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Xuechen Chen
Jinan University
Hetong Zhang
Jinan University
Yishuo Zhai
Jinan University
Ruojin Fu
German Cancer Research Center (DKFZ)
Hongliang Xue
Guangzhou Medical University
Teresa Seum
German Cancer Research Center (DKFZ)
Hengjing Li
Capital Medical University
Tiantian Zhang
Southern Medical University
Sha Li
Jinan University
Jie Jiang
jiangjie@jnu.edu.cn

Jinan University
Hermann Brenner
German Cancer Research Center (DKFZ)

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Xuechen Chen[a,b,c#]

Hetong Zhang[a#]

Yishuo Zhai[a#]

Ruojin Fu[d,e]

Hongliang Xue[f,g]

Teresa Seum[d,e]

Hengjing Li[h]

Tiantian Zhang[i*]

Sha Li[a,b,c*]

Jie Jiang[a,b,c*,]

Hermann Brenner[j]

[a]GBA Institute of Real-World Value and Evidence, College of Pharmacy, Jinan University, Guangzhou, People's Republic of China

[b]State Key Laboratory of Bioactive Molecules and Druggability Assessment, Jinan University, Guangzhou, People's Republic of China

[c]International Cooperative Laboratory of Traditional Chinese Medicine Modernization and Innovative Drug Development of Ministry of Education (MOE) of China, Jinan University

[d]Division of Clinical Epidemiology of Early Cancer Detection, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

[e]Heidelberg Medical Faculty, Heidelberg University, Heidelberg, Germany

[f]Department of Nutrition, School of Public Health, Guangzhou Medical University, Guangzhou, China

[g]The Key Laboratory of Advanced Interdisciplinary Studies, The First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China

[i]School of Pharmaceutical Sciences, Southern Medical University, Guangzhou, People's Republic of China

[j]Cancer Prevention Graduate School, German Cancer Research Center (DKFZ), Heidelberg, Germany

[#]These authors contributed equally to this work

Correspondence:

*Prof. Tiantian Zhang, School of Pharmaceutical Sciences, Southern Medical University, No.1838, Shatai North Road, Baiyun District, Guangzhou 510515, People's Republic of China.

E-mail: ztt_84@126.com

*Prof. Sha Li, GBA Institute of Real-World Value and Evidence, College of Pharmacy, Jinan University, No.855, East Xingye Avenue, Panyu District, Guangzhou 511436, People's Republic of China.

E-mail: tlisha@jnu.edu.cn

*Prof. Jie Jiang: GBA Institute of Real-World Value and Evidence, College of Pharmacy, Jinan University, No.855, East Xingye Avenue, Panyu District, Guangzhou 511436, People's Republic of China.

E-mail: jiangjie@jnu.edu.cn

Abstract

Background: Evidence on steatotic liver disease (SLD)-specific colorectal cancer (CRC) risk and implications for screening is limited. We aimed to estimate how many years earlier individuals with SLD, including metabolic dysfunction-associated SLD (MASLD), metabolic and alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD), reach equivalent CRC risk versus those without.

Methods: The primary outcome was incident CRC. We used Cox regression models to estimate adjusted hazard ratios (aHRs), population attributable fractions (PAFs), and risk advancement

periods (RAPs). A newly developed framework with age-specific national CRC incidence rates was also applied to estimate risk-adapted CRC screening starting ages in large European countries.

Results: 191,837 participants were included. Compared with no SLD, aHRs (95% CIs) for CRC were 1.17 (1.05–1.32) for MASLD, 1.41 (1.21–1.63) for MetALD, and 1.58 (1.27–1.95) for ALD; PAFs were 4.2%, 3.3%, and 1.6%, respectively; the PAF for MASLD and MetALD was higher than that of family history of CRC (2.4%). These associations were independent of family history of CRC and cardiometabolic risk factors. Consistent with RAPs, these subtypes reached average-risk CRC incidence 2–6 years earlier than individuals without. Results were similar across countries despite variation in absolute incidence.

Conclusions: Individuals with SLD show a graded increase in CRC risk corresponding to 2-6 years earlier risk attainment, supporting their consideration in risk-adapted CRC screening strategies.

Keywords: colorectal cancer, risk stratification, screening age, MASLD

Background

Colorectal cancer (CRC) remains a leading cause of cancer incidence and mortality worldwide.[1] Current CRC screening strategies targeted at average-risk individuals are age-based, typically starting from 50 years,[2] with some lowering the starting age to 45.[3,4] However, this one-size-fits-all approach may fail to identify individuals at elevated risk due to non-age-related factors, thereby limiting the efficiency of early detection efforts. While earlier screening is recommended for individuals with a family history of CRC, the relatively low prevalence of family history limits its contribution to the overall population-level burden of disease.[5,6] Moreover, other important CRC-related risk determinants are not routinely incorporated into existing screening recommendations.

