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Non-alcoholic fatty liver degree and long-term risk of incident inflammatory bowel disease: A large-scale prospective cohort study

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) and inflammatory bowel disease (IBD) have shown similar worsening epidemic patterns globally and shared various overlapping pathophysiological mechanisms. However, evidence on the relationship between NAFLD and IBD risk is lacking. We aimed to investigate the associations between long-term risk of incident IBD and NAFLD in a large prospective cohort.

Methods: Participants from the United Kingdom Biobank cohort (https://biobank.ndph.ox.ac.uk/) who were free of IBD and alcoholic liver disease at baseline were enrolled. Baseline non-alcoholic fatty liver degree was measured by the well-established fatty liver index (FLI). The outcomes of interest included incident IBD, ulcerative colitis (UC), and Crohn's disease (CD). Multivariable Cox proportional hazard regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Among 418,721 participants (mean FLI: 48.11 ± 30.11), 160,807 (38.40%) participants were diagnosed as NAFLD at baseline. During a median of 12.4 years' follow-up, 2346 incident IBD cases (1545 UC, 653 CD, and 148 IBD-unclassified) were identified. Due to limited events, those IBD-unclassified were combined in UC or CD when examining the associated risk of UC or CD, separately. Compared with the lowest quartile of FLI, the highest quartile showed a separately 36.00%, 25.00%, and 58.00% higher risk of incident IBD ($HR_{Q4\ vs.\ Q1}$ = 1.36, 95% CI: 1.19–1.55, P_{trend} <0.001), UC ($HR_{Q4\ vs.\ Q1}$ = 1.25, 95% CI: 1.07–1.46, P_{trend} = 0.047), and CD ($HR_{Q4\ vs.\ Q1}$ = 1.58, 95% CI: 1.26–1.97, P_{trend} <0.001) after multivariable adjustment. Compared with non-NAFLD, NAFLD participants had a significantly higher risk of incident IBD (HR = 1.13, 95% CI: 1.04–1.24) and CD (HR = 1.36, 95% CI: 1.17–1.58).

Conclusions: Higher degree of non-alcoholic fatty liver is associated with increased risk of incident IBD. Interventions aimed at improving NAFLD may be a potential targeted strategy for the detection and treatment of IBD.

Keywords: Non-alcoholic fatty liver disease; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Cohort study

Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is characterized by non-infectious chronic gastrointestinal inflammation. In Europe and North America, the burden remains high with the prevalence of IBD exceeded 0.3%.[1] In Africa, Asia, and South America, where previously considered as low risk of IBD, the incidence has been rapidly rising.[1,2]. It has been reported that IBD is associated with an increased risk of various extraintestinal disorders, including arthritis, sclerosing cholangitis, depression, dementia, and cancer, which severely impacts the quality of life, shortens lifespan, and also brings heavy economic burden to the whole society.[3–7] Hence, it is critically important to further investigate the potential etiological factors.[8,9]

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Non-alcoholic fatty liver disease (NAFLD) is defined as excessive hepatic steatosis in the absence of specific causes (i.e., alcohol consumption, hepatitis B or C virus [HBV/HCV] infection), which has become the leading cause of cirrhosis and hepatocellular carcinoma worldwide.[10] Recently, the burden of NAFLD is rising globally from 10% to 25%, which parallels with a rise in IBD.[11–14] Moreover, growing interest has been aroused recently in the coincidence of NAFLD and IBD, given the shared pathophysiological mechanisms of these two conditions, including increased intestinal permeability owing to impaired mucosal barrier function, chronic inflammation, microbiota dysbiosis, and endocrinal changes.[9,12,15,16] However, evidence is lacking on the

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relationship between NAFLD and long-term risk of incident IBD. All previous studies adopted cross-sectional or case-control design with prevalent IBD cases, rather than prospective cohort design with incident IBD cases.[17–20] Therefore, the causality could not be confirmed due to the lacking of temporal sequence of early exposure (NAFLD) and later outcome incidence (IBD). Additionally, most studies were with small sample size and neglected to adjust multiple potential confounders. To the best of our knowledge, the association between NAFLD, as well as fatty liver degree, and the risk of incident IBD has not been thoroughly examined in a large-scale prospective cohort.

Thus, we aimed to comprehensively investigate the long-term risk of incident IBD associated with NAFLD as well as fatty liver degree in a large prospective population-based United Kingdom (UK) Biobank cohort.

Methods

Study population

The UK Biobank cohort comprised 502,461 participants aged 37–73 years recruited in the UK between 2006 and 2010. Specific details of UK Biobank cohort have been previously described.[21] The cohort was approved by the UK North West Multicenter Research Ethics Committee (No. 21/NW/0157) and all participants signed informed consent forms. After excluding those who were with missing non-alcoholic fatty liver index (FLI), withdrew informed consent, and who were with prevalent diagnosis of cancer, IBD, and alcoholic liver disease (ALD), a total of 418,721 participants were included in the analysis (Figure 1 and Supplementary Table 1, http://links.lww.com/CM9/B734).

