

ORIGINAL RESEARCH

Metabolic syndrome, metabolic comorbid conditions and risk of early-onset colorectal cancer

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ABSTRACT

Objective Factors that lead to metabolic dysregulation are associated with increased risk of early-onset colorectal cancer (CRC diagnosed under age 50). However, the association between metabolic syndrome (MetS) and early-onset CRC remains unexamined.

Design We conducted a nested case-control study among participants aged 18–64 in the IBM MarketScan Commercial Database (2006–2015). Incident CRC was identified using pathologist-coded International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and controls were frequency matched. MetS was defined as presence of ≥ 3 conditions among obesity, hypertension, hyperlipidaemia and hyperglycaemia/type 2 diabetes, based on ICD-9-CM and use of medications. Multivariable logistic regressions were used to estimate ORs and 95% CIs.

Results MetS was associated with increased risk of early-onset CRC (n=4673; multivariable adjusted OR 1.25; 95% CI 1.09 to 1.43), similar to CRC diagnosed at age 50–64 (n=14928; OR 1.21; 95% CI 1.15 to 1.27). Compared with individuals without a metabolic comorbid condition, those with 1, 2 or ≥ 3 conditions had a 9% (1.09; 95% CI 1.00 to 1.17), 12% (1.12; 95% CI 1.01 to 1.24) and 31% (1.31; 95% CI 1.13 to 1.51) higher risk of early-onset CRC ($p_{\text{trend}} < 0.001$). No associations were observed for one or two metabolic comorbid conditions and CRC diagnosed at age 50–64. These positive associations were driven by proximal (OR per condition 1.14; 95% CI 1.06 to 1.23) and distal colon cancer (OR 1.09; 95% CI 1.00 to 1.18), but not rectal cancer (OR 1.03; 95% CI 0.97 to 1.09).

Conclusions Metabolic dysregulation was associated with increased risk of early-onset CRC, driven by proximal and distal colon cancer, thus at least in part contribute to the rising incidence of early-onset CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and cause of cancer death globally.¹ Even though the incidence rate of CRC declined rapidly among screening-aged individuals 65 years or older,¹ the incidence of early-onset CRC in adults younger than 50 has been increasing in the USA,¹ Europe² and worldwide.³ In the USA, early-onset CRC has been increasing since the mid-1990s,¹ driven largely by rectal tumours. However, data

Significance of this study

What is already known about this subject?

- Obesity and prolonged sitting are associated with increased risk of early-onset colorectal cancer (CRC), indicating that metabolic dysregulation may contribute to the rising incidence of early-onset CRC.
- Metabolic syndrome (MetS) among young adults has been increasing worldwide in the past decades, but its association with early-onset CRC remains unexamined.

What are the new findings?

- Leveraging real-world claims data that captured over 4600 early-onset CRC, we found that MetS was associated with a 25% increased risk of early-onset CRC, driven by proximal and distal colon cancers as compared with rectal cancer. The strength of this association was similar to that for CRC diagnosed between age 50 and 64.
- Number of metabolic comorbid conditions was positively associated with risk of early-onset CRC in a dose-dependent fashion, with a stronger linear relationship, compared with CRC diagnosed between age 50 and 64.

How might it impact on clinical practice in the foreseeable future?

- Metabolic dysregulation, as indicated by MetS and increased number of metabolic comorbid conditions, may in part contribute to the rising incidence of early-onset CRC.
- MetS may be useful in tailoring clinical algorithms to assess risk of early-onset CRC among younger adults.
- Prevention of MetS is likely critical for CRC prevention at all ages.

collected between 2012 and 2016 suggest that incidence rates rose by 1.8% annually for tumours in the proximal and distal colon as well as in the rectum.¹ Compared with older cases, early-onset CRCs are more likely to present with unique histopathological (eg, mucosal and signet cell⁴) and molecular features^{4,5} (eg, higher rates of *TP53/CTNNB1*⁶ and consensus molecular type 1,⁷ and deregulated redox



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homeostasis).⁸ These emerging distinct features along with an alarming increase across all anatomic sites highlight the urgent need to re-evaluate putative risk factors associated with average-onset CRC.

Accumulating evidence suggests that obesity⁹ and sedentary lifestyle¹⁰ may contribute to the development of early-onset CRC. Although the underlying mechanisms have not been fully elucidated, obesity¹¹ and sedentary behavior¹² both lead to metabolic dysregulation. Metabolic syndrome (MetS),¹³ a constellation of metabolic disorders including high blood pressure, high triglyceride, central obesity and low high-density lipoprotein, has been linked with about 13% increased risk of CRC.^{14–17} However, these studies did not specifically evaluate the associations with early-onset CRC. Notably, in the past decades, the prevalence of MetS has increased dramatically worldwide as a consequence of urbanisation, increasing obesity and sedentary lifestyle.¹⁸ In the USA, the prevalence of MetS was 6.7% among aged 20–29 and approximately 13% among aged 30–39 between 1988 and 1994,^{19,20} while the numbers rose to 19% for the combined age group between 2003 and 2012.²¹ Besides obesity,²² the rising incidence of other metabolic comorbid conditions such as hypertension²³ and diabetes²⁴ in younger adults has also been reported in the USA and other countries,²⁵ where a similar rise in early-onset CRC has been documented.³ Thus far, the association between MetS and early-onset CRC remains unexamined in the US population.