Emerging epidemiological studies from Asian populations have reported heterogeneity in CRC risk across steatotic liver disease (SLD) subtypes.[7,8] The recently proposed SLD classification [9] stratifies patients according to cardiometabolic risk factors and alcohol consumption, replacing the term “non-alcoholic fatty liver disease” with a more etiologically based

framework. Higher risks have been observed in alcohol-associated liver disease (ALD) and metabolic and alcohol-associated liver disease (MetALD) compared with metabolic dysfunction-associated SLD (MASLD), although available evidence remains limited and requires further confirmation across diverse populations.[7,8] Furthermore, a recent Delphi consensus statement recommends earlier CRC screening for patients with MASLD.[10] However, whether newly defined SLD subtypes confer sufficiently elevated and heterogeneous CRC risk to warrant subtype-specific, risk-adapted screening strategies remains unknown. Addressing this gap is crucial given the global rise in metabolic disease among younger adults,[11] for whom tailored screening approaches may offer additional health benefit.

To address this gap, we used data from the UK Biobank, a large prospective population-based cohort, to quantify CRC risk associated with different SLD subtypes in a predominantly White population. We applied the risk advancement period (RAP) metric [12] to estimate how many years earlier individuals with specific SLD subtypes reach equivalent CRC risk compared with individuals without SLD. In addition, we translated relative risk estimates into absolute risk-based screening age differences using established national CRC incidence data from European population.[13,14] Together, these analyses aim to provide an evidence-based framework for risk-adapted CRC screening strategies in individuals with metabolic liver disease.

Methods

Study population

This prospective cohort study was based on data from the UK Biobank study, a large, population-based cohort comprising over 500,000 individuals aged 40 to 69 years at the time of recruitment between 2006 and 2010. Ethical approval for the UKB was granted by the North West–Haydock Research Ethics Committee (Reference: 21/NW/0157), and all participants provided written informed consent at the time of enrolment. Further details of the UK Biobank protocol have been published elsewhere [15]. This research was conducted in accordance with the Declaration of Helsinki. We excluded participants with a history of cancer (except for non-melanoma skin cancer) or CRC screening at or prior to baseline, those with a history of other liver

disease (eg, alcoholic liver disease, viral hepatitis, alcohol or drug use disorders, see **Supplementary Table S1** for diagnoses codes), and those with missing information on key variables for the current analysis. A flowchart illustrating participant inclusion is shown in **Figure 1**.

Definitions of SLD and its subtypes

We used the Fatty Liver Index (FLI) as a surrogate marker of hepatic steatosis in the absence of direct imaging or biopsy data. Hepatic steatosis was defined by an FLI ≥ 60, a threshold validated against ultrasound with 96 % sensitivity, 92.5 % specificity, and an area under the receiver-operating-characteristic curve of 0.92.[16] The FLI is calculated from body mass index (BMI, kg/m²), waist circumference (WC, cm), γ-glutamyltransferase (GGT, U/L), and serum triglycerides (TG, mmol/L) as

$$FLI = (e^{(y)} / (1 + e^{(y)})) * 100,$$

where $y = (0.953 * \ln(\text{triglycerides})) + (0.139 * BMI) + (0.718 * \ln(GGT)) + (0.053 * \text{waist circumference}) - 15.745$.

Definition of MASLD [9] required evidence of hepatic steatosis without excessive amount of alcohol consumption (< 20g/d and 30g/d for females and males, respectively) , and with at least one of the following cardiometabolic risk factors: 1) overweight or obesity: BMI ≥ 25 kg/m² or WC > 94 cm for men or > 80 cm for women; 2) prediabetes or diabetes: glycated hemoglobin (HbA1c) ≥ 5.7% (39 mmol/mol), diagnosis of type 2 diabetes, self-reported diabetes, or treatment for type 2 diabetes; 3) hypertension: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive medications). 4) high triglyceride: elevated triglyceride levels (defined as plasma triglyceride ≥ 1.70 mmol/L, or ongoing lipid-lowering therapy); 5) low high-density lipoprotein (HDL) cholesterol: reduced levels of HDL cholesterol (HDL cholesterol was ≤1.0 mmol/L in men or ≤1.3 mmol/L in women, or if the individual was receiving lipid-lowering treatment). Codes for data extraction and definition from the UK Biobank are listed in **Supplementary Table S2** and **Table S3**. Those who had MASLD but consumed greater amounts of alcohol per day were classified into the group with MetALD (20-50 g/d and 30-60 g/d for females

and males, respectively). ALD was defined as steatotic liver disease in the presence of alcohol consumption exceeding 50 g/day in females or 60 g/day in males.