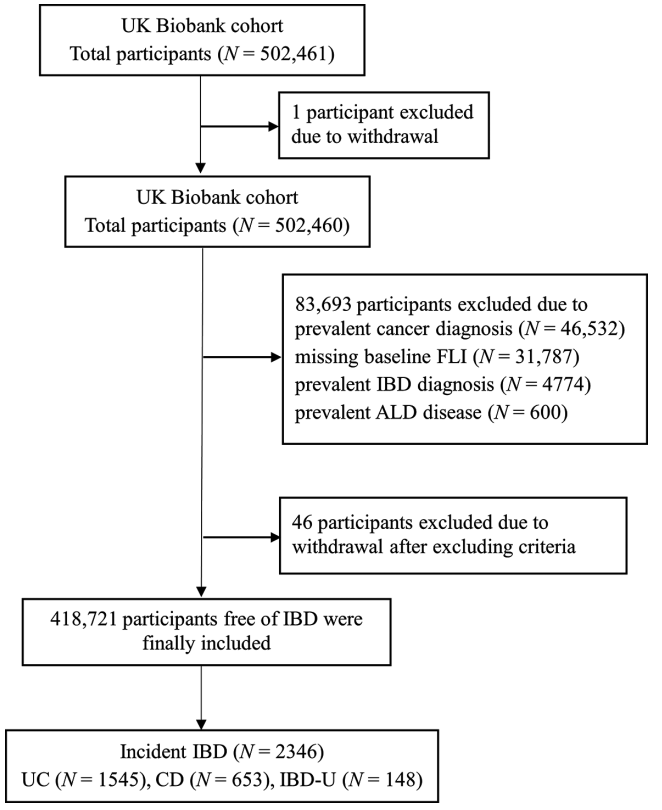

Figure 1: Flowchart of the study population. ALD: Alcoholic liver disease; CD: Crohn's disease; FLI: Fatty liver index; IBD: Inflammatory bowel disease; IBD-U: IBD-unclassified; UC: Ulcerative colitis; UK: United Kingdom

Assessment of baseline non-alcoholic fatty liver degree and NAFLD

Baseline non-alcoholic fatty liver degree was measured by the well-established index, FLI, which was defined using routine measurements in clinical practice including body mass index (BMI), waist circumstance (WC), triglycerides (TG), and gamma-glutamyl transferase (GGT).[22] It has been proven to be a reliable index with good accuracy of transient elastography-determined NAFLD, which has been externally validated and widely accepted in population-based studies.[22–24] Firstly, FLI was categorized into quartiles, with the lowest quartile as a reference group. Secondly, per standard deviation (SD) change of FLI was additionally used to assess the risk of IBD associated with the fatty liver degree. Meanwhile, NAFLD was defined as FLI ≥60, which has proven to be with comparable accuracy of liver ultrasonography and validated in a nationally representative sample of the western general population.

Furthermore, hepatic steatosis index (HSI), another well-established indicator of non-alcoholic fatty liver with excellent accuracy, which consists of sex, alanine aminotransferase (ALT), aspartate aminotransferase (AST), BMI, and diabetic status, was also used in our study.[25,26] Likewise, participants with baseline HSI ≤36 were classified as the non-NAFLD group, while other participants with baseline HSI >36 were considered as the presence of NAFLD in sensitivity analysis.[25,27]

Outcome ascertainment

The outcome of interest was defined as the first diagnosis of IBD (UC or CD) during the follow-up period by June 30, 2021. Incident IBD diagnosis was ascertained using primary care and hospital inpatient data obtained from Hospital Episode Statistics for England, the Scottish Morbidity Record for Scotland, and Patient Episode Database for Wales.[28] Ascertainment of IBD subtype (UC, CD, or IBD-unclassified [IBD-U]) was based on International Classification of Disease-10 (ICD-10) codes (K51 for UC and K50 for CD) [Supplementary Table 2, http://links.lww.com/CM9/B734]. Participants who were diagnosed as both UC and CD were defined as IBD-U. Overall, 2346 incident cases of IBD were identified, with 1545 UC, 653 CD, and 148 IBD-U. However, due to limited events, we combined IBD-U in UC or CD when examining the associated risk of UC or CD, separately. Hence, 1693 cases of UC and 801 CD cases were used to investigate the associated risk of UC or CD.

Covariates

Based on prior epidemiological evidence,[2,3] potential covariates included age (continuous), sex (female or

male), Townsend deprivation index (TDI) (quartiles), education level (non-university, university), ethnicity (non-White, White), smoking (never, previous, current), alcohol drinking (never, previous, current), International Physical Activity Questionnaire (IPAQ) (low, moderate, high), type 2 diabetes (yes or no), hormone treatment (yes or no), and non-steroidal anti-inflammatory drugs (NSAIDs) usage (yes or no). The TDI is a measure of socioeconomic position with a deprivation score. The IPAQ is a self-reported measure of internationally comparable health-related physical activity. Hormone treatment was defined by self-reported hormone replacement therapy, oral contraceptive pill, or minipill. NSAIDs usage was defined by self-report of regular taking aspirin, ibuprofen, or paracetamol in the questionnaire.

Statistical analysis

Participants were followed from baseline until the first exact date of IBD diagnosis (UC or CD), exact date of death, or exact date of loss to follow-up, or June 30, 2021 (censored date). Baseline characteristics were described by mean ± standard deviation (SD) or median (Q_1, Q_3) for continuous variables and absolute number with proportion for categorical variables. Comparison of baseline characteristics among different groups was conducted by analysis of variance test for continuous variables and Chi-squared test for categorical variables. Poisson regression was conducted to calculate the cumulative incidence of IBD, UC, and CD per 100,000 person-years. Multivariable Cox proportional hazard regression was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) between non-alcoholic fatty liver degree (FLI quartiles, per SD change of FLI) as well as NAFLD and incident IBD, UC, or CD.

In addition to the unadjusted model, three adjusted models were conducted. In Model 1, age at baseline and sex were adjusted. In addition to age and sex, Model 2 included the following variables: TDI, education level, ethnicity, smoking status, and alcohol drinking status. In Model 3, IPAQ, type 2 diabetes, hormone treatment, and NSAIDs usage were additionally adjusted. Trend analyses were additionally calculated by using median value (10.5, 32.1, 61.1, and 88.5) of each FLI quartile. Moreover, restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles were tested for potential non-linearity of FLI and risk of IBD, UC, or CD via Model 3.

