

ORIGINAL ARTICLE

Risk of nonalcoholic fatty liver disease and associations with gastrointestinal cancers

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Abstract

Metabolic syndrome may contribute to the rising incidence of multiple gastrointestinal (GI) cancers in recent birth cohorts. However, other than hepatocellular carcinoma, the association between nonalcoholic fatty liver disease (NAFLD) and risk of non-liver GI cancers is unexplored. We prospectively examined the associations of NAFLD risk with GI cancers among 319,290 participants in the UK Biobank (2006–2019). Baseline risk for NAFLD was estimated using the Dallas Steatosis Index, a validated prediction tool. Multivariable Cox models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) according to NAFLD risk categories: low (<20%), intermediate (20%–49%), and high (≥50%). We also examined the associations by age of cancer diagnosis (earlier onset [<60] vs. ≥ 60). A total of 273 incident liver cancer and 4789 non-liver GI cancer cases were diagnosed. Compared with individuals at low risk for NAFLD, those at high risk had 2.41-fold risk of liver cancer (RR = 2.41, 95% CI: 1.73–3.35) and 23% increased risk of non-liver GI cancers (RR = 1.23, 95% CI: 1.14–1.32) (all $p_{\text{trend}} < 0.001$). Stronger associations were observed for men and individuals who were obese (all $p_{\text{interaction}} < 0.05$). NAFLD-associated elevated risk was stronger for earlier-onset cancers. For each 25% increase in NAFLD risk, the RRs for earlier-onset cancers were 1.32 (95% CI: 1.05–1.66) for esophageal cancer, 1.35 (95% CI: 1.06–1.72) for gastric cancer, 1.34 (95% CI: 1.09–1.65) for pancreatic cancer, and 1.10 (95% CI: 1.01–1.20) for colorectal cancer. **Conclusion:** NAFLD risk was associated with an increased risk of liver and most GI cancers, especially those of earlier onset.

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INTRODUCTION

Gastrointestinal (GI) cancers account for about 30% of new cancer cases and 39% of cancer deaths globally.^[1] Over the past three decades, the incidence of liver cancer doubled between 1990 and 2015 in the United States and most European countries.^[2] For several GI cancers, such as colorectal cancer (CRC), drastic increase among younger ages and recent birth cohorts was observed in the United States and United Kingdom.^[3,4] The substantial increase in obesity,^[5] diabetes,^[6] and metabolic dysregulation^[7] in the past several decades has been hypothesized to contribute to this alarming rise in cancer incidence, especially among younger adults; however, the evidence thus far is limited.

Accumulating evidence suggests that metabolic dysregulation may contribute to the development of GI cancers. Metabolic syndrome (MetS), a constellation of metabolic abnormalities including abdominal obesity, abnormal glucose metabolism, hypertension, elevated triglyceride, and low high-density lipoprotein cholesterol, has been linked with about 21% increased risk of overall GI cancers and 25% increased risk of early-onset CRC (age < 50 years), respectively.^[8,9] As such, it is hypothesized that nonalcoholic fatty liver disease (NAFLD), the hepatic manifestation of MetS that currently affects at least one-quarter of the world population,^[10] may contribute to the etiology of GI cancers. While NAFLD is a well-established risk factor for hepatocellular carcinoma (HCC),^[11] studies on its association with extrahepatic cancers are limited. A recent meta-analysis reported associations between NAFLD and increased risk of multiple GI cancers, including esophageal, gastric, pancreatic, and CRC.^[12] However, the power/sample size for each cancer endpoint was limited, and most of the studies included were from Asian countries where body fat distribution and other risk factors are different from the US/European populations. Misclassifications due to marked underreporting of NAFLD in clinical records^[13] and poor sensitivity of ultrasonography to detect mild hepatic steatosis^[14] may further bias the effect estimates.

To address these knowledge gaps, we leveraged the UK Biobank, a large, well-established longitudinal cohort, to prospectively examine the association between NAFLD and risk of GI cancer, especially those of earlier age of onset. To estimate an individual's underlying risk of NAFLD, we used the Dallas Steatosis Index (DSI),^[15,16] a clinical prediction tool based on readily available clinical predictors, derived and validated against the near-gold standard for hepatic steatosis (MR spectroscopy).

METHODS

Study population

The UK Biobank is a population-based prospective study with over 500,000 participants aged 37–73 years old, recruited and assessed across 22 assessment centers across the United Kingdom in 2006–2010.^[17] The UK Biobank has approval from the North West Multicenter Research Ethics Committee, the National Information Governance Board for Health & Social Care, and the Community Health Index Advisory Group in Scotland. Informed consent with electronic signature was obtained from all participants. The proposal of the current study was approved by the UK Biobank in November 2019 (Application ID: 55288).

Among 423,280 participants with information on DSI components, we excluded participants with malignant cancers and alternative liver disease (self-report of infectious or noninfectious hepatitis during any of the structured nurse interviews or the presence of hepatitis B or C) before baseline. Due to synergy between alcohol-associated and metabolic-dysfunction associated fatty liver disease, we restricted our primary analyses to 319,290 participants who reported alcohol intake frequency at never or special occasions only, one to three times per month and one to four times per week^[18] at the study baseline (Figure S1).