To address this knowledge gap that is critical for both the aetiology, prevention and early detection of CRC, we utilised the IBM MarketScan Commercial Databases (2006–2015), a longitudinal database that contains individual-level, deidentified healthcare claims data of over 113 million young and middle-aged adults from all geographic areas of the USA to examine comprehensively the associations between MetS, number of metabolic comorbid conditions and risk of early-onset CRC.

METHODS

Study population

We conducted a nested case–control study in the MarketScan databases, a longitudinal database that contains deidentified, individual-level healthcare claims data of commercially insured individuals from all geographic areas of the USA.²⁶ The database captures information on outpatient and inpatient insurance-reimbursable services, prescription drugs, demographic information, eligibility status and type of health plan. As information for individuals aged 65 and above was not available, we restricted our analyses to 113 million adults aged 18–64 between 2006 and 2015, and required at least 2 years of enrolment and prescription drug coverage prior to the index dates, as well as 90 days of enrolment after index to derive metastatic status. Institutional review board approval was not required for this deidentified limited dataset analysis.

Ascertainment of cases and controls

All patients aged 18–64 years diagnosed with incident CRC from 2006 to 2015 were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM code: 153.0–153.9, 154.0, 154.1 and 154.8). To reduce false positives, we required pathologist coding for CRC and assigned the first pathology date as the index date. CRCs were further classified into proximal colon (hepatic flexure: 153.0; transverse colon: 153.1; caecum: 153.4; appendix: 153.5; ascending colon: 153.6), distal colon (descending colon: 153.2; sigmoid colon: 153.3; splenic flexure: 153.7), unspecified

colon (153.8–153.9) and rectal cancer (rectosigmoid junction: 154.0; rectum: 154.1) according to anatomical site. CRC metastatic status was also derived based on diagnosis or liver/lung metastatic treatment up to 90 days after the index date.²⁷

We excluded patients with CRC with one or more codes for personal history of any cancer or genetic susceptibility to other malignant neoplasm as identified by ICD-9-CM codes prior to 2 years of the index dates. We further excluded patients with CRC with cancer in the 2 years before index as identified by cancer diagnosis codes from the Healthcare Cost and Utilization Project's Clinical Classification Software.²⁸ We excluded all cancers except CRC and non-melanoma skin cancer. One inpatient facility claims and/or two outpatient provider claims 31–365 days apart were required to identify preindex cancer for exclusion based on Klabunde *et al.*²⁹

Individuals without CRC were identified as controls and were matched up to 8:1 ratio with the CRC cases using frequency matching on age group, sex, geographical region (Northeast, North Central, South, West, unknown) and full years of health insurance enrolment before index. Controls were required to have 2 years of prior and at minimum 90 days of postindex medical coverage. The following age groups were used for matching: 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59 and 60–64. Controls were selected such that the distribution of their index dates matched the distribution of case index dates. To do this, potential controls were assigned random index dates after the first 2 years of enrolment but prior to the last 90 days of enrolment to allow time to identify outcomes. Frequency matching was then performed by year along with the matching variables mentioned above. Potential controls were excluded if they had a code of any of the following: personal history of any cancer, genetic susceptibility to other malignant neoplasm and cancers other than non-melanoma skin cancer in the 2 years before index.

Ascertainment of MetS and metabolic comorbid conditions

Since around 95% of patients with cancer received treatment within 90 days from diagnosis in the USA,³⁰ we restricted our exposure assessment to start from 91 days before the index dates to reduce the influence of clinical visits before CRC diagnosis that may differentially increase the detection of MetS among the case group. MetS was defined using either ICD-9-CM code (277.7) or the presence of at least three of the following four conditions: obesity/overweight³¹ (278.00–278.03, 649.1, 793.91, V85.3–V85.4, V85.54), hypertension (401–405), hyperlipidaemia (272.0–272.2, 272.4, 272.9) and hyperglycaemia/type 2 diabetes (790.2, 790.21–790.22, 790.29, 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92). The identification of diabetes also used an algorithm based on Klabunde *et al.*²⁹ Using National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria,³² we also defined MetS based on use of prescription medications for hypertension, hyperlipidaemia and hyperglycaemia. Specifically, we defined individuals who used ≥ 90 days of any antihypertensive, lipid-lowering, antidiabetic medications as regular users. Our estimates of the prevalence of hypertension, hyperlipidaemia and hyperglycaemia/type 2 diabetes were comparable to other national estimates.^{33,34}

Assessment of covariates

We extracted information on sociodemographic factors: employment status, residence and health plan. In addition, potential

confounders, including inflammatory bowel diseases (IBD), family history of gastrointestinal (GI) neoplasm and regular use of prescription non-steroidal anti-inflammatory drugs (Rx NSAIDs) between 91 days and 2 years before the index dates were extracted.³⁰ Regular Rx NSAIDs users included individuals who received ≥ 90 days of Rx NSAIDs among this period. We also extracted information related to healthcare utilisation within 91 days and 2 years before the index dates, including outpatient visits, screening colonoscopies, other colonoscopies, faecal occult blood test and the Charlson Comorbidity Index³⁵ (derived without taking into account type 2 diabetes and confirmed using the algorithm based on Klabunde *et al.*)²⁹

Statistical analyses

We evaluated the association between MetS and risk of early-onset CRC as the main analyses. In addition, we examined the dose-response relationship between number of metabolic comorbid conditions and risk of early-onset CRC. As secondary analyses, we investigated the above associations according to anatomical site of the tumour and metastatic status, and whether the identified associations differ according to sex, age,⁸ residence, geographic region³⁶ and outpatient visits.