Additional subgroup analyses were conducted by age at baseline (<45 years, 45–59 years, or ≥60 years), sex (male or female), alcohol drinking (never, previous, current), and smoking (never, previous, current). Effect modification was tested by adding interaction items for subgroups.

Sensitivity analyses were performed to investigate the robustness of the results. First, participants diagnosed with IBD within 2 years, 3 years, or 5 years after enrollment were excluded, in order to avoid detection bias. Second, incident ALD cases were excluded to avoid the influence of alcohol intake. Third, competing risk models were conducted by considering lost-to-follow-up and death as competing events, since those participants could have onset of IBD if they were not lost to follow-up or not dead. The incidents of other diseases were not considered as exclusive for the onset of IBD. Fourth, participants with HBV/HCV seropositivity were excluded.

Additionally, similar sensitivity analyses were conducted by using HSI as a measurement of fatty liver degree and NAFLD diagnosis via Model 3, including excluding incident IBD cases within 2 years, 3 years, or 5 years after baseline, excluding incident ALD cases, excluding participants with HBV/HCV seropositivity or performing competing risk model.

All statistical analyses were conducted using R statistical software Version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS software Version 9.4 (SAS Institute, Cary, North Carolina, USA). A two-sided P value <0.05 was considered to be statistically significant.

Results

Baseline characteristics

At baseline, the average age of total 418,721 enrolled participants was 56.22 ± 8.11 years. The cohort consisted of 223,043 (53.27%) females. The mean FLI was 48.11 ± 30.11. Overall, 160,807 (38.40%) participants had NAFLD diagnosis. Compared with the lowest FLI quartile, participants in higher quartiles were more likely to be older, to be male, to be in a higher quartile of TDI, to have a higher proportion of non-university education level, to be current smoking, to be diagnosed with diabetes, to have a higher level of BMI, WC, TG, GGT, ALT, and AST, and to have a lower IPAQ result [Table 1]. Baseline characteristics according to NAFLD status were shown in Supplementary Table 3, http://links.lww.com/CM9/B734.

Baseline non-alcoholic fatty liver degree and risk of incident IBD, UC, and CD

The rate of loss to follow-up in this cohort was 0.26% (1082/418,721). Overall, 2346 incident IBD (1693 UC and 801 CD) occurred during the median follow-up period of 12.4 years. The incidence densities of IBD, UC, and CD were 46.21 (95% CI: 44.37–48.11), 33.34 (95% CI: 31.79–34.97), and 15.78 (95% CI: 14.72–16.91) per 100,000 person-years, respectively.

Restricted cubic spline adjusting all covariates indicated baseline FLI was linearly associated with the risk of IBD, UC, and CD (P = 0.147, 0.157, and 0.588, respectively, Supplementary Figure 1, http://links.lww.com/CM9/B734). Compared with the lowest, the highest FLI quartile was associated with significantly higher risk of IBD ($HR_{Q4\ vs.\ Q1}$ = 1.36, 95% CI: 1.19–1.55, P_{trend} <0.001), UC ($HR_{Q4\ vs.\ Q1}$ = 1.25, 95% CI: 1.07–1.46, P_{trend} = 0.005), and CD ($HR_{Q4\ vs.\ Q1}$ = 1.58, 95% CI: 1.26–1.97, P_{trend} <0.001), respectively [Figure 2].

Table 1: Baseline characteristics according to quartile of baseline FLI in the UK Biobank cohort.