Outcome and follow-up

The primary outcome was CRC incidence, identified through linkage with hospital inpatient records and national cancer registries using ICD 10 codes starting with C18-C20 during the follow-up. For the current analysis, complete cancer follow-up data was available up to 31 December 2020 for England, 30 November 2021 for Scotland, and 31 December 2016 for Wales.

Statistical analysis

Baseline characteristics of the study population were summarized using median and interquartile range (IQR) for continuous variables, and counts with percentages (%) for categorical variables in the whole study population.

To evaluate the association between SLD status and CRC risk, Cox proportional hazards regression models were constructed, with time-to-event defined from baseline to CRC diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. The proportional hazards assumption was checked using Schoenfeld residuals, revealing no significant violations. The basic model was adjusted for age (continuous). Then we additionally adjusted for sex (male, female), Townsend deprivation index (in quartiles), educational level (college/university degree, other), smoking status (not current/current), alcohol consumption frequency (never, 1-3 times a month, 1-4 times a week, or daily or almost daily), frequent use of aspirin (defined as taking aspirin most days of the week for the last 4 weeks, yes/no), and family history of CRC (yes/no). In the fully adjusted model, we further adjusted for cardiometabolic risk factors and the Fibrosis-4 (FIB-4) index. The FIB-4 index, derived from age, aspartate aminotransferase, alanine aminotransferase, and platelet count, was a non-invasive marker of liver fibrosis severity.[17] Population attributable fractions (PAFs), which quantify the proportions of CRC cases attributable to certain risk factors, were also calculated using Levin's formula for family history and SLD.[18]

RAPs were calculated to estimate the age difference at which individuals with specific SLD subtype reach the equivalent CRC risk as those without SLD. Specifically, RAPs were derived by

dividing the estimated regression coefficient (β) for each SLD subtype by the β-coefficient for age, obtained from multivariable Cox proportional hazards models where age was modeled as a continuous variable. Calculation of RAPs and its 95% confidence intervals (95% CIs) was described in detail in the work by Brenner et al.[12] We further calculated RAPs according to obesity or diabetes among individuals with SLD. Risk-adapted screening ages were then derived by translating RAPs into equivalent shifts in screening initiation age in three scenarios: average-risk screening at age 50 years, average-risk screening at age 45 years, and high-risk screening at age 40 years for individuals with a family history of CRC.

Subgroup analyses were performed stratified by age (<55 vs. ≥55 years), sex (male vs. female), and FIB-4 index (low vs. high, categorized by the cohort median of 1.2). Effect modification was evaluated by incorporating multiplicative interaction terms between SLD status and each stratification variable in fully adjusted Cox proportional hazards models. Sensitivity analyses were conducted by excluding incident CRC cases occurring within the first, second, and third year of follow-up to minimize potential reverse causation.

We conducted analogous calculations by additionally extracting the national CRC incidence following a previously developed analytical framework.[13,14] Specifically, we extracted the most-updated 5-year cumulative CRC incidence (%) for each 5 years of age between 30 and 55 (see **Supplementary Table S4**) in four major European countries with large populations (Germany, France, UK, Italy) as well as the United States and Canada from two sources: the Surveillance, Epidemiology, and End Results (SEER) database (2018-2022) [19] and the GLOBOCAN 2022 database.[20] Details regarding these two data sources are described in **Supplementary Methods**. We assumed that the average risk among the non-SLD population at any given age corresponds to the population-level average risk. To estimate 5-year cumulative CRC risks for individuals with specific SLD subtypes, we multiplied the age-specific average cumulative risks (at ages 30, 35, 40, 45, 50, and 55) by the relative risk estimates derived from our UK Biobank analysis. Using the cumulative incidence observed in average-risk individuals at benchmark ages at age 50 or 45 years, we identified the corresponding ages at which individuals with MASLD, MetALD or ALD reached the equivalent levels of risk.

All statistical analyses were conducted using R version 4.4.3. All P-values were two-sided, and statistical significance was set at $P < 0.05$.

Results

Baseline characteristics of study participants

We included 191,837 participants who were free of cancer, had no history of CRC screening or liver disease, and had complete data for analysis (**Figure 1**). **Table 1** summarizes the baseline characteristics of study participants. 63.3% of participants had no SLD, 25.5% had MASLD, 8.4% had MetALD, and 2.8% had ALD. 2371 incident cases of CRC were identified during a median (IQR) follow up of 11.9 (11.1, 12.5) years. The median age at recruitment was 55 years (IQR 48, 61), with a relatively balanced sex distribution (53.6% female). The majority of participants were of White ethnicity (94.5%) and had not attained a college/university education (65.3%). 10.8% of participants were current smokers, and 22.2% reported drinking alcohol daily or almost daily. The median vegetable and fruit intake was four tablespoons and two pieces per day, respectively. The prevalence of overweight/obesity, pre-diabetes/diabetes, dyslipidemia, high triglyceride, and low HDL cholesterol were 70.0%, 17.3%, 71.4%, 45.8%, and 18.6%, respectively. Medication use was also assessed with 14.5% of participants taking lipid-lowering therapy, 18.9% on antihypertensive medication, 3.2% using glucose-lowering medication, and 12.0% reporting frequent aspirin use.