Multivariable logistic regressions were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We first adjusted for the matching factors including age (year), sex (male, female), duration of insurance enrolment (years) and region (Northeast, North Central, South, West, unknown). We then additionally adjusted for health insurance plan (Preferred Provider Organisation, Health Maintenance Organisation and others), residence (rural, urban, unknown) and the following factors between 91 days and 2 years prior to the index dates: outpatient visits (>5 times, ≤ 5 times), Charlson Comorbidity Index without diabetes (continuous), IBD (yes, no), family history of GI neoplasm (yes, no), screening colonoscopy (yes, no), other colonoscopies (yes, no), faecal occult blood test (yes, no) and regular Rx NSAIDs use (yes, no). Tests for trend were conducted using the number of comorbid conditions as a continuous variable. P for heterogeneity was calculated with polytomous logistic regression to examine whether the association between MetS and risk of CRC differed by anatomic sites (colon, rectal cancer; proximal, distal colon, unspecified colon) and metastatic status (metastasis, non-metastasis). P for interaction was calculated by Wald test using the cross-product terms of MetS and each stratification factor. All analyses were performed in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A total of 4673 early-onset CRC cases and 40832 frequency-matched controls were included in our primary analyses for early-onset CRC (table 1). In addition, 14 928 patients with CRC diagnosed between age 50 and 64 years old were frequency matched to 132 120 matched controls. The mean age of diagnoses of the early-onset CRC cases was 43, of which 64.4% were colon cancer and 35.6% were rectal cancer. Compared with controls, early-onset CRC cases had more outpatient visits and greater Charlson Comorbidity Index between 91 days and up to 2 years before the index dates.³⁰ They were also more likely to have IBD, colonoscopies other than for screening and faecal occult blood test from 91 days to up to 2 years before the index dates. Among participants under age 50, 6.0% of the early-onset CRC had MetS compared with only 4.3% of the controls.

MetS was associated with increased risk of early-onset CRC (OR 1.25; 95% CI 1.09 to 1.43), after adjusting for matching

factors, potential confounders and factors associated with healthcare utilisation (table 2). Also, the number of metabolic comorbid conditions was positively associated with risk of early-onset CRC in a dose-dependent fashion. Compared with individuals without any metabolic comorbid conditions, those with 1, 2 or ≥ 3 metabolic conditions had a 9% (OR 1.09; 95% CI 1.00 to 1.17), 12% (OR 1.12; 95% CI 1.01 to 1.24) and 31% (OR 1.31; 95% CI 1.13 to 1.51) higher risk of early-onset CRC ($p_{\text{trend}} < 0.001$), respectively. The positive association between MetS and risk of early-onset CRC was similar when restricted to individuals without IBD (OR 1.23; 95% CI 1.07 to 1.42, online supplemental table S1), and according to sex (female, male), residence (rural, urban), geographic region (South, others) or outpatient visits (>5 times, ≤ 5 times, figure 1 and online supplemental table S2, (all $p_{\text{interaction}} > 0.5$). The association between MetS and CRC appeared stronger for individuals aged 40–44 (OR 1.45; 95% CI 1.12 to 1.89), followed by age 45–49 (OR 1.22; 95% CI 1.03 to 1.44). However, although OR was similar for individuals under 40, the association was not significant for this age group (OR 1.18; 95% CI 0.77 to 1.79), which could be due to limited power. No interaction between age and MetS was identified ($p_{\text{interaction}} = 0.883$).

We further evaluated these associations according to anatomical site and metastatic status (table 3 and online supplemental table S2). Overall, the association between MetS and early-onset CRC was significant for colon cancer (OR 1.38; 95% CI 1.18 to 1.62) but not for rectal cancer (OR 1.04; 95% CI 0.83 to 1.32), although p for heterogeneity was not significant ($p_{\text{heterogeneity}} = 0.076$). A closer investigation within colon cancer showed similar associations between MetS and risk for proximal, distal and unspecified colon cancer ($p_{\text{heterogeneity}} = 0.627$). Similar associations were also observed with the number of metabolic comorbid conditions. Each additional metabolic comorbid condition was associated with a 10% increased risk of overall colon cancer (OR 1.10; 95% CI 1.05 to 1.15), 14% increased risk for proximal cancer (OR 1.14; 95% CI 1.06 to 1.23), 9% increased risk for distal cancer (OR 1.09; 95% CI 1.00 to 1.18) and 8% increased risk for unspecified colon cancer (OR 1.08; 95% CI 1.01 to 1.15). However, the positive linear association between metabolic comorbid condition was not observed for rectal cancer (OR 1.03; 95% CI 0.97 to 1.09). The association between MetS and risk of CRC was not significantly different by metastatic status ($p_{\text{heterogeneity}} = 0.951$, online supplemental table S2).