Characteristics	Total (*N* = 418,721)	Quartile 1 (*n* = 104,680)	Quartile 2 (*n* = 104,682)	Quartile 3 (*n* = 104,680)	Quartile 4 (*n* = 104,679)	*P* values
Age (years)	56.22 ± 8.11	54.22 ± 8.21	56.64 ± 8.08	57.19 ± 7.97	56.82 ± 7.81	<0.001*
Female	223,043 (53.27)	86,137 (82.29)	58,996 (56.36)	42,401 (40.51)	35,509 (33.92)	<0.001†
Ethnicity						<0.001†
Non-white	23,536 (5.62)	5028 (4.80)	6277 (6.00)	6629 (6.33)	5602 (5.35)	
White	393,647 (94.01)	99,349 (94.91)	98,010 (93.63)	97,635 (93.27)	98,653 (94.24)	
Unknow	1538 (0.37)	303 (0.29)	395 (0.37)	416 (0.40)	424 (0.41)	
Education level						<0.001†
Non-university	276,466 (66.03)	60,921 (58.20)	67,596 (64.57)	71,460 (68.26)	76,489 (73.07)	
University	137,341 (32.80)	42,861 (40.94)	35,935 (34.32)	31,821 (30.40)	26,724 (25.53)	
Unknow	4914 (1.17)	898 (0.86)	1151 (1.11)	1399 (1.34)	1466 (1.40)	
Townsend deprivation index	–1.31 ± 3.09	–1.52 ± 2.96	–1.47 ± 3.01	–1.34 ± 3.08	–0.90 ± 3.25	<0.001*
Q1 (≤–3.63)	105,594 (25.22)	28,254 (26.99)	27,725 (26.49)	26,759 (25.56)	22,856 (21.83)	<0.001†
Q2 (–3.62–2.12)	104,826 (25.03)	26,893 (25.69)	26,991 (25.78)	26,561 (25.37)	24,381 (23.29)	
Q3 (–2.11–0.58)	104,669 (25.00)	26,237 (25.06)	26,072 (24.91)	25,964 (24.80)	26,396 (25.22)	
Q4 (>0.58)	103,118 (24.63)	23,172 (22.13)	23,773 (22.71)	25,259 (24.13)	30,914 (29.53)	
Unknow	514 (0.12)	124 (0.13)	121 (0.11)	137 (0.14)	132 (0.13)	
Smoking status						<0.001†
Never	230,332 (55.01)	65,516 (62.59)	60,436 (57.73)	55,377 (52.90)	49,003 (46.81)	
Previous	142,454 (34.02)	29,321 (28.01)	32,989 (31.51)	37,409 (35.74)	42,735 (40.82)	
Current	43,873 (10.48)	9482 (9.06)	10,785 (10.30)	11,343 (10.84)	12,263 (11.71)	
Unknow	2062 (0.49)	361 (0.34)	472 (0.46)	551 (0.52)	678 (0.66)	
Alcohol drinking						<0.001†
Never	18,361 (4.39)	4514 (4.31)	4474 (4.27)	4609 (4.40)	4764 (4.55)	
Previous	14,479 (3.46)	3338 (3.19)	3177 (3.03)	3514 (3.36)	4450 (4.25)	
Current	384,868 (91.92)	96,642 (92.32)	96,785 (92.46)	96,276 (91.97)	95,165 (90.91)	
Unknow	1013 (0.23)	186 (0.18)	246 (0.23)	281 (0.27)	300 (0.29)	
IPAQ						<0.001†
Low	63,221 (15.10)	11,567 (11.05)	13,524 (12.92)	16,071 (15.35)	22,059 (21.07)	
Moderate	138,141 (32.99)	35,162 (33.59)	34,636 (33.09)	34,883 (33.32)	33,460 (31.96)	
High	137,816 (32.91)	39,356 (37.60)	37,182 (35.52)	33,780 (32.27)	27,498 (26.27)	
Unknow	79,543 (19.00)	18,595 (17.76)	19,340 (18.47)	19,946 (19.06)	21,662 (20.70)	
BMI (kg/m^2)						<0.001†
<18.5	2087 (0.50)	2047 (1.96)	33 (0.03)	7 (0.01)	0 (0)	
18.5–24.9	131,605 (31.43)	84,597 (80.81)	37,639 (35.96)	8682 (8.29)	687 (0.66)	
25.0–29.9	180,420 (43.09)	17,954 (17.15)	62,876 (60.06)	71,987 (68.77)	27,603 (26.37)	
≥30.0	104,609 (24.98)	82 (0.08)	4134 (3.95)	24,004 (22.93)	76,389 (72.97)	
Diabetes	10,548 (2.52)	466 (0.45)	1209 (1.15)	2388 (2.28)	6485 (6.20)	<0.001†
Hormone treatment	18,206 (4.35)	8830 (8.44)	4906 (4.69)	2805 (2.68)	1665 (1.59)	<0.001†
NSAIDs use	166,008 (39.65)	34,742 (33.19)	38,634 (36.91)	42,654 (40.75)	49,978 (47.74)	<0.001†
WC (cm)	90.34 ± 13.44	75.24 ± 6.28	85.93 ± 6.01	94.01 ± 6.21	106.17 ± 9.85	<0.001*
TG (mg/dL)	154.37 ± 90.95	90.94 ± 34.08	128.08 ± 51.86	168.57 ± 73.37	229.86 ± 115.08	<0.001*
GGT (U/L)	26.30 (18.50, 40.90)	17.30 (14.10, 22.20)	23.00 (18.00, 31.10)	30.60 (22.90, 43.50)	44.20 (30.80, 69.10)	<0.001‡
ALT (U/L)	20.20 (15.44, 27.51)	15.46 (12.64, 19.15)	18.59 (14.98, 23.43)	22.42 (17.65, 29.01)	28.06 (21.12, 38.13)	<0.001‡
AST (U/L)	24.40 (21.00, 28.80)	22.50 (19.60, 26.10)	23.70 (20.60, 27.50)	25.00 (21.60, 29.20)	27.00 (22.90, 32.70)	<0.001‡
FLI	48.11 ± 30.11	10.72 ± 4.97	32.44 ± 7.65	61.04 ± 8.53	88.24 ± 7.00	<0.001*
FLI ≥60	160,807 (38.40)	0 (0)	0 (0)	56,128 (53.62)	104,679 (100.00)	<0.001†
HSI	35.61 ±5.89	30.21 ± 2.78	33.44 ± 3.10	36.50 ± 3.55	42.28 ± 5.43	<0.001*
HSI >36	172,226 (41.29)	2167 (2.08)	20,889 (20.02)	55,143 (52.86)	94,027 (90.33)	<0.001†

Data are presented as means ± standard deviation, *n* (%), or median (Q_1, Q_3). *Analysis of variance; †Chi-squared test; ‡Kruskal-Wallis test. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; FLI: Fatty liver index; GGT: Gamma-glutamyl transferase; HSI: Hepatic steatosis index; IPAQ: International Physical Activity Questionnaire; NSAIDs: Non-steroidal anti-inflammatory drugs; TG: Triglycerides; WC: Waist circumstance.