Associations of SLD subtypes with CRC risk

As shown in **Table 2**, individuals with SLD had significantly increased risk of CRC compared to those without SLD. After full adjustment, the HRs (95% CIs) were 1.17 (1.05,1.32) for MASLD, 1.41 (1.21, 1.63) for MetALD, and 1.58 (1.27, 1.95) for ALD. The PAFs ranged from 1.6% to 4.2% for different SLD subtypes. Notably, MASLD (4.2%) and MetALD (3.3%) had higher PAFs than family history of CRC (2.4%). The interaction between SLD subtypes and family history of CRC did not reach statistical significance ($P = .94$).

In subgroup analyses, although the associations appeared stronger in younger or male participants, and those with high FIB-4, the difference did not reach statistical significance

(**Supplementary Tables S5-S7**). Sensitivity analyses demonstrated robust associations after excluding participants who developed CRC within the first, second, and third year of follow-up (**Supplementary Table S8**).

Risk-adapted screening age of CRC according to SLD subtypes

CRC risk associated with MASLD, MetALD, and ALD were translated into RAPs in **Table 3**. The corresponding RAPs (95% CIs) were 2.1 (0.6, 3.5), 4.4 (2.5, 6.3), and 5.9 (3.1, 8.7) years, respectively, indicating that people with these SLD subtypes reach comparable CRC risks 2 to 6 years earlier than those without SLD. Besides, obesity and diabetes were associated with higher CRC risk and correspondingly greater risk advancement, with the most pronounced effects observed among individuals with coexisting diabetes and ALD (RAP 7.3, 95% CI 2.4, 12.2). When translated into risk-adapted screening initiation ages, a clear gradient was observed across SLD subtypes in three scenarios. For example, in scenario 1 (reference age 50 years), screening initiation shifted to approximately 48 years for MASLD, 46 years for MetALD, and 44 years for ALD. These shifts were further accentuated in individuals with obesity or diabetes. We also estimated risk-adapted starting ages for screening according to SLD subtype among individuals with a family history (scenario 3). Using the commonly recommended starting age of 40 years for individuals with a family history but without SLD as the reference, the corresponding risk-adapted starting ages were 34 years for ALD, 36 years for MetALD, and 38 years for MASLD.

Exemplary calculation of risk-adapted CRC screening ages according to SLD status is illustrated in **Figure 2**, based on the estimated cumulative 5-year CRC risks from ages 30 to 50 in the UK and relative risks of SLD derived from the UK Biobank study. Dots indicate risk estimates at 5-year intervals, with interpolated values shown as colored lines. Horizontal lines mark the reference 5-year CRC risk at age 45 or 50 for individuals without SLD. In the UK, individuals with ALD reached the equivalent CRC risk of a 50-year-old without SLD at approximately age 46 (95% CI 45 48), and those with MetALD and MASLD reached this risk level at about ages 47 (46 48) and 48 (47 49), respectively. Using age 45 as the reference, the corresponding risk-adapted starting ages were approximately 41 (40 43) for ALD, 42 (41 43) for MetALD, and 43 (42 44) for MASLD.

Table 4 summarizes the risk-adapted starting ages for CRC screening across countries in North America and Europe. Using 50 years as the reference starting age, the overall pattern of earlier screening for higher-risk SLD subtypes was consistent across all countries, with Canada showing the earliest recommended starting age at 44 (95% CI 42 47). Compared to those without SLD, individuals with MASLD, MetALD and ALD reached the reference risk level approximately 2 to 3 years, 3 to 4 years, and 4 to 6 years earlier, with starting ages ranging from 47 to 48 years, 46 to 47 years, and 44 to 46 years, respectively. These results were very consistent with the estimated RAPs. Similar patterns were observed when using 45 years as the reference starting age.

Discussion

In this large, population-based cohort study, we observed that individuals with SLD, particularly those with ALD and the mixed metabolic-alcohol subtype MetALD, had significantly increased risk of CRC. These SLD-associated CRC risk were independent of cardiometabolic risk factors and family history of CRC. Furthermore, our results extended current evidence linking metabolic dysfunction to CRC risk by providing subtype-specific risk estimates under the updated SLD framework. Notably, individuals with MASLD, MetALD, and ALD reached CRC risk thresholds comparable to those of average-risk individuals at recommended screening ages (45 or 50 years) 2 to 6 years earlier, and even earlier in combination with diabetes or obesity, suggesting that SLD may serve as a useful indicator for risk-adapted screening initiation.