Among adults aged 50–64, MetS was identified among 14.7% of the cases and 12.6% of the controls (table 2). Similar to that among younger adults, MetS was associated with increased risk of CRC diagnosed at 50–64 (OR 1.21; 95% CI 1.15 to 1.27). In comparison to individuals without any metabolic comorbid condition, adults with one or two metabolic comorbid conditions were not at higher risk of CRC, and increased risk of CRC was only observed among individuals with ≥ 3 metabolic conditions (OR 1.22; 95% CI 1.15 to 1.29; $p_{\text{trend}} < 0.001$), with stronger associations for colon compared with rectal cancer (online supplemental table S3).

DISCUSSION

Leveraging real-world healthcare claims data that covers 113 million US adults aged 18–64 and 4673 early-onset CRC, we found that MetS and metabolic comorbid conditions were associated with increased risk of early-onset CRC, and the findings remained significant after adjusting for potential confounders and indicators for healthcare utilisation. We also found that the

Table 1 Characteristics of participants according to CRC status, MarketScan database (2006–2015)**

	Age 18–49, Participants No. (%)		Age 50–64, Participants No. (%)	
	Case (n=4673)	Control (n=40 832)	Case (n=14 928)	Control (n=1 32 120)
Age at index date, mean, year	43.0±5.8	42.8±5.8	57.2±4.3	57.2±4.3
Female	2248 (48.1)	19920 (48.8)	6619 (44.3)	59576 (45.1)
Region				
Northeast	684 (14.6)	5920 (14.5)	2092 (14.0)	18624 (14.1)
North Central	1088 (23.3)	9240 (22.6)	3957 (26.5)	33856 (25.6)
South	2085 (44.6)	18024 (44.1)	6423 (43.0)	56096 (42.5)
West	776 (16.6)	7304 (17.9)	2342 (15.7)	22592 (17.1)
Unknown	40 (0.9)	344 (0.8)	114 (0.8)	952 (0.7)
Residence				
Urban	3935 (84.2)	34773 (85.2)	12044 (80.7)	109413 (82.8)
Rural	702 (15.0)	5742 (14.1)	2778 (18.6)	21792 (16.5)
Unknown	36 (0.8)	317 (0.8)	106 (0.7)	915 (0.7)
Full-time employment	3002 (64.2)	27260 (66.8)	7157 (47.9)	65070 (49.3)
Insurance enrolment, mean, year	4.2±1.8	4.1±1.8	4.4±1.9	4.4±1.9
Health insurance plan				
PPO	2847 (60.9)	24002 (58.8)	8917 (59.7)	76997 (58.3)
HMO	698 (14.9)	6787 (16.6)	1795 (12.0)	19343 (14.6)
Other	1128 (24.1)	10043 (24.6)	4216 (28.2)	35780 (27.1)
Number of outpatient visits, mean*	6.0±6.4	5.3±6.0	6.8±7.1	7.0±7.3
Charlson Comorbidity Index, mean*†	0.10±0.5	0.06±0.4	0.15±0.6	0.12±0.5
MetS‡	280 (6.0)	1763 (4.3)	2195 (14.7)	16602 (12.6)
Hypertension§	1207 (25.8)	8917 (21.8)	7397 (49.6)	62242 (47.1)
Hyperlipidaemia§	982 (21.0)	7824 (19.2)	6133 (41.1)	56838 (43.0)
Hyperglycaemia/type 2 diabetes§	384 (8.2)	2652 (6.5)	2731 (18.3)	20774 (15.7)
Obesity*	321 (6.9)	2155 (5.3)	983 (6.6)	7625 (5.8)
IBD*	219 (4.7)	1059 (2.6)	470 (3.2)	3415 (2.6)
Family history of GI neoplasm*	51 (1.1)	402 (1.0)	150 (1.0)	2483 (1.9)
Screening colonoscopy*	49 (1.1)	830 (2.0)	223 (1.5)	10074 (7.6)
Other colonoscopy*	173 (3.7)	740 (1.8)	678 (4.5)	6773 (5.1)
Faecal occult blood test*	335 (7.2)	2432 (6.0)	1777 (11.9)	18304 (13.9)
Regular Rx NSAIDs use¶	159 (3.4)	1462 (3.6)	943 (6.3)	10244 (7.8)
Tumour site				
Colon	3009 (64.4)	–	10166 (68.1)	–
Rectal	1664 (35.6)	–	4762 (31.9)	–

*Between 91 days and 2 years before the index dates.

†Charlson Comorbidity Index was calculated without accounting for diabetes.

‡MetS was defined using ICD-9-CM codes or the presence of at least three of the following conditions: obesity, hypertension, hyperlipidaemia and hyperglycaemia/type 2 diabetes.

§Hypertension, hyperlipidaemia and hyperglycaemia/type 2 diabetes were identified based on ICD-9-CM codes between 91 days and 2 years before the index dates or regular use of medications (≥90 days of use between 91 days and 2 years before the index dates) for the corresponding condition.

¶Regular Rx NSAIDs use was defined as use of ≥90 days between 91 days and 2 years before the index dates.

