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Metabolic-Associated Fatty Liver Disease is Associated with Colorectal Adenomas in Young and Older Korean Adults

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Word count: abstract 250 words, **text** 4,453words

Figure number: 1**, Table** number: 4 (Supplementary table number: 3)

Abbreviations:

BMI : body mass index

BP : blood pressure

CI: Confidence intervals

CRA : colorectal adenoma

CRC : colorectal cancer

HbA1c: Glycated hemoglobin

HOMA-IR : homeostatic model assessment for of the insulin resistance

HR: Hazard ratios

hs-CRP: High-sensitivity C-reactive protein

MAFLD : metabolic dysfunction-associated fatty liver disease

NAFLD : non-alcoholic fatty liver disease

Conflict of interest statement: The authors declare that they have no competing interests.

Acknowledgement: We extend our sincere gratitude to the dedicated staff members of the Kangbuk Samsung Health Study for their unwavering commitment, diligent efforts, and invaluable support.

Data availability statement: The data are not publicly available because of institutional review board restrictions (the data were not collected in a manner that could be widely distributed). However, the analytical codes are available from the corresponding author upon request.

Funding statement. This study was supported by the SKKU Excellence in Research Award Research Fund, Sungkyunkwan University (2021), and by the National Research Foundation of Korea, funded by the Ministry of Science, ICT, and Future Planning (NRF-2021R1A2C1012626). CDB is supported in part by the Southampton National Institute for Health and Care Research Biomedical Research Centre NIHR *grant code,* NIHR203319.

Abstract

Background & Aims: Given that the majority of colorectal cancers (CRCs) develop from high-risk adenomas, identifying risk factors for high-risk adenomas is important. The relationship between metabolic dysfunction-associated fatty liver disease (MAFLD) and the risk of colorectal adenoma in young adults remains unclear. We aimed to evaluate this relationship in adults <50 (younger) and ≥50 (older) years of age.

Methods: This cross-sectional study included 184,792 Korean adults (80% <50 years of age) who all underwent liver ultrasound and colonoscopy. Participants were grouped into those with and without MAFLD and classified by adenoma presence into no adenoma, low-risk adenoma, or high-risk adenoma (defined as ≥3 adenomas, any ≥10 mm, or adenoma with high-grade dysplasia/villous features).

Results: The prevalence of low- and high-risk adenomas among young and older adults was 9.6% and 0.8% and 22.3% and 4.8%, respectively. MAFLD was associated with an increased prevalence of low- and high-risk adenomas in young and older adults. Young adults with MAFLD had a 1.30 (95% CIs 1.26–1.35) and 1.40 (1.23–1.59) times higher prevalence of low- and high-risk adenomas, respectively, compared to those without MAFLD. These associations were consistent even in lean adults (BMI < 23 kg/m^2) and those without a family history of colorectal cancer.

Conclusion: MAFLD is associated with an increased prevalence of low- and high-risk adenomas in Korean adults, regardless of age or obesity status. Whether reducing metabolic risk factors, such as MAFLD, reduces the risk of precancerous lesions and ultimately reduces the risk of early-onset CRC requires further investigation.

Keywords: Metabolic Dysfunction-Associated Fatty Liver Disease; Obesity; Young-Onset

Colorectal Adenoma.

Lay Summary

The incidence of early-onset CRC is rising, and the most of colorectal cancers develop from high-risk adenomas. The relationship between MAFLD and the risk of colorectal adenoma in young adults was unclear until this study. In this large cohort of Korean adults undergoing colonoscopy, MAFLD is associated with an increased prevalence of low- and high-risk colorectal adenomas in young and older adults, regardless of sex, obesity status, and a family history of colon cancer.

Introduction

Despite an overall decrease in the global incidence of colorectal cancer (CRC),[1] the incidence of early-onset CRC (<50 years) has increased.[2] The majority of CRCs develop from high-risk adenomas. The annual transition rate from high-risk adenoma to CRC is estimated to be 2–6%. [3] Colorectal adenomas (CRAs) are classified as low- and high-risk adenomas, according to size, degree of dysplasia, and the presence of a villous component.[4-6] The detection and removal of CRAs is likely to be the most effective strategy to prevent CRC.[7] Risk factors specific to young- or early-onset CRAs have not been well characterized, and adults aged <50 years are not routinely screened for CRC detection, which includes colonoscopy or fecal blood tests. A better understanding of the risk factors for early-onset CRA/CRC is crucial for developing screening strategies for young adults at risk of CRC.

Metabolic dysfunction-associated fatty liver disease (MAFLD) is being increasingly used to redefine and reclassify non-alcoholic fatty liver disease (NAFLD), which commonly co-occurs with metabolic syndrome.[8,9] MAFLD affects approximately 25% of the global adult population,[10] and its increase among young adults is a cause for concern.[11] While studies have explored the relationship between MAFLD/NAFLD and CRC,[12-15] there are limited data on the association between MAFLD and the risk of CRA in young adults. There is a strong relationship between obesity and MAFLD; hence, MAFLD can also occur in lean adults, with a prevalence of 4.1–34%.[16,17] A recent study[18] reported a stronger association between MAFLD and CRA in non-obese adults than in obese adults. However, the clinical implications of lean MAFLD on the development of CRC and its precursors remain unclear.

We aimed to examine the association between MAFLD and low- and high-risk adenomas in young adults and to determine whether this association differs by sex and obesity.

Methods

We used retrospective deidentified data from the Kangbuk Samsung Health Study,[19] a cohort study of Korean adults that began in 2002. The Kangbuk Samsung Health Study mainly comprises employees of companies or local government organizations and their spouses who undergo routine health examinations every 1–2 years at Kangbuk Samsung Hospital, Seoul and Suwon, South Korea.[19] In this study, we focused on adults who underwent colonoscopy as part of a comprehensive health screening program from 2015 (when a standardized report was introduced for colonoscopy) to 2020. Under the Industrial Safety and Health Law in Korea, employees are required to undergo annual or biannual health examinations. Most participants were employees of companies or local government organizations and their spouses. The remaining participants were registered individually for the program.