Recent studies in Asian populations have reported an elevated risk of colorectal cancer (CRC) among individuals with MetALD or ALD compared with MASLD.[7,8] In the present study, we adjusted for a similar but more comprehensive set of potential covariates than in previous analyses, consistent with earlier studies. Park et al reported higher CRC risk among patients with MASLD (aHR 1.20; 95% CI, 1.17–1.24) and MetALD (aHR 1.26; 95% CI, 1.20–1.33) using data from the National Health Insurance Service database in Korea [7]; however, their analysis did not account for prior cancer screening, which may have influenced the observed associations. In contrast, Kimura et al reported stronger associations for ALD (aHR 1.73; 95% CI, 1.59–1.87),

MetALD (aHR 1.36; 95% CI, 1.28–1.45), and MASLD (aHR 1.28; 95% CI, 1.22–1.35).[8] The difference in effect estimates between studies may be attributable to variations in covariate adjustment strategies and population characteristics, including differences in the handling of metabolic factors such as overweight and obesity. We extended these results to a predominantly White population, suggesting that the association between SLD subtypes and CRC risk vary slightly across different ethnic and geographic contexts. Moreover, our analysis translates these risks into practical screening implications, reinforcing the clinical relevance of incorporating SLD subtypes into CRC prevention strategies.

The elevated CRC risk observed among individuals with SLD may be explained by several interrelated biological pathways. Metabolic dysfunction, including chronic low-grade inflammation, insulin resistance, and hyperinsulinemia, may promote colorectal carcinogenesis through activation of insulin-like growth factor signaling and downstream proliferative pathways.[21] In addition, gut microbiota dysbiosis and impaired intestinal barrier function may contribute to systemic metabolic and inflammatory disturbances, providing a potential mechanistic link between SLD and colorectal cancer.[22] Alcohol exposure represents a key additional factor in ALD and MetALD, and is a well-established risk factor for colorectal cancer.[23–25] In these subtypes, chronic alcohol consumption may further exacerbate gut–liver axis dysfunction by increasing intestinal permeability, inducing oxidative stress, and promoting accumulation of carcinogenic metabolites such as acetaldehyde. Taken together, these metabolic, microbial, and alcohol-related mechanisms may act synergistically to drive a graded increase in colorectal cancer susceptibility across SLD subtypes, consistent with the observed risk gradient from MASLD to MetALD to ALD.

As outlined above, early identification of CRC in this high-risk population may facilitate timely interventions and alleviate the healthcare burden associated with advanced-stage disease. Nonetheless, implementing targeted CRC screening in individuals with SLD presents several challenges. Limited awareness of MAFLD/NAFLD among both healthcare providers and patients may contribute to the under-recognition of individuals at increased risk for CRC.[26,27] Moreover, the high global prevalence of MAFLD raises important concerns regarding the cost-effectiveness and optimal allocation of healthcare resources for large-scale screening, which remain

insufficiently studied.[28] Further research is also warranted to assess the cost-effectiveness of more personalized screening strategies as shown in our study. Additional barriers might include lack of knowledge, disparities in healthcare access, and financial constraints, particularly in resource-limited settings.[29,30] Addressing these multifaceted challenges will require joint efforts from clinical practice, public health policy, and translational research to establish efficient, evidence-based screening strategies tailored to this expanding at-risk population.

This study has several strengths. Leveraging the updated SLD classification, we provided timely evidence on the differential CRC risk across MASLD, MetALD, and ALD subtypes in a large, well-characterized European cohort. The use of population-attributable fractions and risk advancement periods enhanced the interpretability and public health relevance of our findings. Moreover, by integrating UK Biobank-derived relative risks with the most updated age-specific CRC incidence data from GLOBOCAN and SEER, we estimated risk-adapted screening ages across countries, offering practical insights for precision prevention.

Several limitations should be acknowledged when interpreting our findings. First, hepatic steatosis was defined using non-invasive surrogate markers rather than imaging or histological confirmation. Although these markers have been validated and demonstrate relatively high sensitivity and specificity, their use may still have introduced a degree of exposure misclassification. Specifically, individuals without hepatic steatosis but with elevated BMI or triglyceride levels may have been misclassified as having steatosis, whereas some individuals with true steatosis but relatively normal metabolic profiles may have been misclassified as non-steatotic. This non-differential misclassification is likely to have biased the observed associations toward the null, potentially underestimating the true effects. A subset of UK Biobank participants (n = 9,879) underwent MRI-based hepatic fat assessment, but the small sample size limited reliable analysis of colorectal cancer outcomes. Second, the UK Biobank cohort is not fully representative of the general population due to the healthy volunteer effect and limited ethnic diversity, which may affect the generalizability of results.[31] Besides, we applied UK-derived relative risks to other countries assuming similar effects across populations due to the limited evidence on SLD subtype–specific CRC risk. Nevertheless, a recent meta-analyse of cohort studies (HR 1.25, 95% CI 1.15–1.36 overall; HR 1.17, 95% CI 1.04–1.31 in European studies) for