**Mean±SD and percentages were presented for continuous and categorical variables, respectively.

CRC, colorectal cancer; HMO, Health Maintenance Organisation; ICD-9-CM, International Classification of Diseases, ninth Revision, Clinical Modification; MetS, metabolic syndrome; PPO, Preferred Provider Organisation; Rx NSAIDs, prescription non-steroidal anti-inflammatory drugs.

positive associations were largely driven by proximal and distal colon cancer but not rectal cancer. Due to the substantial rise in the prevalence of MetS among younger populations^{19–21} and the increase in early-onset CRC across all the anatomic sites of the colon and rectum,¹ our findings suggest that MetS and metabolic dysregulation may contribute in part to the rising incidence of early-onset CRC.

Studies examining the association between MetS and early-onset CRC are thus far limited. In line with our findings, prior colonoscopy-based cross-sectional studies from Europe³⁷ and Korea³⁸ reported that among individuals under age 50, MetS was associated with increased risk of colonic lesions primarily

consisting of adenomas. We also examined the association between MetS and risk of CRC among adults aged 50–64, and reported similar strength of association compared with prior studies that reported positive associations between MetS and CRC among an older population.¹⁴ It is worth noting that we observed a stronger association for CRC diagnosed at age 40–44 compared with that for CRC diagnosed at age 45–49. We also identified a more apparent linear relationship between the number of metabolic comorbid conditions and early-onset CRC compared with that for CRC diagnosed at age 50–64. Collectively, these findings reiterate the importance of MetS in CRC aetiology and prevention. Our findings also lend preliminary

Table 2 MetS, metabolic comorbid conditions and risk of CRC

	Participants with conditions, No. (%)		Multivariable-adjusted OR (95% CI)*	Multivariable-adjusted OR (95% CI)†
	Cases	Controls		
Age 18–49				
MetS	280 (6.0)	1763 (4.3)	1.39 (1.22 to 1.60)	1.25 (1.09 to 1.43)
Number of comorbid conditions‡				
0	2847 (60.9)	26 729 (65.5)	1 (reference)	1 (reference)
1	1048 (22.4)	8525 (20.9)	1.15 (1.06 to 1.24)	1.09 (1.00 to 1.17)
2	519 (11.1)	3957 (9.7)	1.22 (1.10 to 1.35)	1.12 (1.01 to 1.24)
≥3	259 (5.5)	1621 (4.0)	1.48 (1.29 to 1.70)	1.31 (1.13 to 1.51)
Per condition			1.12 (1.08 to 1.16)	1.07 (1.03 to 1.11)
P _{trend}			<0.001	<0.001
Age 50–64				
MetS	2195 (14.7)	16 602 (12.6)	1.20 (1.14 to 1.26)	1.21 (1.15 to 1.27)
Number of comorbid conditions‡				
0	5520 (37.0)	49 434 (37.4)	1 (reference)	1 (reference)
1	3987 (26.7)	36 165 (27.4)	0.99 (0.95 to 1.03)	1.03 (0.99 to 1.08)
2	3282 (21.9)	30 304 (22.9)	0.97 (0.92 to 1.01)	1.01 (0.96 to 1.06)
≥3	2139 (14.3)	16 217 (12.3)	1.18 (1.12 to 1.24)	1.22 (1.15 to 1.29)
Per condition			1.03 (1.02 to 1.05)	1.05 (1.03 to 1.07)
P _{trend}			<0.001	<0.001

*Adjusted for matching factors including age (year), sex (male, female), duration of insurance enrolment (year) and region (Northeast, North Central, South, West, unknown).

†In addition to matching factors, the models were also adjusted for health insurance plan (PPO, HMO, others), residence (rural, urban, unknown) and the following factors within 91 days to 2 years prior to the index dates: outpatient visits (>5 times, ≤5 times), Charlson Comorbidity Index without diabetes (continuous), IBD (yes, no), family history of GI neoplasm (yes, no), screening colonoscopy (yes, no), other colonoscopy (yes, no), faecal occult blood test (yes, no) and regular Rx NSAIDs use (yes, no).

‡Metabolic comorbid conditions included obesity, hypertension, hyperlipidaemia and hyperglycaemia/type 2 diabetes.

CRC, colorectal cancer; HMO, Health Maintenance Organisation; MetS, metabolic syndrome; PPO, Preferred Provider Organisation; Rx NSAID, prescription non-steroidal anti-inflammatory drugs.

support to a stronger role of metabolic dysregulation in early-onset CRC. Interestingly, the positive associations between MetS and CRC appeared stronger for proximal and distal colon cancers as compared with rectal cancer, for both early-onset CRC and CRC diagnosed at 50–64, the latter also being in line with prior studies among older adults.^{16 39} Although studies have reported higher prevalence of MetS⁴⁰ and early-onset CRC³⁶ in the southern states, our stratified analysis suggests that the associations between MetS and early-onset CRC were similar in the South versus in other geographic regions.