Participants with a history of CRC/inflammatory bowel disease/colorectal polyps, incomplete colonoscopies, poor bowel preparations, or missing data on body mass index (BMI)/liver ultrasound/alcohol consumption or history of colorectal polyp were excluded. Participants who did not undergo biopsy for colorectal polyps owing to anticoagulant medication or referral for polypectomy, with no data available on the results at the same hospital, were also excluded (Figure 1). Because some participants met more than one exclusion criterion, the final sample for analysis consisted of 184,792 participants.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC 2023-03-005). The requirement for informed consent was waived owing to the use of deidentified data collected during routine screening.

Measurements

The health check-up program involved a standardized questionnaire survey and various

measurements, including physical examination, fasting blood measurements, transabdominal ultrasound, and other procedures, as described previously.[20] Average daily alcohol consumption was calculated from the frequency of alcohol consumption per week and the amount of alcohol consumed per drinking day. Physical activity was determined using the validated Korean version of the International Physical Activity Questionnaire–short form. A family history of colorectal cancer was defined as the presence of colon cancer in at least one first-degree relative at any age.

Trained nurses measured resting blood pressure (BP) and anthropometric parameters. Participants with a BMI ≥ 23 kg/m^2 (the cutoff for overweight/obesity in Asians)[21] were classified as overweight/obese.

Blood samples were collected after ≥10 hours of fasting. Fasting serum measurements included lipid profiles and liver enzyme, glucose, high-sensitivity C-reactive protein (hs-CRP), and insulin levels. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated as fasting blood insulin (mU/mL) × fasting blood glucose (mmol/L)/22.5. Diabetes was defined as fasting serum glucose ≥126 mg/dL (7 mmol/L), HbA1c ≥ 6.5% (48 mmol/mol), or current use of insulin/glucose-lowering drugs.

Colonoscopic Examination and CRA Definition

Participants underwent colonoscopy that involved bowel preparation using 2 L of Coolprep® (Taejoon Pharmaceuticals Co. Ltd., Seoul, Korea), followed by insertion of an EVIS LUCERA CV-260 colonoscope (Olympus Medical Systems, Tokyo, Japan) from the rectum to the cecum by experienced gastroenterologists/general surgeons. Polypoid lesions were biopsied or removed and subsequently assessed by experienced pathologists.

Adenomas are classified according to their size, number, and histological features. High-risk

adenomas were defined as at least three adenomas, adenomas ≥10 mm, or adenomas with high-grade dysplasia/a villous component.[4-6] Participants diagnosed with low- and high-risk adenomas were classified as high-risk.

MAFLD and Liver Fibrosis Assessment

Experienced radiologists, who were blinded to the study, conducted abdominal ultrasonography and diagnosed hepatic steatosis using standard criteria, including a diffuse increase in fine echoes in the liver parenchyma compared to those in the kidney or spleen parenchyma, deep beam attenuation, and bright vessel walls.[20,22] Abdominal ultrasound was performed on the same day as that of the health examination, prior to colonoscopy. Fatty liver diagnosis showed substantial inter- and excellent intra-observer reliability (kappa statistic: 0.74 and 0.94, respectively).[20] MAFLD was defined as hepatic steatosis, detected by ultrasound and meeting metabolic criteria, including overweight/obesity (BMI ≥ 23 kg/m^2 in Asians), diabetes, or at least two metabolic abnormalities: (a) waist circumference ≥ 90 cm (men) or ≥80 cm (women), (b) BP ≥ 130/85 mmHg or receiving BP-lowering drugs, (c) serum triglycerides ≥ 150 mg/dL or receiving specific treatment, (d) serum high-density lipoprotein < 40 mg/dL (men) or <50 mg/dL (women), (e) prediabetes (fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L] or HbA1c 5.7–6.4% [39–46 mmol/mol]), (f) HOMA-IR index ≥ 2.5, or (g) hs-CRP > 2 mg/dL.[9] Participants were categorized into two groups: those without MAFLD and those with MAFLD. Participants who had fatty liver but did not meet the criteria for MAFLD were classified as belonging to the no MAFLD group.

Hepatic steatosis was originally recorded as mild, moderate, or severe.[20] Mild hepatic steatosis was characterized by a slight increase in liver echogenicity. Moderate hepatic steatosis was identified by a mildly compromised visualization of the intrahepatic vasculature and diaphragm, coupled with increased liver echogenicity. Severe hepatic steatosis was indicated by a significant rise in liver echogenicity, hindered penetration of the posterior

segment of the right lobe, and inadequate or absent visualization of the intrahepatic vasculature and diaphragm.[20,22] However, due to the limited number of cases with severe steatosis, these cases were combined with moderate steatosis. We also used the Fibrosis-4 (FIB-4) and NFS (NAFLD fibrosis score) score, validated non-invasive indices of advanced fibrosis, to evaluate HS severity.[23] The FIB-4 index was calculated for each of the subjects as (age×AST (U/L)/platelet count ($\times 10^9$/L)/$\sqrt{ALT}$(U/L)) and was classified into low and intermediate/high groups based on 1.30 points. NFS was calculated as: –1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG or diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet ($\times 10^9$/l) – 0.66 × albumin (g/dl). The NFS cut-off points were defined as <-1.455 (low risk) and ≥-1.455 (intermediate/high risk) for predicting probability of advanced fibrosis.[23]

Statistical Analyses

Participants' characteristics are summarized according to MAFLD status. We evaluated the distribution of continuous variables, making the necessary adjustments. To examine the age-specific relationship between MAFLD and CRA, we conducted separate analyses of young and older adults. To estimate prevalence ratios and 95% confidence intervals (CIs) for low- and high-risk adenomas in adults with MAFLD compared to those without MAFLD, we used participants without adenomas as the reference group in the multinomial logistic regression analysis. The models were adjusted for age and sex and further adjusted for potential confounders (center, year of screening, smoking status, alcohol intake, educational level, a history of cardiovascular disease, and a family history of colon cancer). Subgroup analysis was performed to examine the associations between sex (male *vs*. female), overweight/obesity (BMI ≥ 23 kg/m^2) (yes *vs*. no), diabetes (yes *vs*. no), a family history of colorectal cancer (yes *vs*. no) and number of metabolic abnormalities (<2 or *vs*. ≥ 2).