MASLD and CRC were very consistent with the results of our study, supporting the plausibility of these illustrative projections.[32] Third, exposures such as metabolic traits and lifestyle factors were only assessed at baseline, and we could not account for changes over time or the impact of disease progression. Fourth, residual confounding cannot be completely excluded, despite adjustment for a wide range of potential confounders. Fifth, alcohol intake was self-reported due to the practical limitations of objectively measuring long-term consumption in large cohorts, which may be subject to recall bias and misclassification. These limitations warrant cautious interpretation and underscore the need for external validation in other populations and with clinically confirmed SLD diagnoses.

Conclusions

Our findings provide evidence to inform more refined, risk-adapted CRC screening strategies. While current guidelines rely heavily on age and family history, our results highlight that individuals with ALD, MetALD, and MASLD may reach equivalent CRC risk levels several years earlier than those without SLD. Importantly, compared with family history, SLD subtypes were more prevalent and conferred comparable or even greater absolute risk. Incorporating SLD status into risk stratification models could therefore improve the efficiency of screening programs by identifying high-risk individuals who may benefit from earlier intervention. These data support moving beyond one-size-fits-all screening toward personalized strategies that reflect an individual's metabolic and hepatic health profile.

List of abbreviations

ALD, alcohol-related liver disease; BMI, body mass index; CRC, colorectal cancer; FLI, Fatty Liver Index; GGT, γ-glutamyltransferase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-related liver disease; PAF, population attributable fractions; RAP, risk advancement periods; SEER, Surveillance, Epidemiology, and End Results; SLD, steatotic liver disease; TG, triglycerides; WC, waist circumference

Declarations

Ethics approval and consent to participate

This study was based on the UK Biobank study that has obtained approval as a Research Tissue Bank (RTB) from the North West Multi-center Research Ethics Committee (renewed approval in 2021: 21/NW/0157). The North West Multi-Centre Research Ethics Committee approved the collection and use of UKBiobank data. All participants provided written informed consent. Institutional review board approval was waived for this analysis because of the publicly available and deidentified data.

Consent for publication

Consent for publication is not applicable because this study does not contain any individual person's data in any form (including individual details, images, or videos).

Avaliablility of data and materials

This research has been conducted using the UK Biobank resource under application number 66591. This work used data provided by patients and collected by the NHS as part of their care and support. The UK Biobank is an open-access resource and bona fide researchers can apply to use the UK Biobank dataset by registering and applying at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access/. Further information is available from the corresponding author upon request.

Competing Interests

The authors report no conflicts of interest in this work.

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Authors' Contributions

X.C.: Conceptualization, Formal analysis, Methodology, Funding acquisition, Writing-original draft, Writing-review & editing. H.Z.: Formal analysis, Methodology, Writing-review & editing. Y.Z.: Formal analysis, Methodology, Writing-review & editing. R.F.: Data curation, Writing-review & editing. H.X.: Writing-review & editing. T.S.: Writing-review & editing. H.L.: Writing-review & editing. T.Z.: Writing-review & editing. S.L.: Conceptualization, Supervision, Writing-review & editing. J.J.: Conceptualization, Supervision, Writing-review & editing. H.B.: Data curation, Conceptualization, Writing-review & editing.

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494

495 **Table 1.** Basic Characteristics of study participants

Characteristics	N	%
No. of participants	191,837	
SLD status		
No SLD	121,403	63.3
MASLD	48,850	25.5
MetALD	16,170	8.4
ALD	5414	2.8
Incident CRC cases	2371	1.2
Demographics and lifestyle factors		
Age at recruitment (years), median (IQR)	55 (48, 61)	
Sex		
Female	102,867	53.6
Male	88,970	46.4
Ethnicity		
White	181,214	94.5
Other	10,623	5.5
Education		
College /University	66,643	34.7
Other	125,194	65.3
Townsend deprivation index (quartile), N (%)		
1 (least deprived)	48,365	25.2
2	47,857	24.9
3	47,761	24.9
4 (most deprived)	47,854	24.9
Smoking, N (%)		
Not current	171,164	89.2
Current	20,673	10.8
Alcohol consumption (g/d), median (IQR)	13.3 (3.9, 26.1)	
Alcohol consumption frequency		
Never	15,646	8.2
1-3 times a month	23,850	12.4
1-4 times a week	109,760	57.2
Daily or almost daily	42,581	22.2
Vegetable intake (tablespoons/d), median (IQR)	4 (3, 6)	
Fruit intake (pieces/d), median (IQR)	2 (1, 4)	
Processed meat consumption, N (%)		
Never	18,135	9.5
Less than once a week	56,676	29.5
Once a week	56,417	29.4

≥2 times a week	60,609	31.6
Metabolic characteristics		
Overweight/obesity	134,194	70.0
Pre-diabetes/diabetes	33,137	17.3
Hypertension	136,949	71.4
High triglyceride	87,795	45.8
Low HDL cholesterol	35,777	18.6
Other characteristics		
FIB-4, median (IQR)	1.2 (0.9, 1.5)	
Lipid-lowering medication	27,801	14.5
Antihypertensive medication	36,177	18.9
Glucose-lowering medication	6112	3.2
Frequent use of aspirin	22,954	12.0
Family history of CRC	17,053	8.9

Note: N (%) were presented unless indicated otherwise.