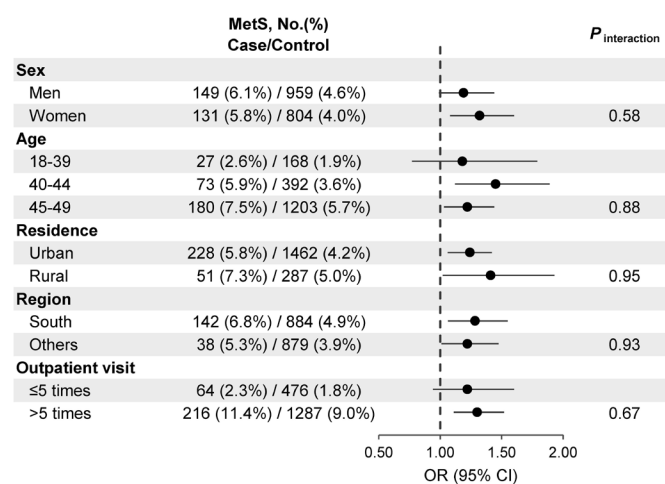


Figure 1 Stratified analyses for MetS and risk of early-onset CRC. The multivariable models were adjusted for the same set of covariates as in model † of Table 2, except for the stratification factor. CRC, colorectal cancer; MetS, metabolic syndrome.

Mechanisms linking MetS and CRC risk remain to be fully elucidated. Insulin resistance has been indicated as one of the most important mediators, in which insulin and insulin-like growth factors may promote cancer development through their proliferative and antiapoptotic effects.^{41 42} Obesity, especially central/visceral, in association with high blood free fatty acids and peripheral insulin resistance, has been also suggested as an underlying factor of MetS as well as CRC carcinogenesis.⁴¹ In obesity, a chronic low-grade inflammatory state mediated by elevated cytokines such as tumour necrosis factor- α , interleukin-6 and C-reactive protein would trigger immune cell response and promote cancer development.⁴³ The gut bacterial microbiome, mechanistically involved in CRC pathogenesis,⁴⁴ was found to capture substantial (~22%–36%) variations in metabolic disorders.⁴⁵ Bile acids as key regulators of systemic metabolism may play direct roles in nutrient absorption, and also link the gut microbiota to hepatic and intestinal metabolism.⁴⁶ Dysregulation of bile acids and bile acid–microbiota crosstalk disruption in MetS may contribute to the development of CRC.^{46 47} In addition, MetS could also serve as a surrogate for other established lifestyle factors for CRC, such as sedentary behaviour,^{10 48} Western diet,^{49 50} chronic stress^{51 52} and circadian disruption.^{53 54} A recent large-scale Mendelian randomisation analysis showed that genetically predicted waist circumference (independent of body mass index) and concentrations of low-density lipoprotein and total cholesterol were independently associated with risk of CRC, serving as strong support for the causal role of metabolic dysregulation in CRC.⁵⁵ Mechanistic investigations into MetS and colorectal carcinogenesis at younger ages are thus far lacking and warranted. As mucinous adenocarcinoma and signet ring cell carcinoma are more common with younger age at onset⁵⁶ and the majority of early-onset CRC are microsatellite stable,⁴

Table 3 MetS, metabolic comorbid conditions and risk of early-onset CRC according to anatomical site

	Participants with conditions, No (%)		Multivariable-adjusted OR (95% CI)*	P _{heterogeneity}
	Cases	Controls		
Colon cancer				
MetS	197 (6.6)	1763 (4.3)	1.38 (1.18 to 1.62)	
Per comorbid condition†			1.10 (1.05 to 1.15)	
P _{trend}			<0.001	
Proximal				
MetS	59 (6.6)	1763 (4.3)	1.37 (1.04 to 1.81)	0.627‡
Per comorbid condition†			1.14 (1.06 to 1.23)	
P _{trend}			<0.001	
Distal				
MetS	52 (6.0)	1763 (4.3)	1.25 (0.94 to 1.68)	
Per comorbid condition†			1.09 (1.00 to 1.18)	
P _{trend}			0.040	
Unspecified				
MetS	86 (7.0)	1763 (4.3)	1.48 (1.18 to 1.87)	
Per comorbid condition†			1.08 (1.01 to 1.15)	
P _{trend}			0.028	
Rectal cancer				
MetS	81 (5.0)	1763 (4.3)	1.04 (0.83 to 1.32)	0.076§
Per comorbid condition†			1.03 (0.97 to 1.09)	
P _{trend}			0.375	

*Adjusted for the same set of covariates in the multivariate model † of table 2.

†Metabolic comorbid conditions included obesity, hypertension, hyperlipidaemia, hyperglycaemia/type 2 diabetes.

‡P for heterogeneity was calculated using polytomous logistic regression to examine whether the association between MetS and risk of early-onset CRC differed by anatomic site (proximal, distal, unspecified colon), adjusting for the same set of covariates as in model † of table 2.

§P for heterogeneity was calculated using polytomous logistic regression to examine whether the association between MetS and risk of early-onset CRC differed by anatomic site (colon, rectum), adjusting for the same set of covariates as in model † of table 2.
CRC, colorectal cancer; MetS, metabolic syndrome.

future investigations according to tumour histopathologic and molecular characteristics will be critical in elucidating the mechanisms linking MetS and early-onset CRC.