Additionally, we conducted sensitivity analyses to investigate the presence of a dose-response relationship between MAFLD with a low probability of advanced fibrosis and MAFLD with an intermediate/high probability of advanced fibrosis (indicated by a low fibrosis score versus an intermediate and high fibrosis score for both FIB-4 and NFS scores), and the prevalence of low- and high-risk CRA. Likelihood ratio tests were used to compare models with and without multiplicative interaction terms. All statistical analyses were conducted using Stata (version 17.0; StataCorp LP, College Station, TX, USA). Significance was set at a two-tailed $P < 0.05$.

Results

The mean (standard deviation) age of the 184,792 participants was 42.6 (9.4) years, with 80.4% of participants aged <50 years (Table 1). Young and older adults with MAFLD were more likely to be male and had a higher prevalence of diabetes, hypertension, and lipid-lowering medication use. They were also more likely to have unhealthy metabolic profiles and higher liver enzymes and were less likely to be physically active.

Table 2 presents the prevalence of low- and high-risk adenomas, according to the presence of MAFLD, in young and older adults. In young adults, the prevalence of low- and high-risk adenomas was 9.6% and 0.8 %, respectively, whereas in older adults, the prevalence of low- and high-risk adenomas was 22.3% and 4.8%, respectively. MAFLD was associated with an increased prevalence of low- and high-risk adenomas in young and older adults, without a significant interaction of age (*P* interaction = 0.464). After adjusting for potential confounders, young adults with MAFLD had a 1.3 (95% CI: 1.26–1.35) times higher prevalence of low-risk adenomas and a 1.4 (95% CI: 1.23–1.59) times higher prevalence of high-risk adenomas compared to those without MAFLD. Similarly, in older adults, MAFLD

was associated with a 1.28 (95% CI: 1.21–1.34) and 1.53 (95% CI: 1.39–1.69) times higher prevalence of low- and high-risk adenomas, respectively.

The association between MAFLD and low- and high-risk adenomas in young and older adults did not differ by sex, overweight/obesity status, diabetes, two features of metabolic abnormalities, or a family history of colorectal cancer (Tables 3 and 4). A higher prevalence of adenomas in MAFLD was consistently observed even in lean adults (BMI <23 kg/m^2) and those without diabetes or a family history of colon cancer.

Supplementary Tables 1 and 2 provides sensitivity analyses that employ noninvasive fibrosis markers to evaluate the impact of MAFLD severity. In young adults, the multivariable-adjusted prevalence ratios (PRs) with 95% confidence intervals (CIs) for low-risk CRA, comparing no MAFLD (reference) with low or intermediate/high NFS, were 1.29 (1.24–1.34) and 1.53 (1.38–1.71), respectively. In older adults, the corresponding PRs (95% CI) were 1.27 (1.20–1.35) and 1.28 (1.19–1.38). Similarly, for high-risk CRA, in young adults, the multivariable-adjusted PRs (95% CIs) comparing no MAFLD (reference) with low or intermediate/high NFS were 1.38 (1.21–1.57) and 1.64 (1.20–2.25), respectively. In older adults, the corresponding PRs were 1.59 (1.42–1.79) and 1.44 (1.26–1.65). The association between MAFLD severity based on NFS and CRA differed by age group, with a significant interaction (P for interaction=0.026). When using FIB-4 instead of NFS, the patterns were similar, but the interaction by age group was not statistically significant (P for interaction=0.184) (Supplementary Tables 1 and 2).

In sensitivity analysis using the degree of hepatic steatosis on ultrasonography (Supplementary Table 3), we observed that the prevalence of CRA increased with the degree of hepatic steatosis, showing a clear trend from no MAFLD to mild MAFLD and then to moderate-to-severe MAFLD in both young and older adults. Specifically, among young

adults, the multivariable-adjusted PRs (95% CI) for high-risk CRA, comparing no MAFLD (reference) with mild MAFLD or moderate-to-severe MAFLD, were 1.31 (1.14–1.50) and 1.79 (1.46–2.19), respectively. Similarly, in older adults, the corresponding PRs (95% CI) were 1.47 (1.32–1.63) and 2.00 (1.53–2.46), respectively.

Discussion

In this large study of young and older Korean adults who underwent colonoscopy as part of a comprehensive health screening program, we observed a positive association between MAFLD and the prevalence of low- and high-risk adenomas. This association was consistent across subgroups stratified by sex, obesity, and a family history of colorectal cancer. Our findings suggest that MAFLD (a hepatic phenotype with a metabolically unhealthy status) may play a role in the development of colorectal neoplasms and may help explain the recent increase in the incidence of early-onset CRC in young adults.

Earlier studies, including a systematic review,[24-26] reported a moderate increase in the incidence and prevalence of CRA in patients with NAFLD. However, limited studies[18,27] have investigated the relationship between MAFLD and CRA, especially early-onset CRA, with the distinction between low- and high-risk CRAs. A new definition of MAFLD was introduced in 2019,[9] with an emphasis on the role of metabolic dysfunction in the pathogenesis of fatty liver disease. Our study, which included the largest number of participants among studies examining the relationship between MAFLD and CRA in young and older adults, supports the notion that MAFLD is an independent modifiable risk factor for low- and high-risk CRAs.

The incidence of early-onset CRC is increasing at an alarming rate worldwide,[28] with the prevalence of young-onset CRA estimated to be 4.2% before and 10.0% after 1995 (the year around which the incidence of early-onset CRC began to increase).[29] In our study, the

prevalence of young-onset CRA was 10.4%, even after excluding participants with a history of colorectal polyps. This highlights the need for additional research in risk factors for early-onset CRA. Risk factors for CRA in young adults have not been well characterized. Our findings support the role of MAFLD as an independent risk factor for colorectal neoplasms, regardless of age, and early-onset CRA as a metabolically driven neoplasm.

In the subgroup analysis, the association between MAFLD and CRA did not differ by sex. The absolute prevalence of CRA was found to be lower in women compared to men, consistent with previous study findings. Although the association between MAFLD and CRA appeared to be stronger in young women than in young men, this difference was not statistically significant (P for interaction = 0.720). Among young individuals without MAFLD, women had the lowest prevalence of CRA, indicating a clear contrast with those with MAFLD and resulting in stronger relative ratios than observed in men. Additionally, other recent studies have shown that the presence of NAFLD or other metabolic abnormalities reduced protection against cardiovascular diseases and type 2 diabetes in premenopausal women.[30-33] This may occur, at least in part, because hepatic fat represents increased metabolic stress in premenopausal women, which could offset the protective effect of estrogen.

