



Risk Factors for Early-Onset Colorectal Cancer: A Systematic Literature Review

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ABSTRACT

The incidence of early-onset colorectal cancer (EOCRC) among individuals younger than 50 years has continued to increase, although its underlying etiological factors remain incompletely understood. This study aimed to identify the most consistently reported risk factors for EOCRC and examine their interrelationships based on current scientific evidence. A systematic literature review was conducted involving 27 primary research articles published between 2021 and 2026. The literature search and study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Methodological quality was assessed using Joanna Briggs Institute (JBI) critical appraisal tools, and thematic relationships were mapped using VOSviewer. The findings identified four major categories of EOCRC risk factors. The first category comprised general and abdominal obesity, metabolic syndrome, type 2 diabetes mellitus, hyperglycemia, hypertriglyceridemia, hypertension, and inflammatory bowel disease. The second category included alcohol consumption, sugar-sweetened beverage intake, proinflammatory and hyperinsulinemic dietary patterns, smoking, and sedentary behavior, while vitamin D intake was associated with a potentially protective effect. The third category involved antibiotic exposure, with associations varying according to age at exposure, duration of use, antibiotic spectrum, and tumor subsite. The fourth category encompassed family history, polygenic risk scores, genetic variants, accelerated biological aging, and birth-related and parental characteristics. VOSviewer analysis identified ten clusters highlighting interrelationships among metabolic, lifestyle, microbiome-related, genetic, and early-life factors. The review concluded that obesity, metabolic disorders, inflammatory bowel disease, unhealthy dietary patterns, and family history were the most consistently reported risk factors for EOCRC, whereas associations involving antibiotic exposure and birth-related characteristics warranted further targeted investigation.

INTRODUCTION

Colorectal cancer diagnosed before the age of 50 years is classified as early-onset colorectal cancer (EOCRC) and has become an increasing public health concern because its rising incidence contrasts with the declining incidence observed among older adults. In the United States, approximately 158,850 new colorectal cancer cases and 55,230 deaths are projected for 2026, including 24,640 cases and 3,890 deaths among individuals younger than 50 years (Siegel et al., 2026). The incidence among individuals aged 20–49 years increased by an average of 3% annually between 2013 and 2022, while mortality among those younger than 50 years has increased by approximately 1% annually since 2004 (Siegel et al., 2026). These trends suggest that the increasing burden of EOCRC requires further investigation into its underlying etiological factors and the development of more targeted early detection strategies.

Research on EOCRC risk factors has examined familial characteristics, medical conditions, lifestyle behaviors, dietary patterns, and socioeconomic factors. Archambault et al.

(2021) analyzed 3,767 EOCRC cases and 4,049 controls across 13 epidemiological studies and identified associations with lower educational attainment, red meat consumption, alcohol consumption patterns, and nonuse of regular nonsteroidal anti-inflammatory drugs. Chang et al. (2021) reported that a family history of colorectal cancer, sedentary behavior of at least 10 hours per day, sugar-sweetened beverage consumption, and a Western dietary pattern were associated with increased EOCRC risk among Ontario residents aged 20–49 years. Danial et al. (2022) identified family history, inflammatory bowel disease, obesity, diabetes, alcohol consumption, smoking, and hyperlipidemia as factors associated with EOCRC. Variations in the strength of these associations suggested that genetic, metabolic, and behavioral factors contributed differently across populations.

Metabolic factors have received considerable attention because the increasing prevalence of obesity and metabolic disorders among younger individuals has coincided with rising EOCRC incidence. Chen et al. (2021) found that metabolic syndrome was associated with a 25% higher EOCRC risk in an analysis involving 4,673 cases. Jin et al. (2022) reported a 19% higher risk among individuals with metabolic syndrome, with risk increasing alongside the number of metabolic syndrome components. Li et al. (2022) found that type 2 diabetes mellitus was associated with increased EOCRC risk, particularly among individuals with poorly controlled diabetes and related complications. Song et al. (2023) demonstrated that persistent general and abdominal obesity were associated with increased EOCRC risk in a nationwide cohort of more than 3.3 million participants. Chang et al. (2024) identified an association between persistent hypertriglyceridemia and early-onset rectal cancer. Similarly, Luo et al. (2024) reported an association between elevated blood glucose levels and EOCRC incidence across two prospective cohorts. Although these findings generally indicated positive associations, the magnitude of risk and affected tumor subsites varied across metabolic indicators.

Dietary patterns and lifestyle behaviors have also demonstrated associations with EOCRC risk. Hur et al. (2021) found that women consuming at least two servings of sugar-sweetened beverages daily had more than twice the EOCRC risk of those consuming fewer than one serving weekly. Yue et al. (2021) reported that hyperinsulinemic dietary and lifestyle patterns were associated with increased colorectal cancer risk among younger women. Kim et al. (2021) found that total vitamin D intake of at least 450 IU daily was associated with lower EOCRC risk compared with intake below 300 IU daily. Jin et al. (2023) identified a dose-dependent association between alcohol consumption and EOCRC risk, particularly for distal colon and rectal cancers. Chen et al. (2022) similarly reported an association between high alcohol consumption and early-onset colorectal cancer, although early onset was defined as diagnosis before age 55 years. Li et al. (2023) applied the same age threshold and identified associations involving current smoking and smoking history. These differences in age definitions limited direct comparisons with studies defining EOCRC as diagnosis before age 50 years.