Our study has several strengths. First, we conducted a nested case-control study within a large, prospectively maintained, real-world claim-based dataset to examine the association between MetS and pathologically confirmed early-onset CRC. Second, MetS and metabolic comorbid conditions were defined by both ICD-9-CM and use of prescription medications, whereas prior claim-based studies that focused on MetS utilised only ICD-9 diagnosis codes.^{57 58} Third, to reduce influence of detection bias such that CRC diagnoses may increase the likelihood of detection of concomitant comorbid conditions including MetS,⁵⁹ we defined our exposures starting 91 days before the index dates.³⁰ The similar strengths of associations for both non-metastatic and metastatic disease further supported the robustness of our findings. Furthermore, we have also adjusted for a list of variables associated with healthcare utilisation such as outpatient visits, Charlson Comorbidity Index and colonoscopies. Our stratified analyses according to outpatient visits lend strong support for the robustness of the findings.

Study limitations include using obesity as a proxy for central obesity,³¹ as well as the known undercoding of obesity within claims data.⁶⁰ Thus, we have likely underestimated the prevalence of MetS. Moreover, according to prior^{32 61} and the most recent harmonised (2009) definitions,⁶² MetS represents complex biochemical and arterial pressure alterations that precede cardiometabolic diseases. As such, cut points for abnormal blood pressure and levels of triglycerides, high-density lipoprotein cholesterol and fasting glucose have been designed explicitly for men and women and vary by population. As lab values were not

available in the MarketScan database, we relied on ICD codes for such identification, which could lead to further underestimation of MetS. To address this, we also leveraged medication data to define MetS. Collectively, these non-differential misclassifications are likely to bias the associations towards the null, but limit us from estimating the population attributable risk of MetS for early-onset CRC. Moreover, potential confounding could not be ruled out as lifestyle factors such as smoking and physical activity were not available, both of which have been linked to MetS^{48 63} and CRC^{64 65} in older populations. Since these lifestyle factors are relatively moderate risk factors for MetS and CRC, the potential impact of the confounding is expected to be modest. Understanding the association between MetS and early-onset CRC within each race/ethnicity group is critical. Minority populations have higher prevalence of MetS,^{66 67} comparable/ higher rates of early-onset CRC,^{68 69} but early-onset CRC rates have been relatively stable in the past two decades in sharp contrast to the steep increase among non-Hispanic whites.^{1 68 69} Unfortunately, the MarketScan database does not include race/ethnicity information. Validation in diverse populations as well as studies elucidating the time lag between MetS onset and elevated risk of early-onset CRC will shed light on the aetiology and preventative strategies. Finally, CRC diagnosed at age 50–64 was not sufficiently representative of late-onset CRC as the median age of diagnosis is 66.¹ Additional studies comparing the strengths of associations with a much older population are warranted.

In conclusion, findings from this large nested case-control study based on real-world claims data lend strong support to the role of MetS and metabolic comorbid conditions in early-onset CRC. Given the substantial increase in the prevalence of these conditions at the population level, our data indicate

that metabolic dysregulation may at least in part contribute to the rising incidence of early-onset CRC. Prevention of MetS among younger adults should be further prioritised in the context of cancer prevention. Due to established care models for cardiometabolic diseases,⁷⁰ MetS may also serve as a promising avenue for risk-based CRC screening among younger adults.

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SUPPLEMENTARY APPENDIX:**Metabolic Syndrome, Metabolic Comorbid Conditions, and Risk of Early-Onset Colorectal Cancer**

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Supplementary table S1. Metabolic syndrome, metabolic comorbid conditions and risk of colorectal cancer among adults without inflammatory bowel diseases

	Participants with conditions, No. (%)		Multivariable-adjusted OR (95% CI)†	Multivariable-adjusted OR (95% CI)‡
	Cases	Controls		
Age 18-49				
Metabolic syndrome	259 (5.8)	1694 (4.3)	1.36 (1.19 to 1.56)	1.23 (1.07 to 1.42)
No. of comorbid conditions*				
0	2729 (61.3)	26134 (65.7)	1 (reference)	1 (reference)
1	1992 (22.3)	8244 (20.7)	1.14 (1.05 to 1.23)	1.09 (1.00 to 1.18)
2	495 (11.1)	3840 (9.7)	1.21 (1.09 to 1.34)	1.12 (1.01 to 1.24)
≥3	238 (5.3)	1555 (3.9)	1.44 (1.25 to 1.66)	1.28 (1.10 to 1.49)
Per condition			1.11 (1.07 to 1.15)	1.07 (1.03 to 1.11)
P _{trend}			<0.001	<0.001
Age 50-64				
Metabolic syndrome	2129 (14.7)	16080 (12.5)	1.21 (1.15 to 1.27)	1.22 (1.16 to 1.28)
No. of comorbid conditions*				
0	5357 (37.1)	48496 (37.7)	1 (reference)	1 (reference)
1	3839 (26.5)	35176 (27.3)	0.99 (0.95 to 1.03)	1.04 (0.99 to 1.08)
2	3186 (22.0)	29328 (22.8)	0.98 (0.94 to 1.03)	1.03 (0.98 to 1.08)
≥3	2076 (14.4)	15705 (12.2)	1.19 (1.13 to 1.26)	1.24 (1.17 to 1.32)
Per condition			1.04 (1.02 to 1.06)	1.05 (1.04 to 1.07)
P _{trend}			<0.001	<0.001

* Metabolic comorbid conditions included obesity, hypertension, hyperlipidemia, hyperglycemia/type 2 diabetes.