The prevalence ratios of CRA were higher in the lean MAFLD group than in the obese MAFLD group, even though the association between MAFLD and high-risk CRAs in young adults was not significant, possibly owing to the small number of participants with high-risk CRAs in this group. This finding is consistent with a previous study[18] showing that non-obese MAFLD is more strongly associated with CRA than obese MAFLD. However, the mechanisms underlying the association between lean MAFLD and CRA remain unclear. Evidence suggests that non-obese or lean MAFLD represents a distinct pathophysiological

entity with metabolic and histological profiles different from those of obese MAFLD.[34] Lean individuals, according to their BMI, are often classified as normal weight, despite having excess body fat or low muscle mass, based on a sophisticated body composition assessment.[35] They may even be classified as metabolically obese, based on further assessment of metabolic profiles, suggesting that lean NAFLD may be an unfavorable metabolic feature in BMI-based misclassified lean individuals. Lean NAFLD is also associated with adverse metabolic effects, such as increased visceral fat, insulin resistance, sarcopenia, and increased levels of proinflammatory cytokines,[36] which are associated with an increased risk of CRC and its precursors. Insulin resistance in NAFLD is closely associated with increased levels of insulin-like growth factor 1 and other growth factors,[37] which are associated with colon carcinogenesis and precancerous and cancerous lesions.[38] A higher prevalence of concomitant sarcopenia or specific gut microbiota profiles has been reported in lean MAFLD,[39] which are also associated with the pathogenesis of CRC.[40] Low muscle mass may be a feature of lean MAFLD, possibly in combination with excess abdominal adipose tissue, decreased protective adipose tissue, and low skeletal muscle mass. Finally, a polymorphism in Transmembrane 6 Superfamily Member 2 (a genetic determinant of lean MAFLD)[34] has been identified that is associated with CRA.[41] Further research using detailed body composition measurements will improve our understanding of the role of lean MAFLD in early-onset CRA.

In this study, the risk of CRA tended to increase with the severity of fatty liver, which is consistent with previous research findings.[27,42,43] Our study is first to demonstrate their association among young adults under the age of 50. Among these young adults, the prevalence of CRA increased with the severity of MAFLD, showing a trend from no MAFLD to MAFLD without advanced fibrosis and MAFLD with advanced fibrosis, particularly in high-risk CRA. The severity of MAFLD is closely related to the risk of colorectal tumors. This association may be attributed to factors such as an inflammatory state, insulin resistance,

decreased serum adiponectin levels, and intestinal bacterial overgrowth, which are more common and severe as MAFLD progresses.[42] Moreover, changes in bile acid patterns associated with increasing fibrosis stages in patients with biopsy-proven NAFLD can alter the composition of the gut microbiota and potentially contribute to colorectal neoplasm development.[44,45] It is worth noting that the natural course of MAFLD indicates that simple steatosis takes an average of 15 years to progress to fibrosis. [46] Recently, there has been a concerning increase in MAFLD cases among adolescents and even in childhood.[11] Consequently, young individuals with MAFLD and a high fibrosis score may have been exposed to the disease for a significant period of time. However, the detailed information about the onset and duration of MAFLD was not available in our study. Furthermore, in older adults, the lack of clarity in the dose-response relationship between fibrosis and CRA could be attributed to the exclusion of the history of colorectal polyps in our study, as past colorectal polyp information was not available. As a result, older adults with a higher risk profile might have been excluded from the study due to the exclusion of participants with a history of colorectal polyps. On the other hand, the observed findings might better reflect the lifetime prevalence of colorectal neoplasms in young adults, as they might have undergone their first colonoscopy during the study. Further studies incorporating comprehensive data on lifetime colorectal neoplasm, MAFLD onset and duration are warranted to enhance our understanding of these relationships and potentially inform preventive measures and treatment strategies for reducing colorectal tumor risk in these populations.

Our study has several limitations. First, fatty liver was diagnosed using sonography instead of biopsy (the gold standard). However, ultrasonography is recommended as a first-line investigation in the clinic due to its non-invasive nature and reasonable accuracy in diagnosing fatty liver compared to histology.[47] According to a meta-analysis of observational studies, conventional ultrasonography demonstrates a sensitivity of 82% and specificity of

80% for detecting hepatic steatosis defined histologically as 5% or more steatotic hepatocytes.[47]

Second, we obtained information about smoking and alcohol consumption, which are important confounders,[41] based on a self-administered questionnaire, potentially leading to errors. Unmeasured factors, such as dietary information, may also have resulted in residual confounding. Third, the study population comprised relatively young and healthy individuals who underwent regular health examinations, limiting the generalizability of the results owing to the early detection and removal of precancerous lesions during screening colonoscopy. However, to minimize bias, we excluded participants with a history of colon polyps, as reported in the questionnaire completed before the examination. Fourth, due to the unavailability of detailed information on the exact size of the polyps as a continuous variable or their specific locations, we were not able to incorporate this extra detail into our study. Further research is necessary to explore whether the results differ based on the size and location of CRA. Finally, this study was conducted in Korea; hence, further research is needed to determine whether our results can be extended to other racial/ethnic groups.

The current CRC screening approach primarily relies on age and family history to determine the suitable time for initiating colonoscopy. However, the alarming increase in early-onset CRC cases necessitates a more comprehensive and precision medicine-oriented strategy to classify adults who could gain from earlier screening.[48] In our study, we demonstrated a significant association between MAFLD and an increased prevalence of colorectal adenomas, in both men and women, and even in lean individuals with a low BMI of <23 kg/m2, and among young adults aged <50 years. Typically, the CRC risk tends to be underestimated in women, lean individuals, or young adults. MAFLD, as a condition defined by ectopic fat in the liver and an increased metabolic risk phenotype, should be considered a potential risk

group within the relatively low-risk population, including young adults, thus warranting consideration of potential earlier screening measures. Further research is required to establish additional detailed conditions for identifying high-risk groups, particularly those under 50 years, who may benefit most from CRC screening.