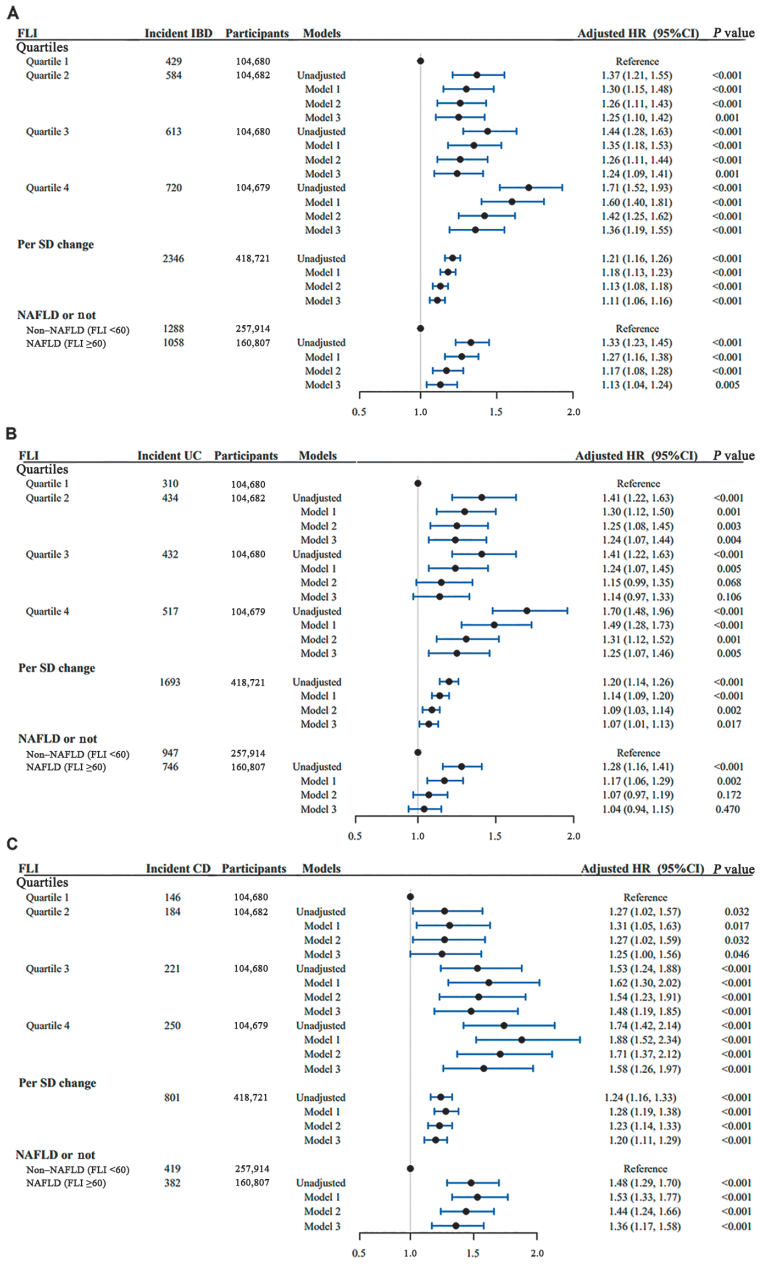

Figure 2: The association between non-alcoholic fatty liver degree and incident IBD (A), UC (B), and CD (C). In unadjusted model, no covariate was adjusted; in Model 1, age and sex were adjusted; in Model 2, age, sex, TDI, education level, ethnicity, smoking, and alcohol drinking were adjusted; in Model 3, age, sex, TDI, education level, ethnicity, smoking, alcohol drinking, IPAQ, type 2 diabetes, hormone treatment, and NSAIDs usage were additionally adjusted. CD: Crohn's disease; CI: Confidence interval; FLI: Fatty liver index; HR: Hazard ratio; IBD: Inflammatory bowel disease; IPAQ: International Physical Activity Questionnaire; NAFLD: Non-alcoholic fatty liver disease; NSAIDs: Non-steroidal anti-inflammatory drugs; SD: Standard deviation; TDI: Townsend Deprivation Index; UC: Ulcerative colitis.

When assessing the risk by per SD change of FLI, an 11.00%, 7.00%, and 20.00% increased risk of incident IBD (HR = 1.11, 95% CI: 1.06–1.16, P_{trend} <0.001), UC (HR = 1.07, 95% CI: 1.01–1.13, P_{trend} = 0.017), and CD (HR = 1.20, 95% CI: 1.11–1.29, P_{trend} <0.001) was detected via Model 3, respectively [Figure 2].

Baseline NAFLD status and risk of incident IBD, UC, and CD

Totally, 1058 (54.65 per 100,000 person-years) and 1288 (41.00 per 100,000 person-years) incident IBD cases were identified in NAFLD and non-NAFLD groups, respectively. Compared with non-NAFLD group, NAFLD participants were associated with a significantly higher risk of incident IBD (HR = 1.13, 95% CI: 1.04–1.24, P = 0.005), particularly higher risk of incident CD (HR = 1.36, 95% CI: 1.17–1.58, P_{trend} <0.001) [Figure 2].

Subgroup analyses by age, sex, smoking, and alcohol-drinking status

The increased UC and CD risks associated with FLI quartiles (quartile 2 and quartile 4) were observed in subgroups

of 45–59 years, ≥60 years, female, and current alcohol drinking [Figure 3]. Interestingly, the significant excess risk of IBD was indicated in females but not in males. However, no effect modification was detected among these subgroups (all $P_{interaction}$ >0.05). [Supplementary Figures 2 and 3, http://links.lww.com/CM9/B734]. No effect modification was detected among those subgroups, except for the significant interaction between sex and FLI quartiles in CD ($P_{interaction}$ = 0.003).

Results of subgroups analyses by per SD change of FLI and NAFLD status were consistent [Supplementary Figures 4 and 5, http://links.lww.com/CM9/B734]. Modification effects were significant between sex and IBD as well as CD both by per SD change ($P_{interaction}$ = 0.028 in IBD and $P_{interaction}$ = 0.012 in CD) and NAFLD status ($P_{interaction}$ = 0.008 in IBD and $P_{interaction}$ = 0.023 in CD).