Ascertainment of gastrointestinal cancers

Incident GI cancer cases were identified through linkage to cancer registries and death records using the International Classification of Diseases, 10th Revision (ICD-10) code C15-C26. Complete follow-up was available up to February 29, 2020, for England and Wales and October 31, 2015, for Scotland. Our primary outcome was a composite of all GI cancers (Table S1). In addition, GI cancers were categorized into earlier onset (EO, before age 60) and later onset (LO, age ≥ 60) cancer according to age when the individual was diagnosed with cancer. We used 60 instead of younger ages as the cutoff due to a limited number of cases in the referent groups (i.e., low risk of NAFLD).

Risk of NAFLD

The primary exposure was predicted NAFLD risk estimated by the DSI. The DSI was derived in the Dallas Heart Study, in which hepatic steatosis was determined by ¹H MR spectroscopy^[15] and externally validated in a subset of the UK Biobank population, in which hepatic steatosis was determined by proton density fat

fraction (PDFF) mapping.^[16] The following clinical predictors routinely available in the primary care setting were used to calculate DSI, including postmenopausal status (according to age at baseline and sex), diabetes status or glucose if not diabetic, hypertension status, alanine aminotransferase (ALT) level, body mass index (BMI), race, and triglyceride level.^[15,16] Based on predicted risk of NAFLD, participants were categorized as low (<20%), intermediate (20%–49%), or high (≥50%) risk of NAFLD. The DSI performed well to discriminate people with versus without NAFLD (C statistic = 0.83, 95% confidence interval [CI]: 0.81–0.84) and outperformed other risk prediction tools.^[15] When applied to 4146 participants in the UK Biobank with PDFF, the low-risk category had a 91% sensitivity to exclude NAFLD, and the high-risk category had 87% specificity to diagnose NAFLD.^[16]

In the current analysis in the UK Biobank, race was categorized into four groups (White, Black, Asian, or other) according to self-reported information collected at baseline (2006–2010). Women were defined as being postmenopausal according to age at baseline and sex. Personal history of diabetes and hypertension was self-reported. Height was measured in a barefoot standing position using a Seca 202 device to the nearest 0.1 cm, and weight was measured by Tanita BC-418MA body composition analyzer to the nearest 0.1 kg. BMI was calculated by dividing weight in kilograms by height in meters squared. Glucose, ALT, and triglycerides were measured in the blood sample collected at the baseline visit. Glucose was measured by hexokinase analysis. ALT was measured by the International Federation of Clinical Chemistry and Laboratory Medicine analysis. Triglycerides were measured by glycerol-3-phosphate-peroxidase analysis.

Assessment of other covariates

Demographic characteristics and health-related behaviors were self-reported at baseline, including age, sex, educational qualifications, current smoking status (never, previous, and current), and pack-years of smoking for individuals who have ever smoked, alcohol intake frequency based on average intake over the past year, and information on family history of CRC. A two-level education variable (pre-college vs. post-college) was created according to educational qualifications. The Townsend Deprivation Index was derived from national census data, with higher scores representing higher levels of socioeconomic deprivation. Physical activity (metabolic equivalent task hours per week, MET-h/week) was calculated as the sum of MET hours each week for walking, moderate activity, and vigorous activity, assessed through the International Physical Activity Questionnaire.^[19]

Statistical analyses

We examined the association between NAFLD risk category (low risk: <20%, intermediate risk: 20%–49%, and high risk: ≥50%) with risk of overall GI cancer, liver cancer, non-liver GI cancers, and each GI cancer subtype. Person-years were accrued from the date of initial assessment center visit until the date of any cancer diagnosis (excluding non-melanoma skin cancer), the end of follow-up (July 31, 2019), or the date of death, whichever came first. Cox proportional hazard models were used to estimate age-adjusted and multivariable-adjusted relative risks (RRs) and 95% confidence intervals (CIs). Test for trend was estimated using predicted NAFLD risk as a continuous variable. In addition to age, the multivariable model was adjusted for sex, education, the Townsend Deprivation Index (in quartile), physical activity (MET-h/week, in quartile), smoking status and intensity, family history of CRC, and alcohol frequency. In addition, we examined the association between NAFLD risk and risk of earlier onset (before age 60) and later onset (age 60 and above) GI cancers, restricting to cancers with more than 50 cases diagnosed before the age of 60 years. We also tested the association of NAFLD risk with cancers that are not known to be strongly associated with metabolic dysregulation, including brain cancer and melanoma.

Stratification analyses according to sex, BMI, diabetes, smoking status, and alcohol consumption status were conducted. For liver cancer, we performed additional stratification according to Fibrosis-4 (FIB-4) index: <1.3, 1.3–2.67, and ≥2.67.^[20] Because of the interaction between alcohol-related and metabolic dysfunction-associated fatty liver disease, we conducted sensitivity analyses among daily alcohol drinkers only. All analyses were performed using R (version 4.0.5) and considered significant with two-sided $p < 0.05$.

RESULTS

Baseline characteristics of the study population according to NAFLD risk categories are found in [Table 1](#). Among 319,290 participants, 119,462 (37%) were at low risk, 106,368 (33%) were at intermediate risk, and 93,460 (30%) were at high risk of NAFLD. Participants with higher NAFLD risk were more likely to be diagnosed with diabetes and hypertension, have higher BMI, glucose, ALT, and triglycerides. For other characteristics, those at higher NAFLD risk tended to be male, have lower socioeconomic status, lower level of education, be physically inactive, ever smokers, and occasional or never alcohol drinkers.