In conclusion, MAFLD is associated with an increased prevalence of low- and high-risk CRAs in young Korean adults. This association is consistent across subgroups stratified by sex, obesity, and a family history of colon cancer. Given that CRAs in young adults may have a metabolic origin, managing metabolic risk factors, such as MAFLD, may help prevent early-onset CRC.

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Figure legend

Figure 1. Flow chart of the study population

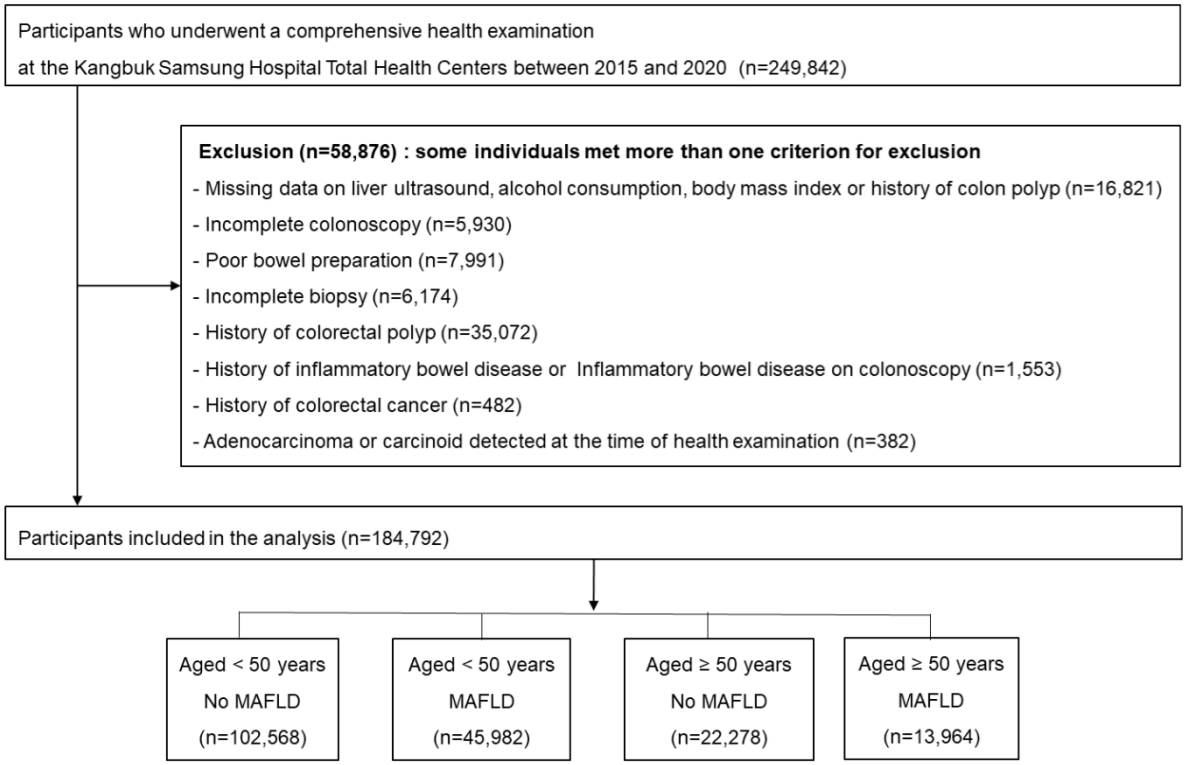

Table 1. Baseline characteristics by MAFLD in young and older adults (N = 184,792)

Characteristics	Young adults aged <50 years		*P*-value	Older adults aged ≥50 years		*P*-value
	No MAFLD	MAFLD		No MAFLD	MAFLD	
Number of participants	102,568	45,982		22,278	13,964	
Age (years)	38.5 (5.9)	39.8 (5.6)	<0.001	57.5 (6.1)	57.5 (5.9)	0.509
Men (%)	51.3	87.3	<0.001	48.7	64.1	<0.001
Seoul center	50.3	52.8	<0.001	67.6	72.3	<0.001
Alcohol intake [c] (%)	34.1	47.2	<0.001	30.1	38.3	<0.001
Current smoker (%)	14.5	26.5	<0.001	13.1	18.0	<0.001
HEPA (%)	16.5	14.2	<0.001	25.4	21.7	<0.001
Educational level [d] (%)	87.8	88.1	0.07	55.5	58.4	<0.001
Obesity [e] (%)	16.2	70.9	<0.001	18.8	58.9	<0.001
Diabetes (%)	0.8	7.9	<0.001	7.1	23.0	<0.001
Hypertension (%)	6.1	19.6	<0.001	24.6	40.8	<0.001
Dyslipidemia medication (%)	1.7	5.5	<0.001	12.2	18.5	<0.001
History of CVD (%)	0.6	0.9	<0.001	4.0	4.5	0.032
Family history of CRC (%)	4.0	3.9	0.614	5.5	5.2	0.368

BMI (kg/m^2) [a]	22.4 (2.7)	26.9 (3.0)	<0.001	22.9 (2.5)	25.8 (2.7)	<0.001
Waist circumference (cm) [a]	78.4 (8.2)	91.3 (7.8)	<0.001	80.2 (7.7)	88.8 (7.2)	<0.001
Systolic BP (mmHg) [a]	107.3 (11.2)	116.6 (11.2)	<0.001	112.4 (12.9)	117.6 (12.6)	<0.001
Diastolic BP (mmHg) [a]	68.9 (8.7)	75.6 (9.0)	<0.001	72.6 (9.3)	76.1 (9.2)	<0.001
Glucose (mg/dL) [a]	91 (10.3)	99.8 (18.5)	<0.001	97.1 (15.3)	107.6 (23.2)	<0.001
Total cholesterol (mg/dL) [a]	189.8 (32.6)	203.8 (36.9)	<0.001	196.7 (38.4)	196.2 (41.8)	0.238
LDL-C (mg/dL) [a]	125.6 (31.9)	144.3 (34.2)	<0.001	134.2 (36.7)	137.2 (39.8)	<0.001
HDL-C (mg/dL) [a]	65.2 (16.3)	49.3 (11.5)	<0.001	63.1 (16.7)	51.8 (13.1)	<0.001
Triglycerides (mg/dL)	69 (51–98)	134 (94–191)	<0.001	75 (54–106)	117 (83–167)	<0.001
ALT (U/L) [b]	19 (14–27)	36 (25–53)	<0.001	21 (17–28)	29 (22–41)	<0.001
GGT (U/L) [b]	18 (13–29)	39 (26–63)	<0.001	21 (15–33)	33 (23–53)	<0.001
hs-CRP (mg/L) [b]	0.4 (0.2–0.7)	0.8 (0.5–1.6)	<0.001	0.4 (0.3–0.8)	0.7 (0.4–1.4)	<0.001
HOMA-IR [b]	1.01 (0.67–1.46)	1.9 (1.33–2.72)	<0.001	0.98 (0.64–1.45)	1.79 (1.24–2.60)	<0.001

Data are [a] mean (standard deviation), [b] median (interquartile range), or percentages.