Sensitivity analyses

Sensitivity analyses by quartiles, per SD change, and NAFLD status measured via FLI showed similar increased risk of IBD, UC, and CD associated with higher degree of fatty liver, except for the non-significant association between NAFLD status and incident UC after excluding IBD participants diagnosed within 2 years, 3 years, and 5 years and excluding participants with ALD or HBV/HCV antigen-positive [Table 2, Supplementary Table 4, http://links.lww.com/CM9/B734]. Further, the competing risk model also showed increased IBD risk associated with FLI quartiles ($HR_{Q4\ vs.\ Q1}$ = 1.36, 95% CI: 1.18–1.55, P_{trend} <0.001). Furthermore, findings of sensitivity analyses by HSI, either considered as per SD change or NAFLD status, were also consistent with principal findings [Supplementary Table 5, http://links.lww.com/CM9/B734].

Discussion

In this large-scale prospective study, significantly increased risks of IBD, UC, and CD were all observed with both higher fatty liver degree and NAFLD status. After adjusting for demographic and clinical characteristics, the highest FLI quartile showed a 36.00%, 25.00%, and 58.00% higher

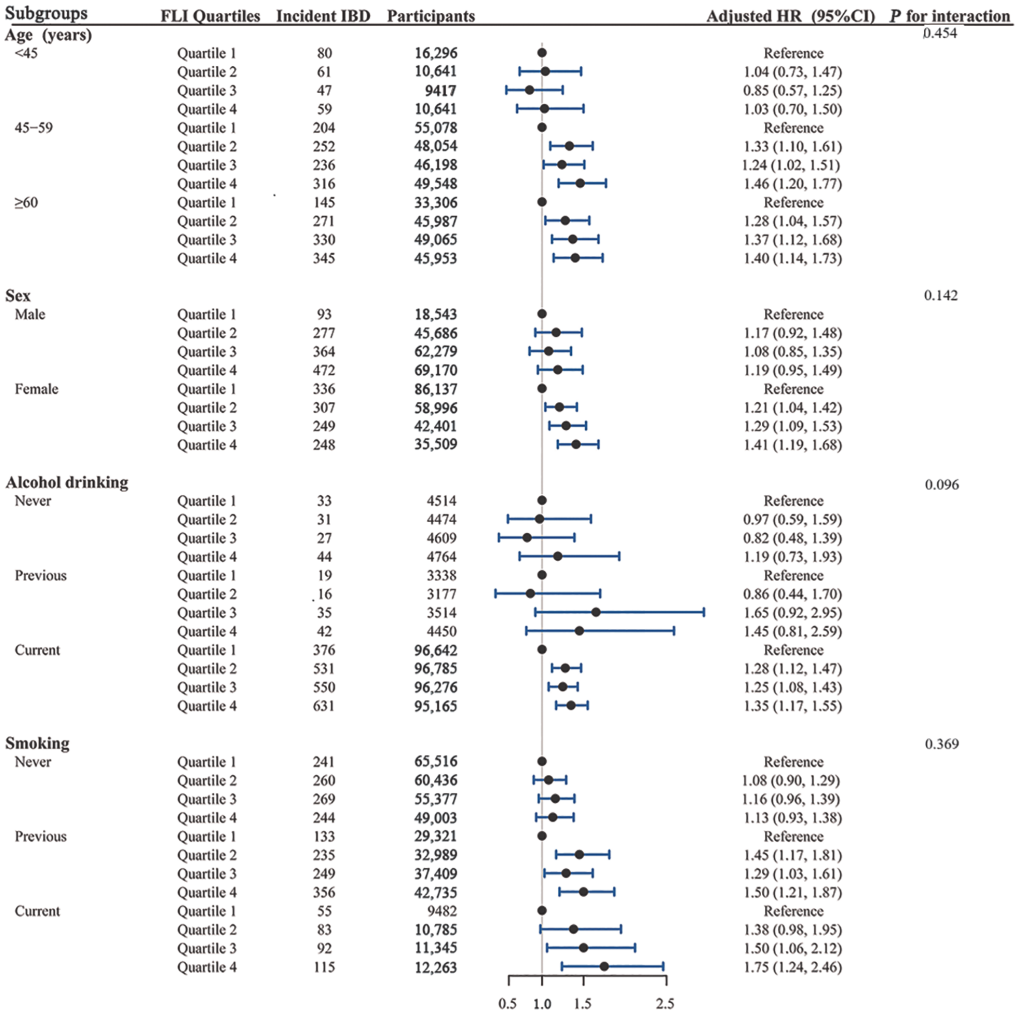

Figure 3: Subgroup analysis for the association between non-alcoholic fatty liver degree and incident IBD. Adjusting age, sex, TDI, education level, ethnicity, smoking, alcohol drinking, IPAQ, type 2 diabetes, hormone treatment, and NSAIDs usage. CI: Confidence interval; FLI: Fatty liver index; HR: Hazard ratio; IBD: Inflammatory bowel disease; IPAQ: International Physical Activity Questionnaire; NSAIDS: Non-steroidal anti-inflammatory drugs; SD: Standard deviation; TDI: Townsend Deprivation Index.

Table 2: Sensitivity analyses regarding the risk of IBD, UC, and CD according to quartiles of baseline FLI.