TABLE 1 Baseline characteristics of 319,290 participants according to NAFLD risk category, UK Biobank 2006–2010

	Predicted NAFLD risk ^a		
	Low	Intermediate	High
No. of participants, n (%)	119,462 (37%)	106,368 (33%)	93,460 (30%)
Predicted NAFLD risk, mean (SD)	10.2 (5.0)	34.0 (8.7)	68.0 (11.9)
Characteristics of DSI component			
Age at baseline (years), mean (SD)	54.7 (8.4)	57.5 (8.0)	57.8 (7.7)
Female, n (%)	80,517 (67%)	55,617 (52%)	44,199 (47%)
Body mass index (kg/m ²), mean (SD)	23.9 (2.6)	27.8 (3.3)	32.1 (4.8)
Race, n (%)			
White	112,795 (94%)	99,660 (94%)	87,254 (93%)
Black	3265 (2.7%)	2045 (1.9%)	590 (0.6%)
Asian	1932 (1.6%)	2911 (2.7%)	3530 (3.8%)
Other	1470 (1.2%)	1752 (1.6%)	2086 (2.2%)
History of diabetes, n (%)	1041 (0.9%)	3373 (3.1%)	13,194 (14%)
History of hypertension, n (%)	37,160 (31%)	58,338 (55%)	68,938 (74%)
Glucose (mg/dl), mean (SD)	86.5 (12.7)	90.6 (17.3)	101 (32.9)
Triglyceride (mg/dl), mean (SD)	101 (41.6)	150 (64.2)	228 (108)
Alanine aminotransferase (IU/L), mean (SD)	16.7 (7.4)	22.9 (11.6)	31.9 (17.1)
Other characteristics			
Townsend index, mean (SD)	−1.4 (3.1)	−1.3 (3.1)	−1.0 (3.2)
Education, n (%)			
Pre-college	67,965 (57%)	67,199 (63%)	62,172 (67%)
Post-college	50,464 (42%)	37,882 (36%)	29,988 (32%)
Family history of colorectal cancer, n (%)	12,290 (10%)	11,937 (11%)	10,659 (11%)
Physical activity (MET-h/week), mean (SD)	47.3 (45.5)	45.3 (46.0)	39.8 (44.5)
Smoking status			
Never smoker, n (%)	75,148 (63%)	61,348 (58%)	49,616 (53%)
Ever smoker, n (%)	43,992 (37%)	44,634 (42%)	43,389 (46%)
Pack-years among ever smokers, mean (SD)	19.4 (16.3)	22.8 (17.5)	26.7 (20.5)
Alcohol intake			
Occasional or never	25,574 (21%)	25,184 (24%)	26,237 (28%)
1–3 times per month	16,457 (14%)	14,785 (14%)	13,521 (14%)
1–4 times per week	77,431 (65%)	66,399 (62%)	53,702 (58%)
Fibrosis-4 index, mean (SD)	1.4 (1.9)	1.3 (3.0)	1.3 (1.3)

Abbreviations: DSI, Dallas Steatosis Index; MET, metabolic equivalent task; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation.

^aCategorized by predicted NAFLD risk derived from the DSI: low: <20%, intermediate: 20%–49%, or high: ≥50%.

Overall GI cancer

During 3,196,537 person-years of follow-up, a total of 5062 GI cancers were diagnosed, including 273 liver cancer and 4789 non-liver GI cancers (Figure 1 and Table 2). After multivariable adjustment, predicted NAFLD risk was associated with an increased risk of overall GI cancer. Compared with those at low risk of NAFLD, individuals at intermediate and high NAFLD risk had 6% ($RR_{\text{intermediate vs. low}} = 1.06$, 95% CI: 0.99–1.14) and 27% ($RR_{\text{high vs. low}} = 1.27$, 95% CI: 1.18–1.36) increased risk of overall GI cancer, respectively ($p_{\text{trend}} < 0.001$). This positive association

was observed for both liver cancer and non-liver GI cancers.

Liver cancer

Compared with participants at low risk of NAFLD, the risk of liver cancer was 31% ($RR_{\text{intermediate vs. low}} = 1.31$, 95% CI: 0.92–1.87) higher for individuals at intermediate risk of NAFLD, and 2.41-fold ($RR_{\text{high vs. low}} = 2.41$, 95% CI: 1.73–3.35) among individuals at high risk of NAFLD ($p_{\text{trend}} < 0.001$) (Table 2). Such positive association did not differ by FIB-4 index, history of