[b] ≥10 g/day; [c] HEPA; [d] college graduate or higher; [e] BMI ≥25 kg/m^2.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CRC, colorectal cancer; CVD, cardiovascular disease; GGT, gamma glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physical activity; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease.

Table 2. Prevalence ratios [a] (95% CI) of CRA by MAFLD

	Young adults aged < 50 years		Older adults aged ≥ 50 years	
	No MAFLD	MAFLD	No MAFLD	MAFLD
Total number	102,568	45,982	22,278	13,964
Low-risk adenoma				
n (%)	8,182 (8.0)	6,086 (13.2)	4,516 (20.3)	3,579 (22.3)
Age- and sex-adjusted PR [a]	1.00 (reference)	1.33 (1.29–1.38)	1.00 (reference)	1.31 (1.24–1.38)
Multivariate-adjusted PR [a]	1.00 (reference)	1.30 (1.26–1.35)	1.00 (reference)	1.28 (1.21–1.34)
High-risk adenoma				
n (%)	532 (0.5)	494 (1.0)	883 (4.0)	861 (6.2)
Age- and sex-adjusted PR [a]	1.00 (reference)	1.49 (1.31–1.69)	1.00 (reference)	1.62 (1.47–1.79)
Multivariate-adjusted PR [a]	1.00 (reference)	1.40 (1.23–1.59)	1.00 (reference)	1.53 (1.39–1.69)

P interaction = 0.464

[a] Estimated from multinomial logistic regression models with outcomes categorized as no adenoma, low-risk adenoma, and high-risk adenoma. The multivariate model was adjusted for age, sex, center, year of screening, smoking status, alcohol intake, educational level, a history of cardiovascular disease, and a family history of colorectal cancer.

Abbreviations: CI, confidence interval; CRA, colorectal adenoma; MAFLD, metabolic dysfunction-associated fatty liver disease; PR, prevalence ratio.

Table 3. Prevalence ratios [a] (95% CI) of CRA by MAFLD according to sex or obesity in adults aged <50 years (*n* = 148,550)

	Total	No MAFLD	MAFLD	*P* interaction
Sex				0.720
Women (*n* = 55,788)				
Low-risk adenoma, *n* (%)	3,383 (6.1)	2,875 (5.8)	508 (8.7)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.32 (1.19–1.46)	
High-risk adenoma, *n* (%)	228 (0.4)	182 (0.4)	46 (0.8)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.67 (1.21–2.32)	
Men (*n* = 92,762)				
Low-risk adenoma, *n* (%)	10,885 (11.7)	5,307 (10.0)	5,578 (13.9)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.29 (1.24–1.35)	
High-risk adenoma, *n* (%)	798 (0.9)	350 (0.7)	448 (1.1)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.46 (1.27–1.68)	
Overweight/obesity (BMI ≥23 kg/m^2)				0.151
No (*n* = 65,034)				
Low-risk adenoma, *n* (%)	4,599 (7.1)	4,346 (6.9)	257 (13.5)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.37 (1.20–1.58)	
High-risk adenoma, *n* (%)	291 (0.5)	271 (0.4)	20 (1.0)	

Multivariate-adjusted PR [a]		1.00 (reference)	1.53 (0.96–2.43)	
Yes (*n* = 83,516)				
Low-risk adenoma, *n* (%)	9,669 (11.6)	3,836 (9.7)	5,985 (13.2)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.20 (1.14–1.25)	
High-risk adenoma, *n* (%)	735 (0.9)	261 (0.7)	474 (1.0)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.31 (1.12–1.53)	
Diabetes				0.414
No (*n* = 144,066)				
Low-risk adenoma, *n* (%)	13,519 (9.4)	8,051 (7.9)	5,468 (12.9)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.29 (1.24–1.34)	
High-risk adenoma, *n* (%)	934 (0.7)	516 (0.5)	418 (1.0)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.44 (1.25–1.65)	
Yes (*n* = 4,484)				
Low-risk adenoma, *n* (%)	749 (16.7)	131 (15.2)	618 (17.1)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.14 (0.93–1.41)	
High-risk adenoma, *n* (%)	92 (2.1)	16 (1.9)	76 (2.1)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.14 (0.66–1.99)	

Number of metabolic abnormality features				0.381
<2 (*n* = 95,443)				
Low-risk adenoma, *n* (%)	7,465 (7.8)	6,104 (7.4)	1,361 (10.9)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.15 (1.07–1.22)	
High-risk adenoma, *n* (%)	473 (0.5)	380 (0.5)	93 (0.8)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.19 (0.94–1.49)	
≥2 (*n* = 48,847)				
Low-risk adenoma, *n* (%)	6,300 (12.9)	1,743 (10.6)	4,557 (14.1)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.21 (1.14–1.28)	
High-risk adenoma, *n* (%)	515 (1.1)	127 (0.8)	388 (1.2)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.33 (1.08–1.63)	
Obesity (BMI ≥25 kg/m^2)				0.290
No (*n* = 99,384)				
Low-risk adenoma, *n* (%)	8,097 (8.2)	6,432 (7.5)	1,665 (12.4)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.22 (1.15–1.30)	
High-risk adenoma, *n* (%)	534 (0.5)	413 (0.5)	121 (0.9)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.25 (1.01–1.54)	