FLI quartiles	Participants (*n*)	Risk of IBD				Risk of UC				Risk of CD			
		IBD	HR (95% CI)	*P* value	P_{trend}	UC	HR (95% CI)	*P* value	P_{trend}	CD	HR (95% CI)	*P* value	P_{trend}
Sensitivity analysis 1: Excluding IBD participants diagnosed within 2 years after baseline (*N* = 418,385)													
Quartile 1	104,613	362	Reference		<0.001	257	Reference		0.017	120	Reference		<0.001
Quartile 2	104,602	504	1.30 (1.13, 1.49)	<0.001		376	1.31 (1.12, 1.55)	0.001		155	1.31 (1.03, 1.67)	0.028	
Quartile 3	104,592	525	1.28 (1.11, 1.48)	<0.001		375	1.21 (1.03, 1.44)	0.024		184	1.56 (1.22, 1.98)	<0.001	
Quartile 4	104,578	619	1.42 (1.23, 1.64)	<0.001		442	1.33 (1.12, 1.57)	0.001		213	1.72 (1.34, 2.19)	<0.001	
Sensitivity analysis 2: Excluding IBD participants diagnosed within 3 years after baseline (*N* = 418,208)													
Quartile 1	104,578	327	Reference		<0.001	232	Reference		0.009	108	Reference		<0.001
Quartile 2	104,540	442	1.26 (1.09, 1.46)	0.002		334	1.29 (1.09, 1.54)	0.003		130	1.23 (0.95, 1.60)	0.117	
Quartile 3	104,558	491	1.33 (1.15, 1.54)	<0.001		350	1.25 (1.05, 1.50)	0.012		173	1.64 (1.27, 2.12)	<0.001	
Quartile 4	104,532	573	1.45 (1.25, 1.69)	<0.001		407	1.34 (1.13, 1.61)	0.001		201	1.82 (1.41, 2.35)	<0.001	
Sensitivity analysis 3: Excluding IBD participants diagnosed within 5 years after baseline (*N* = 417,817)													
Quartile 1	104,503	252	Reference		<0.001	179	Reference		0.004	82	Reference		<0.001
Quartile 2	104,433	335	1.26 (1.06, 1.49)	0.007		253	1.29 (1.06, 1.57)	0.011		98	1.24 (0.92, 1.67)	0.161	
Quartile 3	104,468	401	1.44 (1.22, 1.70)	<0.001		281	1.34 (1.10, 1.63)	0.004		141	1.81 (1.36, 2.41)	<0.001	
Quartile 4	104,413	454	1.53 (1.30, 1.82)	<0.001		318	1.40 (1.14, 1.71)	0.001		165	2.04 (1.53, 2.73)	<0.001	
Sensitivity analysis 4: Excluding incident ALD participants after baseline (*N* = 417,605)													
Quartile 1	104,614	427	Reference		<0.001	310	Reference		0.053	144	Reference		<0.001
Quartile 2	104,545	583	1.26 (1.11, 1.43)	<0.001		433	1.24 (1.07, 1.44)	0.005		184	1.27 (1.02, 1.59)	0.036	
Quartile 3	104,450	613	1.24 (1.09, 1.42)	0.001		432	1.14 (0.98, 1.33)	0.099		221	1.50 (1.20, 1.87)	<0.001	
Quartile 4	103,996	712	1.35 (1.19, 1.54)	<0.001		511	1.25 (1.07, 1.46)	0.006		247	1.59 (1.27, 1.99)	<0.001	
Sensitivity analysis 5: Competing risk model (*N* = 418,721, *N* of competing events for IBD, UC and CD = 26,114, 26,190, and 26,250)													
Quartile 1	104,680	429	Reference		<0.001	310	Reference		0.050	146	Reference		<0.001
Quartile 2	104,682	584	1.26 (1.11, 1.43)	<0.001		434	1.25 (1.07, 1.45)	0.004		184	1.26 (1.01, 1.57)	0.041	
Quartile 3	104,680	613	1.25 (1.09, 1.42)	<0.001		432	1.14 (0.98, 1.34)	0.093		221	1.49 (1.20, 1.86)	<0.001	
Quartile 4	104,679	720	1.36 (1.18, 1.55)	<0.001		517	1.25 (1.07, 1.46)	0.005		250	1.58 (1.26, 1.98)	<0.001	
Sensitivity analysis 6: Excluding HBV or HCV antigen-positive participants after baseline (*N* = 418,489)													
Quartile 1	104,618	429	Reference		<0.001	310	Reference		0.039	146	Reference		<0.001
Quartile 2	104,627	584	1.25 (1.10, 1.42)	0.001		434	1.24 (1.07, 1.44)	0.004		184	1.25 (1.00, 1.56)	0.046	
Quartile 3	104,627	613	1.24 (1.09, 1.41)	0.001		432	1.14 (0.98, 1.33)	0.105		221	1.48 (1.19, 1.85)	<0.001	
Quartile 4	104,617	719	1.35 (1.19, 1.54)	<0.001		516	1.25 (1.07, 1.46)	0.005		250	1.58 (1.26, 1.97)	<0.001	

All adjusted HRs were calculated by adjusting the following covariates: age, sex, TDI, education level, ethnicity, smoking, alcohol drinking, IPAQ, type 2 diabetes, hormone treatment, and NSAIDs use. *P* for trend was calculated by using median value of each FLI Quartile (10.5, 32.1, 61.1, and 88.5). ALD: Alcoholic liver disease; CD: Crohn's disease; CI: Confidence interval; FLI: Fatty liver index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HR: Hazard ratio; IBD: Inflammatory bowel disease; IPAQ: International Physical Activity Questionnaire; TDI: Townsend deprivation index; UC: Ulcerative colitis.

risk of incident IBD, UC, and CD compared with the lowest quartile. NAFLD patients had a 13.00% and 36.00% excess risk of IBD and CD than non-NAFLD participants.