TABLE 2 Predicted NAFLD risk and risk of GI cancers

GI cancers	Predicted NAFLD risk ^a			Per 25% increase in predicted risk	<i>p</i> _{trend} ^b
	Low	Intermediate	High		
Person-years	1,205,617	1,061,337	929,582		
Overall GI cancers					
No. of cases	1426	1720	1916		
Incidence per 100,000 person-years	118.3	162.1	206.1		
Age-adjusted RR (95% CI)	1 [Ref]	1.14 (1.06–1.22)	1.44 (1.34–1.54)	1.19 (1.16–1.22)	<0.001
MV-adjusted RR (95%CI) ^c	1 [Ref]	1.06 (0.99–1.14)	1.27 (1.18–1.36)	1.13 (1.10–1.17)	<0.001
Liver cancer					
No. of cases	50	80	143		
Incidence per 100,000 person-years	4.1	7.5	15.4		
Age-adjusted RR (95% CI)	1 [Ref]	1.47 (1.03–2.10)	2.98 (2.16–4.12)	1.78 (1.58–2.00)	<0.001
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.31 (0.92–1.87)	2.41 (1.73–3.35)	1.65 (1.46–1.86)	<0.001
Non-liver GI cancers					
No. of cases	1376	1640	1773		
Incidence per 100,000 person-years	114.1	154.5	190.7		
Age-adjusted RR (95% CI)	1 [Ref]	1.13 (1.05–1.21)	1.38 (1.28–1.48)	1.16 (1.13–1.20)	<0.001
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.05 (0.98–1.13)	1.23 (1.14–1.32)	1.11 (1.08–1.14)	<0.001
Esophageal cancer					
No. of cases	118	182	224		
Incidence per 100,000 person-years	9.8	17.1	24.1		
Age-adjusted RR (95%CI)	1 [Ref]	1.43 (1.13–1.80)	1.99 (1.59–2.49)	1.33 (1.23–1.45)	<0.001
MV-adjusted RR (95%CI) ^c	1 [Ref]	1.22 (0.97–1.54)	1.54 (1.23–1.94)	1.21 (1.11–1.32)	<0.001
Gastric cancer					
No. of cases	93	126	148		
Incidence per 100,000 person-years	7.7	11.9	15.9		
Age-adjusted RR (95% CI)	1 [Ref]	1.26 (0.96–1.65)	1.68 (1.29–2.18)	1.26 (1.14–1.39)	<0.001
MV-adjusted RR (95%) ^c	1 [Ref]	1.09 (0.83–1.43)	1.31 (1.00–1.71)	1.14 (1.03–1.27)	0.01
Pancreatic cancer					
No. of cases	155	218	223		
Incidence per 100,000 person-years	12.9	20.5	24.0		
Age-adjusted RR (95% CI)	1 [Ref]	1.30 (1.06–1.60)	1.51 (1.23–1.85)	1.21 (1.11–1.31)	<0.001
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.28 (1.04–1.58)	1.46 (1.18–1.80)	1.19 (1.10–1.29)	<0.001
Gallbladder cancer					
No. of cases	11	29	39		
Incidence per 100,000 person-years	0.9	2.7	4.2		
Age-adjusted RR (95% CI)	1 [Ref]	2.39 (1.19–4.79)	3.64 (1.86–7.13)	1.59 (1.28–1.97)	<0.001
MV-adjusted RR (95% CI) ^c	1 [Ref]	2.38 (1.18–4.79)	3.47 (1.75–6.87)	1.54 (1.24–1.93)	<0.001
Small intestine cancer					
No. of cases	36	41	52		
Incidence per 100,000 person-years	3.0	3.9	5.6		

(Continues)

TABLE 2 (Continued)

GI cancers	Predicted NAFLD risk ^a			Per 25% increase in predicted risk	P_{trend}^b
	Low	Intermediate	High		
Age-adjusted RR (95% CI)	1 [Ref]	1.11 (0.71–1.74)	1.59 (1.04–2.44)	1.26 (1.06–1.49)	0.01
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.08 (0.69–1.70)	1.52 (0.98–2.36)	1.24 (1.04–1.48)	0.02
Colorectal cancer					
No. of cases	882	971	1016		
Incidence per 100,000 person-years	73.2	91.5	109.3		
Age-adjusted RR (95% CI)	1 [Ref]	1.05 (0.96–1.15)	1.24 (1.14–1.36)	1.11 (1.07–1.15)	<0.001
MV-adjusted RR (95% CI) ^c	1 [Ref]	0.99 (0.90–1.08)	1.13 (1.03–1.24)	1.07 (1.03–1.11)	<0.001
Anal cancer					
No. of cases	48	36	26		
Incidence per 100,000 person-years	4.0	3.4	2.8		
Age-adjusted RR (95% CI)	1 [Ref]	0.76 (0.49–1.18)	0.62 (0.39–1.01)	0.83 (0.68–1.02)	0.07
MV-adjusted RR (95% CI) ^c	1 [Ref]	0.80 (0.52–1.25)	0.66 (0.40–1.08)	0.85 (0.69–1.04)	0.12

Abbreviations: CI, confidence interval; GI, gastrointestinal; MV, multivariable; NAFLD, nonalcoholic fatty liver disease; RR, relative risk.

^aCategorized by predicted NAFLD risk derived from the DSI: low: <20%, intermediate: 20%–49%, or high: ≥50%.

^bTest for trend was calculated using predicted NAFLD risk as a continuous variable.

^cAdjusted for age (year), sex (female/male), education (pre-college/post-college), the Townsend Deprivation Index (in quartiles), physical activity (MET-h/week, in quartiles), smoking status, and intensity (never smoker, past smoker 1–19 pack-years, past smoker >19 pack-years, past smoker unknown pack-year, current smoker 1–19 pack-years, current smoker >19 pack-years, or current smoker unknown pack-year), family history of colorectal cancer, and alcohol frequency (occasional or never, 1–3 times per month, or 1–4 times per week).

diabetes, smoking status, and alcohol frequency ($p_{\text{interaction}} > 0.05$) (Figure 2 and Figure S2). However, the association was stronger among men ($RR_{\text{per 25% increase}} = 1.93$, 95% CI: 1.64–2.27) than in women ($RR_{\text{per 25% increase}} = 1.39$, 95% CI: 1.15–1.67) ($p_{\text{interaction}} = 0.002$). The association was also stronger among individuals with BMI ≥ 30 kg/m² ($RR_{\text{per 25% increase}} = 2.10$, 95% CI: 1.60–2.75), compared to individuals with a lower BMI ($RR_{\text{per 25% increase}} = 1.44$, 95% CI: 1.21–1.72) ($p_{\text{interaction}} < 0.001$).