Yes (*n* = 49,166)				
Low-risk adenoma, *n* (%)	6,171 (12.6)	1,750 (10.6)	4,421 (13.6)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.15 (1.08–1.22)	
High-risk adenoma, *n* (%)	492 (1.0)	119 (0.7)	373 (1.1)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.31 (1.06–1.62)	
Family history of colorectal cancer				0.925
No (*n* = 142,701)				
Low-risk adenoma, *n* (%)	13,621 (9.6)	7,806 (8.0)	5,815 (13.2)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.30 (1.25–1.35)	
High-risk adenoma, *n* (%)	976 (0.7)	507 (0.5)	469 (1.0)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.48 (1.30–1.70)	
Yes (*n* = 5,849)				
Low-risk adenoma, *n* (%)	647 (11.1)	376 (9.3)	2,719 (15.1)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.30 (1.09–1.54)	
High-risk adenoma, *n* (%)	50 (0.9)	25 (0.6)	25 (1.4)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.67 (0.95–2.92)	

[a] Estimated from multinomial logistic regression models with outcomes categorized as no adenoma, low-risk adenoma, and high-risk adenoma. The multivariate model was adjusted for age, sex, center, year of screening, smoking status, alcohol intake, educational level, a history of cardiovascular disease, and a family history of colorectal cancer.

Abbreviations: BMI, body mass index; CI, confidence interval; CRA, colorectal adenoma; MAFLD, metabolic dysfunction-associated fatty liver disease; PR, prevalence ratio.

Table 4. Prevalence ratios [a] (95% CI) of CRA by MAFLD according to sex or obesity in adults aged >50 years (n = 36,242)

	Total	No MAFLD	MAFLD	*P* interaction
Sex				0.091
Women (*n* = 16,438)				
Low-risk adenoma, *n* (%)	2,775 (16.9)	1,746 (15.3)	1,029 (20.5)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.36 (1.24–1.48)	
High-risk adenoma, *n* (%)	470 (2.9)	281 (2.5)	189 (3.8)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.40 (1.16–1.70)	
Men (*n* = 19,804)				
Low-risk adenoma, *n* (%)	5,320 (26.9)	2,770 (25.5)	2,550 (28.5)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.22 (1.14–1.3)	
High-risk adenoma, *n* (%)	1,274 (6.4)	602 (5.6)	672 (7.5)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.53 (1.36–1.72)	
Overweight/obesity (BMI ≥ 23 kg/m^2)				0.456
No (*n* = 13,690)				
Low-risk adenoma, *n* (%)	2,576 (18.8)	2,228 (18.3)	348 (23.4)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.27 (1.11–1.45)	
High-risk adenoma, *n* (%)	483 (3.5)	403 (3.3)	80 (5.4)	

Multivariate-adjusted PR [a]		1.00 (reference)	1.42 (1.10–1.84)	
Yes (*n* = 22,552)				
Low-risk adenoma, *n* (%)	5,519 (24.5)	2,288 (22.7)	3,231 (25.9)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.16 (1.09–1.23)	
High-risk adenoma, *n* (%)	1,261 (5.6)	480 (4.8)	781 (6.3)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.31 (1.16–1.48)	
Diabetes				0.648
No (*n* = 31,457)				
Low-risk adenoma, *n* (%)	6,812 (21.7)	4,122 (19.9)	2,690 (25.0)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.24 (1.18–1.32)	
High-risk adenoma, *n* (%)	1,397 (4.4)	785 (3.8)	612 (5.7)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.44 (1.28–1.61)	
Yes (*n* = 4,784)				
Low-risk adenoma, *n* (%)	1,283 (26.8)	394 (25.0)	889 (27.7)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.28 (1.11–1.47)	
High-risk adenoma, *n* (%)	347 (7.3)	98 (6.2)	249 (7.8)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.64 (1.27–2.11)	

Number of metabolic abnormality features				0.853
<2 (*n* = 14,296)				
Low-risk adenoma, *n* (%)	2,801 (19.6)	2,307 (18.9)	494 (24.0)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.16 (1.04–1.31)	
High-risk adenoma, *n* (%)	452 (3.2)	362 (3.0)	90 (4.4)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.29 (1.02–1.65)	
≥2 (*n* = 19,553)				
Low-risk adenoma, *n* (%)	4,745 (24.3)	1,832 (22.0)	2,913 (25.9)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.21 (1.12–1.29)	
High-risk adenoma, *n* (%)	1,176 (6.0)	445 (5.4)	731 (6.5)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.27 (1.11–1.44)	
Obesity(BMI ≥25 kg/m^2)				0.05
No (*n* = 23,838)				
Low-risk adenoma, *n* (%)	4,955 (20.8)	3,538 (19.6)	1,417 (24.7)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.24 (1.16–1.34)	
High-risk adenoma, *n* (%)	976 (4.1)	649 (3.6)	327 (5.7)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.47 (1.28–1.70)	

Yes (*n* = 12,404)				
Low-risk adenoma, *n* (%)	3,140 (25.3)	978 (23.4)	2,162 (26.3)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.14 (1.04–1.24)	
High-risk adenoma, *n* (%)	768 (6.2)	234 (5.6)	534 (6.5)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.17 (0.99–1.38)	
Family history of colorectal cancer				0.864
No (*n* = 34,296)				
Low-risk adenoma, *n* (%)	7,619 (22.2)	4,247 (20.2)	3,372 (25.5)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.26 (1.2–1.33)	
High-risk adenoma, *n* (%)	1,656 (4.8)	840 (4.0)	816 (6.2)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.49 (1.35–1.65)	
Yes (*n* = 1,946)				
Low-risk adenoma, *n* (%)	476 (24.5)	269 (22.1)	207 (28.3)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.29 (1.04–1.61)	
High-risk adenoma, *n* (%)	88 (4.5)	43 (3.5)	45 (6.2)	
Multivariate-adjusted PR [a]		1.00 (reference)	1.69 (1.08–2.63)	

[a] Estimated from multinomial logistic regression models as outcomes categorized as low-risk adenoma and high-risk adenoma. The multivariable

model was adjusted for age, sex, center, year of screening examination, smoking status, alcohol intake, education level, history of cardiovascular disease, and family history of colon cancer.

