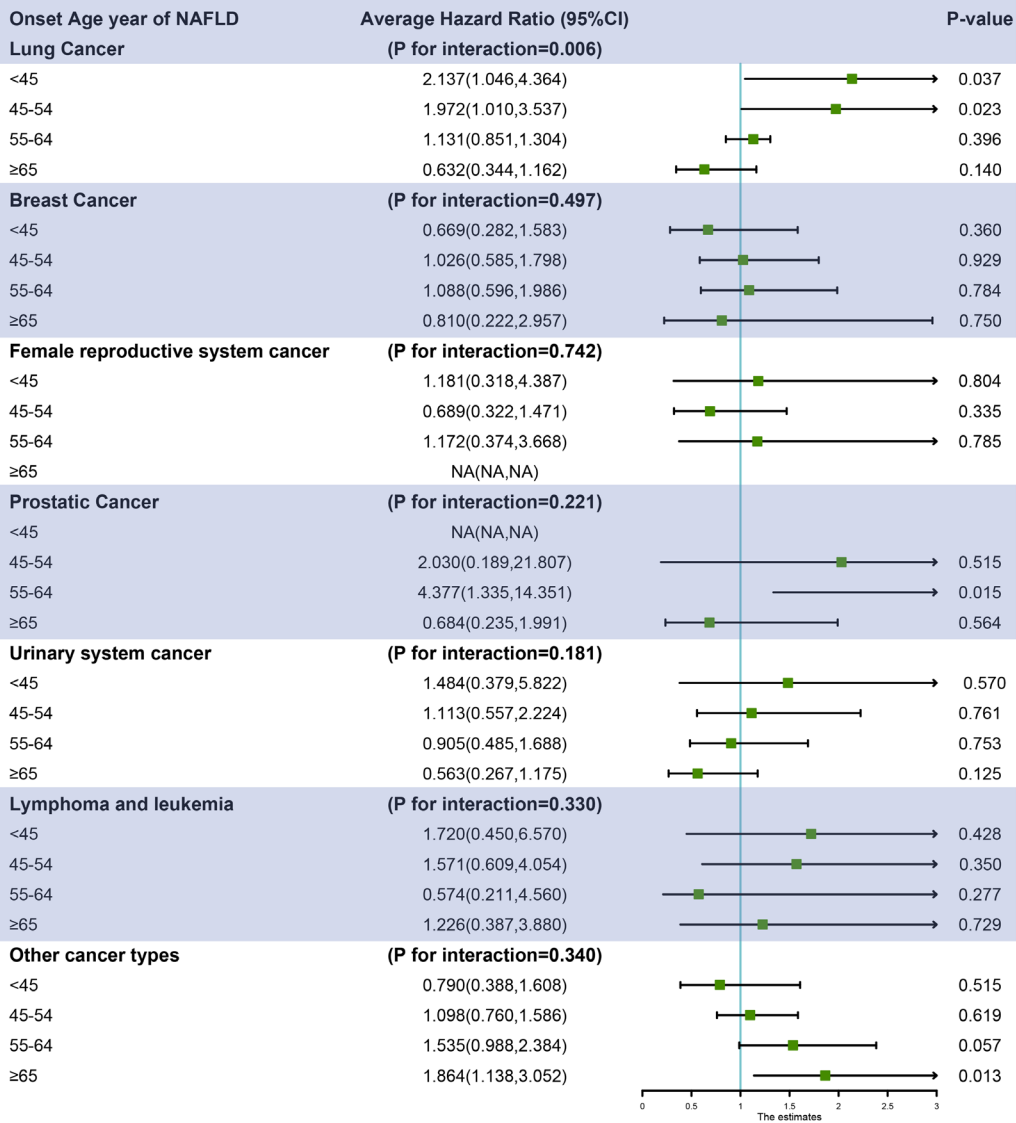
Age of new-onset MAFLD	Average HR (95%CI)	P value
All cancer types		
<45	1.493(1.063,2.100)	0.021
45-54	1.480(1.122,1.952)	0.006
55-64	1.165(0.987,1.377)	0.071
≥65	0.640(0.369,1.112)	0.113
P for interaction ^a	<0.001	
Digestive System Cancers		
<45	1.854(1.333,2.576)	<0.001
45-54	1.851(1.040,3.297)	0.036
55-64	1.020(0.866,1.356)	0.792
≥65	0.730(0.514,1.038)	0.078
P for interaction ^a	0.002	
Liver cancer		
<45	2.362(1.132,4.928)	0.022
45-54	2.131(1.138,3.991)	0.018
55-64	1.109(0.604,2.040)	0.738
≥65	0.569(0.278,1.167)	0.124
P for interaction ^a	<0.001	
Colorectal cancer		
<45	2.033(0.472,8.754)	0.341
45-54	3.908(1.681,5.931)	0.009
55-64	0.971(0.631,1.494)	0.894
≥65	1.178(0.589,2.354)	0.642
P for interaction ^a	0.114	
Lung cancer		
<45	2.015(1.042,4.663)	0.039
45-54	1.894(1.000,3.590)	0.050
55-64	1.139(0.849,1.530)	0.385
≥65	0.617(0.351,1.087)	0.095
P for interaction ^a	0.009	

The model was adjusted for age (continuous), sex (categorical), BMI (continuous), waist circumference (continuous), TC (continuous), TG (continuous), Tbil (continuous), hsCRP (continuous), ALT (continuous), smoking status (categorical), physical activity (categorical), Hypertension (categorical), Diabetes (categorical), Gallbladder polyps (categorical), GSD (categorical).

^a The interaction between NAFLD and its age at diagnosis.

eFigure 1 The Average Hazard Ratios (95% CI) of specific cancers among participants with new-onset NAFLD versus controls across age groups.





eFigure 2 Populations Attributable Fractions (PAFs) of cancer associated with new-onset NAFLD in different ages