Non-liver GI cancers

Compared with participants at low risk of NAFLD, individuals at intermediate or high NAFLD risk had 5% ($RR_{\text{intermediate vs. low}} = 1.05$, 95% CI: 0.98–1.13) and 23% ($RR_{\text{high vs. low}} = 1.23$, 95% CI: 1.14–1.32) increased risk of non-liver GI cancer, respectively ($p_{\text{trend}} < 0.001$). This positive association was observed among all GI cancer subtypes (esophageal, gastric, pancreatic, gallbladder, small intestine, and colorectal; all $p_{\text{trend}} < 0.05$) except for anal cancer. The association between NAFLD risk and non-liver GI cancer were similar among individuals with versus without a history of diabetes, never versus current smokers, and with different alcohol frequency (all $p_{\text{interaction}} > 0.05$) (Figure 3). Similar to liver cancer, a more pronounced association was observed among men ($RR_{\text{per 25% increase}} = 1.15$, 95% CI: 1.10–1.19) than

among women ($RR_{\text{per 25% increase}} = 1.08$, 95% CI: 1.04–1.13) ($p_{\text{interaction}} = 0.005$), and among individuals with BMI ≥ 30 kg/m² ($RR_{\text{per 25% increase}} = 1.12$, 95% CI: 1.05–1.19) than among individuals with BMI < 30 kg/m² ($RR_{\text{per 25% increase}} = 1.07$, 95% CI: 1.03–1.12) ($p_{\text{interaction}} = 0.05$). In sensitivity analyses, the association between NAFLD risk and multiple GI cancers remained largely unchanged when restricted to daily alcohol drinkers (Table S3). No significant relationship was found between NAFLD risk and brain cancer or melanoma (Table S4).

Earlier-onset and later-onset GI cancers

We examined whether the association between NAFLD risk and GI cancer differs by age of onset (earlier onset: <60; later onset: ≥60). Interestingly, for each cancer type, stronger associations were observed for cancers of earlier onset compared with cancers of later onset. For each 25% increase in NAFLD risk, the RRs for earlier onset were 1.32 (95% CI: 1.05–1.66) for esophageal cancer, 1.35 (95% CI: 1.06–1.72) for gastric cancer, 1.34 (95% CI: 1.09–1.65) for pancreatic cancer, and 1.10 (95% CI: 1.01–1.20) for CRC. In contrast, for cancers diagnosed after age 60, the corresponding RRs were 1.20 (95% CI: 1.09–1.32) for esophageal cancer, 1.11 (95% CI: 0.98–1.24) for gastric cancer, 1.18 (95% CI: 1.08–1.29) for pancreatic cancer, and 1.09 (95% CI: 1.04–1.13) for CRC (Table 3).