Abbreviations: HEPA, health-enhancing physically active; PR, prevalence ratio

Table S1. Prevalence ratios [a] (95% CI) of CRA by MAFLD and degree of fibrosis based on FIB-4 [b]

	Young adults aged < 50 years			Older adults aged ≥ 50 years		
	No MAFLD	MAFLD plus low FIB-4	MAFLD plus intermediate/high FIB-4	No MAFLD	MAFLD plus low FIB-4	MAFLD plus intermediate/high FIB-4
Total number	102,508	45,735	2,238	22,269	8,534	5,427
Low-risk adenoma						
n (%)	8,179 (8.0)	5,696 (13.0)	387 (17.3)	4,514 (20.3)	2,036 (23.9)	1,541 (28.4)
Age- and sex-adjusted PR [a]	1.00	1.33 (1.28–1.38)	1.41 (1.25–1.58)	1.00	1.32 (1.24–1.41)	1.29 (1.20–1.38)
Multivariate-adjusted PR [a]	1.00	1.30 (1.25–1.35)	1.33 (1.19–1.50)	1.00	1.28 (1.21–1.36)	1.27 (1.18–1.36)
High-risk adenoma						
n (%)	532 (0.5)	441 (1.0)	53 (2.4)	883 (4.0)	437 (5.1)	424 (7.8)
Age- and sex-adjusted PR [a]	1.00	1.43 (1.26–1.63)	2.27 (1.70–3.04)	1.00	1.63 (1.44–1.84)	1.60 (1.41–1.81)
Multivariate-adjusted PR [a]	1.00	1.35 (1.19–1.54)	2.01 (1.50–2.68)	1.00	1.54 (1.35–1.72)	1.54 (1.36–1.74)

P interaction = 0.184

[a] Estimated from multinomial logistic regression models with outcomes categorized as no adenoma, low-risk adenoma, and high-risk adenoma. The multivariate model was adjusted for age, sex, center, year of screening, smoking status, alcohol intake, educational level, a history of cardiovascular disease, and a family history of colorectal cancer.

Abbreviations: CI, confidence interval; CRA, colorectal adenoma; MAFLD, metabolic dysfunction-associated fatty liver disease; PR, prevalence ratio.

[b] among 184,711 participants with available FIB-4 data

Table S2. Prevalence ratios [a] (95% CI) of CRA by MAFLD and degree of fibrosis based on NFS [b]

	Young adults aged < 50 years			Older adults aged ≥ 50 years		
	No MAFLD	MAFLD plus low NFS	MAFLD plus intermediate/high NFS	No MAFLD	MAFLD plus low NFS	MAFLD plus intermediate/high NFS
Total number	102,508	43,538	2,434	22,269	9,410	4,551
Low-risk adenoma						
n (%)	8,179 (8.0)	5,614 (12.9)	469 (19.2)	4,514 (20.3)	2,269 (24.1)	1,308 (28.7)
Age- and sex-adjusted PR [a]	1.00	1.32 (1.27–1.37)	1.61 (1.45–1.79)	1.00	1.31 (1.23–1.39)	1.31 (1.21–1.41)
Multivariate-adjusted PR [a]	1.00	1.29 (1.24–1.34)	1.53 (1.38–1.71)	1.00	1.27 (1.20–1.35)	1.28 (1.19–1.38)
High-risk adenoma						
n (%)	532 (0.5)	449 (1.0)	45 (1.9)	883 (4.0)	529 (5.6)	332 (7.3)
Age- and sex-adjusted PR [a]	1.00	1.46 (1.29–1.66)	1.83 (1.34–2.49)	1.00	1.70 (1.52–1.91)	1.50 (1.31–1.71)
Multivariate-adjusted PR [a]	1.00	1.38 (1.21–1.57)	1.64 (1.20–2.25)	1.00	1.59 (1.42–1.79)	1.44 (1.26–1.65)

P interaction = 0.026

[a] Estimated from multinomial logistic regression models with outcomes categorized as no adenoma, low-risk adenoma, and high-risk adenoma. The multivariate model was adjusted for age, sex, center, year of screening, smoking status, alcohol intake, educational level, a history of cardiovascular disease, and a family history of colorectal cancer.

Abbreviations: CI, confidence interval; CRA, colorectal adenoma; MAFLD, metabolic dysfunction-associated fatty liver disease; PR, prevalence ratio.

[b] among 184,710 participants with available NFS data

Table S3. Prevalence ratios [a] (95% CI) of CRA by MAFLD and degree of fatty liver based on liver ultrasound [b]

	Young adults aged < 50 years			Older adults aged ≥ 50 years		
	No MAFLD	MAFLD with mild fatty liver	MAFLD with moderate-to-severe fatty liver	No MAFLD	MAFLD with mild fatty liver	MAFLD with moderate-to-severe fatty liver
Total number	102,568	34,100	11,881	22,278	11,919	2,044
Low-risk adenoma						
n (%)	8,182 (8.0)	4,577 (13.4)	1,509 (12.7)	4,516 (20.3)	3,028 (25.4)	551 (27.0)
Age- and sex-adjusted PR [a]	1.00	1.35 (1.29–1.40)	1.30 (1.23–1.38)	1.00	1.29 (1.22–1.36)	1.43 (1.28–1.59)
Multivariate-adjusted PR [a]	1.00	1.27 (1.22–1.33)	1.40 (1.32–1.49)	1.00	1.24 (1.17–1.31)	1.54 (1.39–1.72)
High-risk adenoma						
n (%)	532 (0.5)	375 (1.1)	119 (1.0)	883 (4.0)	741 (6.2)	120 (5.9)
Age- and sex-adjusted PR [a]	1.00	1.50 (1.31–1.72)	1.44 (1.18–1.77)	1.00	1.62 (1.46–1.79)	1.63 (1.33–2.00)
Multivariate-adjusted PR [a]	1.00	1.31 (1.14–1.50)	1.79 (1.46–2.19)	1.00	1.47 (1.32–1.63)	2.00 (1.63–2.46)

P interaction = 0.199

[a] Estimated from multinomial logistic regression models with outcomes categorized as no adenoma, low-risk adenoma, and high-risk adenoma. The multivariate model was adjusted for age, sex, center, year of screening, smoking status, alcohol intake, educational level, a history of cardiovascular disease, and a family history of colorectal cancer.

Abbreviations: CI, confidence interval; CRA, colorectal adenoma; MAFLD, metabolic dysfunction-associated fatty liver disease; PR, prevalence ratio.