Abbreviations: ALD, alcohol-associated liver disease; CRC, colorectal cancer;HDL, high-density lipoprotein; IQR, interquartile range, MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-associated liver disease; SLD, steatotic liver disease;

Table 2. Associations of steatotic liver disease and family history with colorectal cancer risk

Variables	CRC cases (N) /Total (N)	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]	PAF (%)[d]
Age	/	1.08 (1.08, 1.09)			/
SLD					
No SLD	1245/121,403	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	/
MASLD	718/48,850	1.24 (1.12 to 1.36)	1.25 (1.13 to 1.37)	1.17 (1.05 to 1.32)	4.2
MetALD	294/16,170	1.55 (1.36 to 1.77)	1.47 (1.28 to 1.68)	1.41 (1.21 to 1.63)	3.3
ALD	114/5414	1.84 (1.51 to 2.24)	1.63 (1.33 to 2.01)	1.58 (1.27 to 1.95)	1.6
Family history of					
No	2075/174,784	Ref. (1.00)	Ref. (1.00)	Ref. (1.00)	/
Yes	296/17,053	1.31 (1.16 to 1.48)	1.29 (1.14 to 1.46)	1.29 (1.14 to 1.46)	2.4

Note:p value for interaction between SLD subtypes and family history of CRC = 0.94

[a] Adjusted for age and sex.

[b] Additionally adjusted for ethnicity, Townsend deprivation index, educational level, smoking status, alcohol consumption frequency, fruit intake, vegetable intake, processed meat consumption, frequent use of aspirin, and family history of CRC.

[c] Additionally adjusted for prediabetes/diabetes, hypertension, high triglyceride, low HDL cholesterol, overweight/obesity and fibrosis 4 index in the multivariate model.

[d] PAF was estimated based on the fully adjusted Cox proportional hazards model

509 **Abbreviations:** ALD, alcohol-associated liver disease; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MASLD, metabolic
510 dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-associated liver disease; PAF, population attributable fraction; SLD,
511 steatotic liver Disease.
512

513 **Table 3.** Hazard ratio, risk advancement periods and risk-adapted starting ages for colorectal cancer screening according to metabolic dysfunction

514 among individuals with steatotic liver disease

SLD	CRC cases (N) /Total (N)	HR (95% CI)[a]	RAP (95% CI)	Risk-Adapted starting ages of CRC screening (years, 95% CI)		
				Scenario 1 (reference age 50 years)	Scenario 2 (reference age 45 years)	Scenario 3 (family history scenario, reference age 40 years)
No SLD	1245/121,403	Ref. (1.00)	Ref. (0)	50 years	45 years	40 years
MASLD	718/48,850	1.17 (1.05 to 1.31)	2.1 (0.6 to 3.5)	48 (46 to 49)	43 (41 to 44)	38 (36 to 39)
MetALD	294/16,170	1.41 (1.21 to 1.63)	4.4 (2.5 to 6.3)	46 (44 to 47)	41 (39 to 42)	36 (34 to 37)
ALD	114/5414	1.63 (1.33 to 2.01)	5.9 (3.1 to 8.7)	44 (41 to 47)	39 (36 to 42)	34 (31 to 37)
Stratified by metabolic characteristics						
MASLD						
MASLD^{+} obesity^{-}	42/4143	0.88 (0.64 to 1.21)	-1.6 (-5.7 to 2.5)	/	/	
MASLD^{+} obesity^{+}	676/44,707	1.22 (1.10 to 1.36)	2.6 (1.2 to 4.0)	47 (46 to 49)	42 (41 to 44)	
MASLD^{+} diabetes^{-}	451/33,993	1.13 (0.99 to 1.28)	1.6 (0.0 to 3.2)	48 (47 to 50)	43 (42 to 45)	
MASLD^{+} diabetes^{+}	267/14,857	1.31 (1.13 to 1.53)	3.5 (1.5 to 5.5)	46 (44 to 48)	41 (39 to 43)	
MetALD						
MetALD^{+} obesity^{-}	29/1891	1.27 (0.87 to 1.85)	3.1 (-1.8 to 7.9)	/	/	
MetALD^{+} obesity^{+}	265/14,279	1.45 (1.25 to 1.68)	4.8 (2.9 to 6.7)	45 (43 to 47)	40 (38 to 42)	
MetALD^{+} diabetes^{-}	205/12,621	1.32 (1.12 to 1.56)	3.6 (1.5 to 5.8)	46 (44 to 48)	41 (39 to 43)	
MetALD^{+} diabetes^{+}	89/3549	1.71 (1.36 to 2.15)	6.9 (3.9 to 9.9)	43 (40 to 46)	38 (35 to 41)	