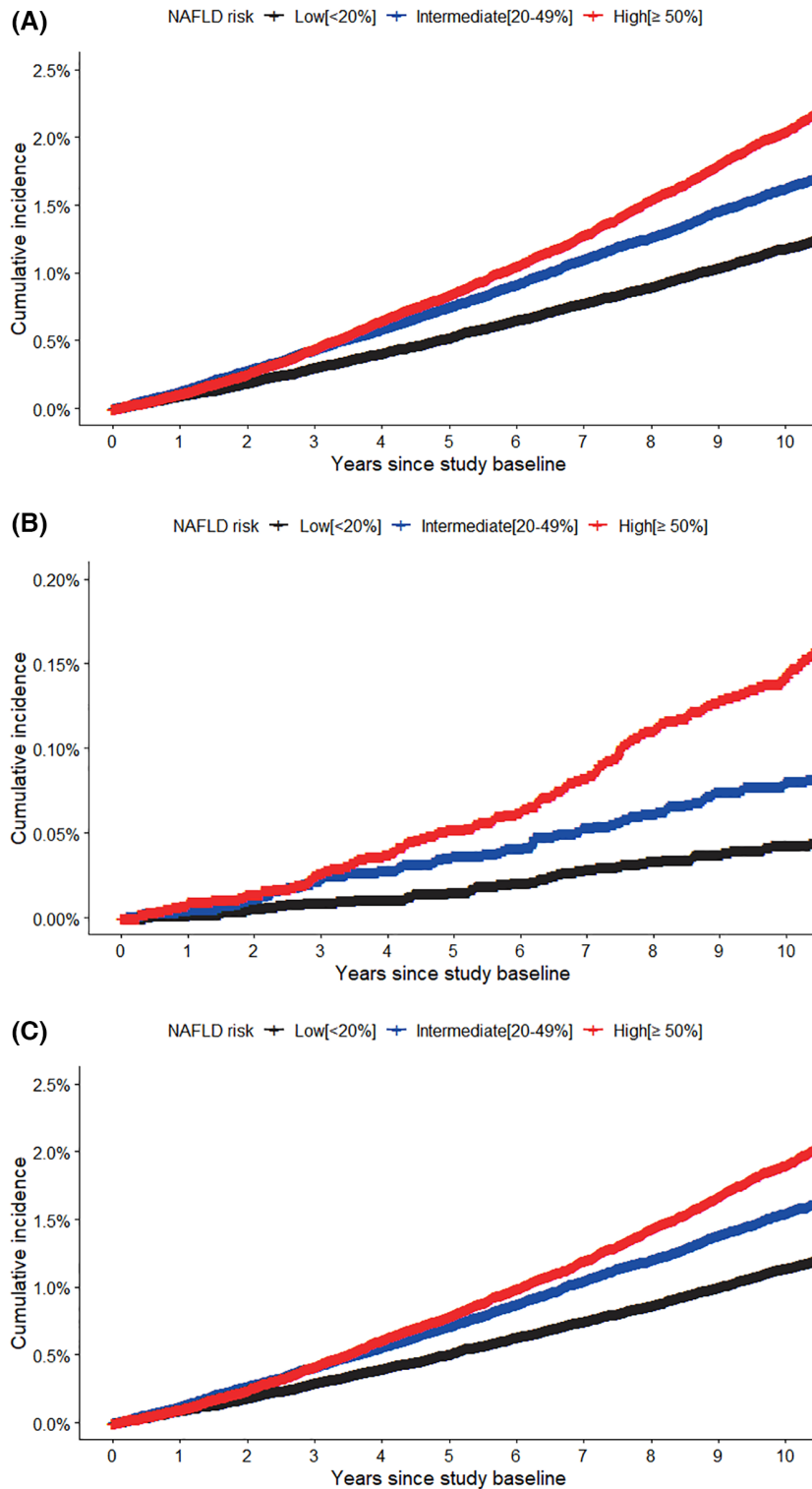


FIGURE 1 Cumulative incidence of cancer curves for nonalcoholic fatty liver disease (NAFLD) risk categories. (A) Overall gastrointestinal (GI) cancers. (B) Liver cancer. (C) Non-liver GI cancers.

DISCUSSION

In this large prospective cohort study, we found that predicted NAFLD risk, estimated by a validated prediction tool, was associated with an increased risk of liver

cancer and non-liver GI cancers (e.g., esophageal, gastric, pancreatic, gallbladder, small intestine, colorectal). Such elevated risks were similarly observed according to history of diabetes, smoking status, and alcohol consumption and were generally stronger among men and individuals with higher BMI. Notably, we also observed

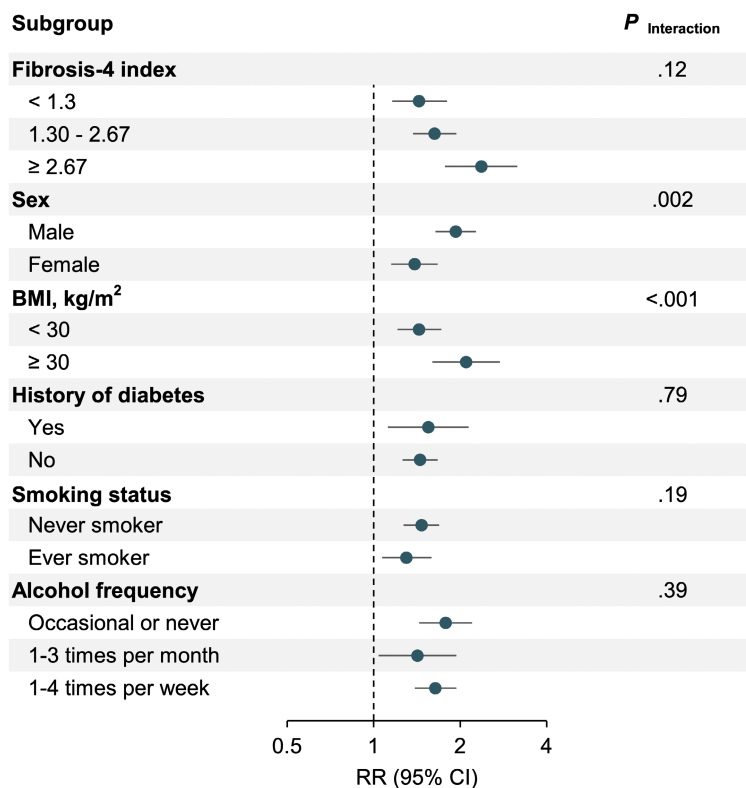


FIGURE 2 Stratified analyses for predicted NAFLD risk (per 25% increase) and risk of liver cancer. All relative risks (RRs) were adjusted for covariates as the multivariable model in Table 2 without the stratifying factor. Abbreviations: BMI, body mass index; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease.

stronger associations between NAFLD risk and esophageal, gastric, pancreatic, and CRC diagnosed before age 60 compared with those diagnosed at later ages. This large-scale study reports positive associations between NAFLD and non-liver GI cancer, especially those of earlier onset. The findings not only highlight the need for additional mechanistic studies but also lend support to the importance of screening for NAFLD in primary care as well as informing cancer screening when NAFLD is clinically recognized.

Although the association of NAFLD with liver cancer is well-established, evidence on whether such association differs by fibrosis stage is inconsistent. One large retrospectively matched cohort study with 296,707 patients with NAFLD in the Veterans Affairs (VA) database reported an increased risk of HCC among patients with NAFLD only among those with cirrhosis.^[21] This differs from results from another VA cohort study of 1500 patients with HCC, in which NAFLD was the leading cause of HCC among patients without cirrhosis.^[22] A recent meta-analysis showed that NAFLD-related HCC was associated with a higher proportion of patients without cirrhosis (38.5% vs. 14.6% for HCC due to other causes).^[23] Our analyses suggest that the positive association between NAFLD risk and liver cancer was consistently observed within each level of FIB-4 index, a well-established indicator of liver cirrhosis. This indicates that NAFLD, regardless of fibrosis

stage, serves as a risk factor for liver cancer. While no statistical interactions were detected, future studies are warranted to validate the slightly stronger association in those with FIB-4 index ≥ 2.67 and potential interaction with liver fat quantity. Additional studies are warranted to confirm our findings and to study the mechanisms that predispose patients with NAFLD to liver cancer, which may include genetic risk factors,^[24] hyperinsulinemia, abnormal bile acid signaling, altered microbiome, and lipotoxicity.^[25]