† Adjusted for matching factors including age (year), sex (male, female), duration of insurance enrollment (year), and region (Northeast, North Central, South, West, unknown).

‡ In addition to matching factors, the models were also adjusted for health insurance plan (PPO, HMO, others), residence (rural, urban, unknown), and the following factors within 90 days to 2 years prior to the index dates: outpatient visits (>5 times, ≤5 times), Charlson Comorbidity Index without diabetes (continuous), family history of gastrointestinal neoplasm (yes, no), screening colonoscopy (yes, no), other colonoscopy (yes, no), fecal occult blood test (yes, no), and regular Rx NSAIDs use (yes, no) HMO, Health Maintenance Organization; PPO, Preferred Provider Organization; Rx NSAIDs, prescription non-steroidal anti-inflammatory drugs.

Supplementary table S2. Stratified analyses of metabolic syndrome and risk of early-onset colorectal cancer

	Participants with conditions, No. (%)		Multivariable-adjusted OR (95% CI)*	P _{interaction} †	P _{heterogeneity} ‡
	Cases	Controls			
Sex					
Men	149 (6.1)	959 (4.6)	1.19 (0.99 to 1.44)	0.581	-
Women	131 (5.8)	804 (4.0)	1.32 (1.08 to 1.60)		
Age, y					
18-39	27 (2.6)	168 (1.9)	1.18 (0.77 to 1.79)	0.883	-
40-44	73 (5.9)	392 (3.6)	1.45 (1.12 to 1.89)		
45-49	180 (7.5)	1203 (5.7)	1.22 (1.03 to 1.44)		
Residence					
Urban	228 (5.8)	1462 (4.2)	1.23 (1.06 to 1.42)	0.670	-
Rural	51 (7.3)	287 (5.0)	1.41 (1.02 to 1.93)		
Region					
South	142 (6.8)	884 (4.9)	1.28 (1.06 to 1.55)	0.938	-
Others§	38 (5.3)	879 (3.9)	1.22 (1.01 to 1.47)		
Outpatient visit					
≤ 5 times	64 (2.3)	476 (1.8)	1.22 (0.94 to 1.60)	0.946	-
> 5 times	216 (11.4)	1287 (9.0)	1.30 (1.11 to 1.52)		
Metastatic status					
Non-metastatic	218 (6.1)	1763 (4.3)	1.24 (1.07 to 1.44)	-	
Metastatic	62 (5.8)	1763 (4.3)	1.28 (0.98 to 1.68)		0.951

* Adjusted for the same set of covariates in the multivariate model † of table 2, except the stratification factor. Age in years was adjusted as continuous variable in each model.

† p for interaction was calculated by Wald test using the cross-product term of metabolic syndrome and each stratification factor, adjusting for the covariates as in model † of table 2.

‡ p for heterogeneity was calculated using polytomous logistic regression to examine whether the association between metabolic syndrome and risk of CRC differed by metastatic status (metastasis, non-metastasis), adjusting for the same set of covariates as in model † of table 2.

§ Other geographic region included Northeast, North Central, West and unknown region.

Supplementary table S3. Metabolic comorbid conditions and risk of colorectal cancer diagnosed at age 50-64 according to anatomical site

	Participants with conditions, No. (%)		Multivariable-adjusted OR (95% CI)†	P _{heterogeneity}
	Cases	Controls		
Colon cancer				
Metabolic syndrome	1590 (15.6)	16602 (12.6)	1.28 (1.21 to 1.36)	
Per comorbid condition*			1.08 (1.06 to 1.10)	
P _{trend}			<0.001	
Proximal				
Metabolic syndrome	542 (16.7)	16602 (12.6)	1.32 (1.19 to 1.45)	0.236‡
Per comorbid condition*			1.12 (1.08 to 1.16)	
P _{trend}			<0.001	
Distal				
Metabolic syndrome	419 (15.3)	16602 (12.6)	1.33 (1.19 to 1.49)	
Per comorbid condition*			1.08 (1.04 to 1.12)	
P _{trend}			<0.001	
Unspecified				
Metabolic syndrome	632 (15.2)	16602 (12.6)	1.23 (1.12 to 1.34)	
Per comorbid condition*			1.05 (1.02 to 1.09)	
P _{trend}			0.001	
Rectal cancer				
Metabolic syndrome	578 (12.6)	16602 (12.6)	1.04 (0.95 to 1.15)	<0.001§
Per comorbid condition*			0.98 (0.95 to 1.01)	
P _{trend}			0.242	

* Metabolic comorbid conditions included obesity, hypertension, hyperlipidemia, hyperglycemia/type 2 diabetes.

† Adjusted for the same set of covariates in the multivariate model † of table 2.

‡ p for heterogeneity was calculated using polytomous logistic regression to examine whether the association between metabolic syndrome and risk of early-onset CRC differed by anatomic site (proximal, distal, unspecific colon), adjusting for the same set of covariates as in model † of table 2.

§ p for heterogeneity was calculated using polytomous logistic regression to examine whether the association between metabolic syndrome and risk of early-onset CRC differed by anatomic site (colon, rectum), adjusting for the same set of covariates as in model † of table 2.