ALD						
ALD^{+} obesity^{-}	15/738	1.65 (0.98 to 2.77)	6.5 (-0.3 to 13.2)	/	/	
ALD^{+} obesity^{+}	99/4676	1.60 (1.28 to 1.99)	6.1 (3.2 to 8.9)	44 (41 to 47)	39 (36 to 42)	
ALD^{+} diabetes^{-}	84/4266	1.54 (1.21 to 1.95)	5.6 (2.4 to 8.7)	44 (41 to 48)	39 (36 to 43)	
ALD^{+} diabetes^{+}	30/1148	1.76 (1.21 to 2.56)	7.3 (2.4 to 12.2)	43 (38 to 48)	38 (33 to 43)	

[a] Adjusted for age, sex, ethnicity, Townsend deprivation index, educational level, smoking status, alcohol consumption frequency, fruit intake, vegetable intake, processed meat consumption, frequent use of aspirin, family history of CRC, prediabetes/diabetes, hypertension, high triglyceride, low HDL cholesterol, overweight/obesity and fibrosis 4 index in the multivariate model. Models were not additionally adjusted for diabetes or obesity when these variables were used for stratification.

Abbreviations: ALD, alcohol-associated liver disease; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-associated liver disease; SLD, steatotic liver disease.

Table 4. Risk-adapted starting ages of colorectal cancer screening according to steatotic liver disease based on relative risk and age-specific cumulative incidence

SLD	CRC Cases (N)/ Total (N)	Relative Risk (95% CI)[a]	Risk-adapted starting age (years to 95% CI)					
			United States[b]	Canada	Germany	United Kingdom	Italy	France
Scenario 1 (screening reference age = 50 years)								
No SLD	1245/121403	Ref.	50	50	50	50	50	50
MASLD	718/48850	1.17 (1.05 to 1.31)	48 (48 to 49)	48 (46 to 49)	48 (48 to 49)	48 (47 to 49)	48 (47 to 49)	47 (46 to 48)
MetALD	294/16170	1.41 (1.21 to 1.63)	47 (46 to 48)	46 (44 to 47)	47 (46 to 48)	47 (46 to 48)	46 (45 to 48)	46 (45 to 48)
ALD	114/5414	1.58 (1.27 to 1.95)	46 (45 to 48)	44 (42 to 47)	46 (45 to 48)	46 (45 to 48)	46 (44 to 47)	45 (43 to 47)
Scenario 2 (screening reference age = 45 years)								
No SLD	1245/121403	Ref.	45	45	45	45	45	45
MASLD	718/48850	1.17 (1.05 to 1.31)	44 (44 to 45)	43 (42 to 44)	44 (44 to 45)	43 (42 to 44)	43 (42 to 44)	43 (42 to 44)
MetALD	294/16170	1.41 (1.21 to 1.63)	42 (41 to 43)	41 (40 to 42)	42 (41 to 43)	42 (41 to 43)	42 (41 to 43)	42 (41 to 43)
ALD	114/5414	1.58 (1.27 to 1.95)	41 (40 to 43)	40 (38 to 42)	41 (40 to 43)	41 (40 to 43)	41 (40 to 43)	41 (39 to 43)

[a]Relative risk was derived from the analysis based on the data from the UK Biobank study. All country- and age-specific cumulative incidence estimate were derived from SEER and GLOBOCAN 2022.

[b]Only non-Hispanic White women in the US was included in the analysis.

Abbreviations: ALD, alcohol-associated liver disease; CI, confidence interval; CRC, colorectal cancer; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-associated liver disease; SLD, steatotic liver disease.

Figure legends

Figure 1. Flowchart of participant selection and exclusion.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; GGT, gamma-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HbA1c, glycated hemoglobin.

Figure 2. Exemplary calculation of risk-adapted starting age for colorectal cancer (CRC) screening according to steatotic liver disease (SLD) subtypes using data from the UK.

Note: Analyses based on relative risk estimates for CRC at any age with the comparison of average risk at 45 (lower dashed line) and 50 years (the upper solid line).

Abbreviations: ALD, alcohol-associated liver disease; CR, cumulative risk; CRC, colorectal cancer; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic and alcohol-associated liver disease; SLD, Steatotic Liver Disease.

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