Emerging data support the associations between NAFLD and several non-liver GI cancers,^[12] including esophageal,^[26–29] pancreatic,^[26,29] and colorectal cancer.^[26–29] However, most of these studies were conducted in Asia with a limited number of outcomes. CRC is among the most studied, yet there were only eight prospective studies with a total of 776 CRC cases, ranging from 15 to 276 cases in each study.^[12] Thus, our analyses, with a total of 4789 incident non-liver GI cancers, including 2869 colorectal cancers, 524 esophageal cancers, and 596 pancreatic cancers, significantly extend the impact of prior findings. In addition, our analyses provided more evidence from Western populations. In addition to prospective examination of the associations with multiple GI cancers in a homogeneous population primarily of European ancestry, we investigated the role of estimated risk of NAFLD, using a validated clinical prediction tool that

TABLE 3 Predicted NAFLD risk and risk of non-liver GI cancers according to age of onset

GI cancers	Predicted NAFLD risk ^a			Per 25% increase in predicted risk	p_{trend}^b
	Low	Intermediate	High		
Earlier onset (age < 60 years)					
Non-liver GI cancers					
No. of cases	321	254	288		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.08 (0.91–1.27)	1.39 (1.17–1.65)	1.15 (1.07–1.23)	<0.001
Esophageal cancer					
No. of cases	17	22	31		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.36 (0.71–2.59)	1.91 (1.03–3.54)	1.32 (1.05–1.66)	0.02
Gastric cancer					
No. of cases	16	21	27		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.46 (0.75–2.84)	1.97 (1.03–3.76)	1.35 (1.06–1.72)	0.01
Pancreatic cancer					
No. of cases	24	33	28		
MV-adjusted RR (95% CI) ^c	1 [Ref]	2.01 (1.17–3.44)	1.97 (1.11–3.50)	1.34 (1.09–1.65)	0.006
Colorectal cancer					
No. of cases	232	158	178		
MV-adjusted RR (95% CI) ^c	1 [Ref]	0.97 (0.79–1.20)	1.29 (1.05–1.59)	1.10 (1.01–1.20)	0.03
Later-onset (age ≥ 60 years)					
Non-liver GI cancers					
No. of cases	1055	1386	1485		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.07 (0.98–1.16)	1.24 (1.14–1.34)	1.12 (1.09–1.16)	<0.001
Esophageal cancer					
No. of cases	101	160	193		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.21 (0.94–1.55)	1.51 (1.18–1.93)	1.20 (1.09–1.32)	<0.001
Gastric cancer					
No. of cases	77	105	121		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.02 (0.76–1.38)	1.21 (0.90–1.62)	1.11 (0.98–1.24)	0.09
Pancreatic cancer					
No. of cases	131	185	195		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.20 (0.96–1.51)	1.42 (1.13–1.78)	1.18 (1.08–1.29)	<0.001
Colorectal cancer					
No. of cases	650	813	838		
MV-adjusted RR (95% CI) ^c	1 [Ref]	1.02 (0.92–1.13)	1.15 (1.03–1.27)	1.09 (1.04–1.13)	<0.001

Abbreviations: CI, confidence interval; GI, gastrointestinal; MV, multivariable; NAFLD, nonalcoholic fatty liver disease; RR, relative risk.

^aCategorized by predicted NAFLD risk derived from the DSI: low: <20%, intermediate: 20%–49%, or high: ≥50%.

^bTest for trend was calculated using predicted NAFLD risk as a continuous variable.

^cMV-adjusted RR (95% CI) was adjusted for age (years), sex (female/male), education (pre-college/post-college), the Townsend Deprivation Index (in quartiles), physical activity (MET-h/week, in quartiles), smoking status, and intensity (never smoker, past smoker 1–19 pack-years, past smoker > 19 pack-years, past smoker unknown pack-year, current smoker 1–19 pack-years, current smoker > 19 pack-years, or current smoker unknown pack-year), family history of colorectal cancer, and alcohol frequency (occasional or never, 1–3 times per month, or 1–4 times per week).

outperformed other risk analysis tools,^[15] including Framingham Steatosis Index,^[30] Hepatic Steatosis Index,^[31] Fatty Liver Index derived from an Italian Cohort,^[32] and the updated Fatty Liver Index derived from the US population.^[33] We observed positive associations between NAFLD risk and most types of GI cancers. A lack of association with anal cancer may reflect the different embryonic origin or viral pathophysiology of this cancer type. In totality, our findings

lend strong support to the role of NAFLD in the etiology of a range of extrahepatic GI cancers.

We also observed stronger associations between NAFLD risk and risk of GI cancers of earlier onset compared with cases diagnosed at older ages. While the underlying mechanisms remain to be explored, these findings are in line with other evidence, suggesting that recent birth cohorts have been exposed to metabolic dysregulation much earlier in life and thus are