Several potential molecular and pathophysiological mechanisms may explain the associated increased risk of IBD. In NAFLD patients, the intestinal barrier dysfunctions could result from alterations in tight junction proteins, such as transmembrane proteins (occluding) and peripheral membrane proteins (zonula occludens).[29,30] In addition, an altered T-helper 17/regulatory T (Th17/Treg) balance, which is associated with metabolic diseases, gut microbiota, and intestinal immune dysfunction, was observed in NAFLD and IBD.[31–34] The low diversity of gut microbiota and thereby alterations in microbiota-derived metabolites have emerged as potential regulators of host metabolism and the immune system, which may contribute to the development of IBD in NAFLD patients.[35–38]

There was a significant increasing trend in CD risk with fatty liver, meanwhile, a weaker association was observed for UC, which was metabolically, immunologically as well as genetically plausible. One reason for the difference might be the alterations in gut metabolites between the two subtypes. Plasma branched-chain amino acid, one of the gut microbiota-derived metabolites, was observed to have an inverse correlation with CD, but no correlation with UC.[39] Immunologically, a growing body of evidence in immunology also suggested that innate immune response was more responsible for

CD, representing a transmural disorder affecting any part of the gut in an intermittent fashion, while epithelial barrier dysfunction was mainly associated with the occurrence of UC lesions, confining to the colon and epithelia mucosa.[40] In addition to immunology, CD and UC also showed genetical differences. Nucleotide-binding oligomerization domain-containing protein 2 (NOD2), modulating immune responses and contributing to immune tolerance, was the gene associated with CD but not UC, which might potentially reflect the biological discrepancies.[41] These shreds of evidence were consistent with our findings that NAFLD might be linked to CD potentially by pathogenesis higher than UC.

Interestingly, the increased risk of IBD associated with higher fatty liver degree and NAFLD was observed in females rather than males in our study. Despite IBD being developed predominantly in females, the sex difference in incident IBD still remained strikingly scarce.[42–44] A potential mechanism may be the mediation by sex hormones, especially female reproductive hormones. Recent animal and experimental studies implicated estrogen dysregulation as a potential role in the pathogenesis of IBD, with the estrogen receptor β subtype mediated intestinal permeability increasing, estrogen-mediated immune protection decreasing and hormone-mediated gut microbial dysbiosis.[45–47] Several epidemiological evidence also suggested the increased risk of UC and CD associated with hormones and contraceptives.[48–50] Furthermore, genetic and epigenetic regulation as well as human microbiota have been shown to support the sex-specific disparity in immune responses. Several critical transcriptional and translational control effectors, the function downstream of activated cytokine receptors, are located on the X chromosome.[51,52] Human microbiota can regulate sex hormones through mediating hydroxysteroid dehydrogenase enzymes, which will directly influence the sex-specific immune-mediated disease.[53,54] Further studies are needed to confirm our findings and elucidate possible mechanisms.

Several epidemiological studies have demonstrated the capability of FLI ≥60 in detecting NAFLD, validated both by liver ultrasonography and liver histology.[55,56] As a steatosis biomarker calculated from anthropometric and metabolic parameters, the FLI was demonstrated to be a useful tool for evaluating NAFLD, especially in the general population.[55,56] Moreover, in the UK Biobank cohort, the WC was objectively measured to be reliable. Besides, subcutaneous abdominal fat reduced the contribution to fatty liver in the elderly, which might limit the use of FLI in clinical practice.[57]

The strengths of this study are the large-scale prospective cohort of the UK Biobank, with the longest follow-up to date and sufficient number of IBD cases, and the ability to adjust for multiple confounders. To the best of our knowledge, this is the first well-designed prospective cohort study focused on the associations between non-alcoholic fatty liver degree as well as NAFLD and incident IBD. The fatty liver degree measured by different approaches (i.e., quartiles, per SD change, NAFLD status) and rigorous sensitivity analyses achieved consistent findings, indicating the robustness of our results.

Although our study provided new insights into the associations between NAFLD and IBD, several limitations still existed. First, the generalizability is limited owing to selection bias of relatively older adults (mean age 56 years) and predominant of White ethnicity (>94%) of the population. Thus, the generalizability of our findings to other general populations is warranted to be confirmed. Second, NAFLD was determined by FLI, instead of liver ultrasound or biopsy, which might lead to misclassification bias. Generally, it was not available to evaluate the diagnosis of NAFLD (especially non-alcoholic steatohepatitis) by biopsy in a large-scale epidemiology cohort. However, FLI has been shown with good ability to discriminate individuals with and without NAFLD, and is widely accepted to measure fatty liver degree in large-scale population-based studies.[22–24] Moreover, results by considering HSI as a measurement of fatty liver degree and NAFLD were consistent, supporting the positive associations. Third, residual confounders such as the family history of IBD, comorbidity of primary sclerosing cholangitis, and dietary style also might confound the associations between FLI and IBD, although we had carefully adjusted the available covariates. Fourth, covariates were not repeatedly assessed in this prospective cohort. Thus, potential confounders, such as smoking and alcohol drinking status, might be changed during the follow-up period, which might alter the association. Fifth, patients with higher FLI are likely to seek healthcare more frequently, leading to more medical testing and diagnosis of IBD than those with lower FLI, which may lead to detection bias. Nevertheless, we performed sensitivity analysis by excluding participants diagnosed with IBD within 2 years, 3 years, or 5 years after baseline, and the results were consistent. Further long-term prospective cohort studies are needed to validate our findings.

In conclusion, this large-scale cohort study showed participants with higher degree of fatty liver as well as NAFLD had an increased risk of IBD, particularly an increased risk of CD. The excess risk was more evident in females. Interventions aimed at improving non-alcoholic fatty liver may be a potential targeted strategy for the detection, diagnosis, and treatment of IBD. Further studies are warranted to confirm our findings and assess the causality between NAFLD and IBD.

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Conflicts of interest

None.

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