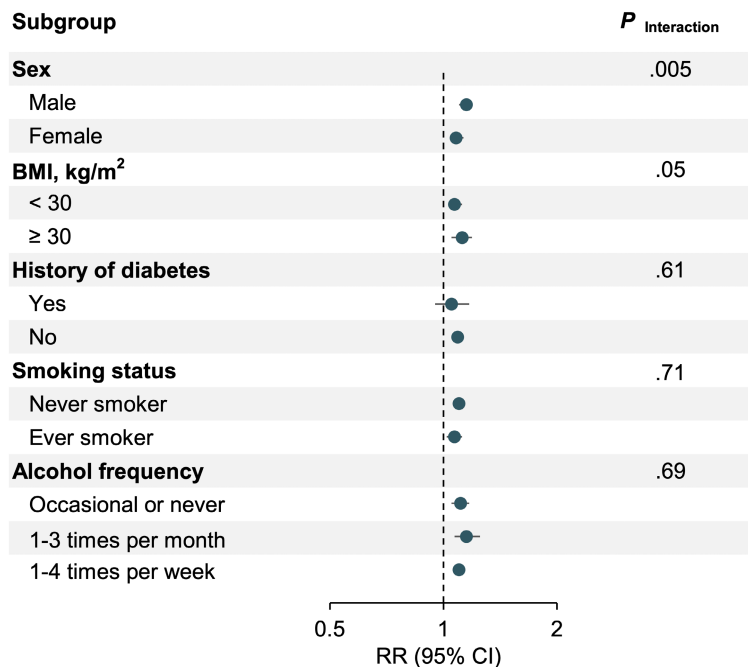


FIGURE 3 Stratified analyses for predicted NAFLD risk (per 25% increase) and non-liver GI cancers. All relative risks (RRs) were adjusted for covariates as the multivariable model in Table 2 without the stratifying factor. Abbreviations: BMI, body mass index; CI, confidence interval; GI, gastrointestinal; NAFLD, nonalcoholic fatty liver disease.

more prone to the associated health consequences. Gut microbiome alterations throughout the life course are hypothesized to mediate these associations.^[34,35] In addition, the stronger association observed among earlier-onset GI cancers may also be driven by genetic risks. Future investigations are warranted to study whether there is a shared genetic predisposition to earlier-onset GI cancers and NAFLD.

The mechanisms underlying the link between NAFLD and non-liver GI cancers have not been fully understood. Because NAFLD is strongly associated with obesity and metabolic syndrome,^[36,37] it is difficult to differentiate whether the association between NAFLD and non-liver GI cancers is caused by shared metabolic risk factors or by NAFLD itself. Compared with a previous review on the associations between GI cancers and BMI,^[38] our RR estimates across GI cancers were different, suggesting the need to further elucidate the role of NAFLD in GI cancer etiology that is dependent and independent of adiposity. Recent studies have emphasized a link between metabolism, low-grade chronic inflammation, and cancer development.^[39] NAFLD is characterized by gut dysbiosis and gut leakiness,^[40] in which the gut microbiota composition and/or signaling could conceivably be changed. These alterations of gut microbiota may lead to increased intestinal permeability,^[41,42] resulting in increased exposure to bacterial metabolites and microbiota-associated molecular patterns (MAMPS).^[40] Lipopolysaccharide, a type of MAMPS, may act on macrophages to alter the

release of cytokines (e.g., interleukin [IL]-1, IL-6, tumor necrosis factor) and activate tumor-promoting inflammation. Low-grade chronic inflammation, as well as fibrosis, has been hypothesized to be among the key drivers of non-liver GI cancers.^[43]

The primary strength of our study is the large number of incident GI cancers, which includes more incident cases than the aggregated number of cases from a recent meta-analysis of cohort studies.^[12] In addition, we used the DSI to estimate NAFLD risk as would have been determined by very sensitive and specific MR-based fat quantification methods.^[44] Compared to using liver ultrasound or ICD codes, this strategy minimizes misclassification in which many mild presentations of NAFLD would be mischaracterized as controls. The decision to use the DSI also provides outcome validation to the proposed DSI-based NAFLD screening programs.^[16] Our study also has limitations. First, residual confounding could not be ruled out. Second, the UK Biobank primarily included a non-Hispanic White population, thus limiting the generalizability of our findings. Third, we have limited power to assess risk of GI cancers diagnosed under age 50. Although most evidence thus far used age 50 to define early-onset CRC, the affected birth cohorts were carrying their elevated risk to older ages,^[45] and an increase in CRC among ages 50–54 were reported in the United States.^[45,46] Because CRC cancer screening starts from age 60 in the United Kingdom,^[47] understanding NAFLD's contribution to CRC diagnosed before age 60

is also important. Fourth, due to the very few GI cancer outcomes in 4615 participants with MR imaging/PDFF data in the UK Biobank, we were unable to perform a sensitivity analysis to validate our results. Fifth, previous studies have suggested that higher liver fat in patients with NAFLD was associated with a higher risk of fibrosis progression.^[48] However, we were not able to explore whether risk of GI cancers would be differentiated among patients with NAFLD with different liver fat content, as the derivation of the DSI converted hepatic steatosis as a binary outcome.^[15]

In summary, NAFLD risk, as estimated by the DSI, is associated with an increased risk of incident liver and non-liver GI cancers. These findings highlight the potential role of tailoring cancer screening for those with NAFLD.

AUTHOR CONTRIBUTIONS

Xiaoyu Zong, Mengyao Shi, and Yin Cao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Scott McHenry, Nicholas O. Davidson, and Yin Cao. *Acquisition, analysis, or interpretation of data:* Scott McHenry, Xiaoyu Zong, Mengyao Shi, and Yin Cao. *Manuscript draft:* Scott McHenry, Mengyao Shi, and Yin Cao. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Xiaoyu Zong, Mengyao Shi, and Yin Cao. *Administrative, technical, and material support, and study supervision:* Yin Cao.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The UK Biobank is an open-access resource. Bona fide researchers can apply to use the UK Biobank data set by registering and applying at <http://ukbiobank.ac.uk/register-apply/>.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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