Evidence regarding antibiotic exposure has remained inconsistent. McDowell et al. (2022) identified an association between oral antibiotic use and early-onset colon cancer but not rectal cancer. Nguyen et al. (2022) found no statistically significant association between overall antibiotic use and EOCRC, although broad-spectrum antibiotic exposure showed a weak positive association. Jiang et al. (2023) reported that repeated or prolonged antibiotic exposure early in life was associated with increased risks of EOCRC and early-onset colorectal adenomas. Conversely, Kane et al. (2025) found no convincing association between oral antibiotic use during adulthood and EOCRC in an analysis involving 1,359 cases and 4,711 controls. Chao et al. (2026) also reported no overall association with broad-spectrum antibiotic use, although cumulative exposure exceeding 90 days suggested an increased risk of early-

onset colon cancer. These discrepancies highlighted the importance of exposure timing, antibiotic spectrum, treatment duration, and tumor subsite when interpreting the evidence.

Early-life characteristics, comorbidities, and genetic susceptibility have provided additional insights into EOCRC risk. Cao et al. (2023) found no significant overall association between cesarean delivery and EOCRC, although increased risk was observed among female offspring. Siddique et al. (2026) reported associations involving male sex, Hispanic ethnicity, higher birth weight among females, and paternal age of at least 35 years. Peeri et al. (2024) found that individuals with two or more older biological siblings had a higher EOCRC risk than those without older biological siblings. Lundqvist et al. (2023) identified associations between EOCRC and inflammatory bowel disease and metabolic disorders, whereas other autoimmune diseases showed no clear association. Laskar et al. (2024) identified novel genetic loci and provided evidence supporting potential causal contributions from body size, metabolic factors, alcohol consumption, and educational attainment. Sandhu et al. (2025) reported associations between EOCRC, polygenic risk scores, and accelerated biological aging. Collectively, these findings suggested that EOCRC susceptibility may be influenced by early-life exposures and interactions among genetic predisposition, metabolic conditions, and environmental factors.

Geographic and methodological differences have further complicated the interpretation of EOCRC risk factors. Pan et al. (2023) identified associations involving alcohol consumption, diabetes, hypertension, fish consumption, and family history of cancer in a Chinese population, although these findings were not entirely consistent with evidence from North America and Europe. Differences in population characteristics, age thresholds, exposure assessment, exposure timing, and tumor subsite classification may explain variations in reported associations. Findings regarding antibiotic exposure remained conflicting, while evidence concerning vitamin D intake, birth characteristics, sibling relationships, biological aging, and genetic interactions was limited. Despite the growing literature, an integrated synthesis examining familial, metabolic, behavioral, dietary, antibiotic-related, early-life, and genetic factors alongside bibliometric mapping remained necessary. This evidence gap was particularly relevant given the increasing incidence of EOCRC and the continued reliance on age-based screening recommendations, with additional consideration of established high-risk conditions. The present study addressed this gap by combining a systematic review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines with VOSviewer-based bibliometric mapping of primary studies published between 2021 and 2026. This approach enabled the identification of recurring associations, thematic relationships, and emerging research priorities.

Therefore, this systematic literature review aimed to identify, compare, and map factors associated with EOCRC risk while examining inconsistencies across existing studies. Specifically, the review synthesized evidence across metabolic, lifestyle, microbiome-related, genetic, and early-life domains; distinguished consistently reported associations from those requiring further investigation; and explored potential relationships among risk factors to inform future research. By integrating systematic evidence synthesis with bibliometric mapping, the study sought to provide a comprehensive understanding of EOCRC risk factors and support the development of prospective investigations and more individualized risk assessment strategies. These findings may assist clinicians, public health professionals, and researchers in refining risk stratification approaches while complementing established colorectal cancer screening recommendations.

METHOD

Study Design

This study employed a systematic literature review (SLR) to identify, evaluate, and synthesize evidence on risk factors for early-onset colorectal cancer (EOCRC) diagnosed before the age of 50 years. The review included cohort, case-control, nested case-control, registry-based, genome-wide association studies (GWAS), and Mendelian randomization studies. It focused on associations between potential risk factors and EOCRC incidence, excluding studies primarily addressing prognosis, treatment outcomes, survival, recurrence, diagnostic delays, or precancerous lesions.

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparent reporting of study identification, selection, and exclusion (Page et al., 2021). Data were synthesized descriptively and thematically based on study design, population characteristics, exposure types, EOCRC definitions, effect estimates, confounding adjustments, and the direction of reported associations. Bibliometric relationships and thematic clusters were analyzed using VOSviewer.

PICO Framework and Literature Search Strategy

The research question was formulated using the PICO framework (Table 1), in which the intervention component was treated as exposure because this study examined disease etiology rather than the effectiveness of a clinical intervention.

Table 1. PICO framework of the study

Component	Operational definition
Population (P)	Individuals diagnosed with invasive colorectal cancer before the age of 50 years and a comparison group without colorectal cancer
Intervention/Exposure (I)	Lifestyle factors, diet, obesity, metabolic disorders, diabetes, alcohol consumption, smoking, antibiotic or medication use, early-life factors, family history, and genetic factors
Comparison (C)	Individuals without EOCRC, unexposed groups, the lowest exposure category, or another comparison group appropriate to the study design
Outcome (O)	EOCRC incidence or risk expressed as OR, RR, HR, or another extractable measure of association

Searches were conducted in PubMed/MEDLINE, Europe PMC, Embase, and Web of Science Core Collection, supplemented by the reference lists of eligible articles, the similar-articles feature, forward citation tracking, and publisher websites. The publication period was restricted to 2021–2026, and English-language articles were selected because all eligible and accessible primary studies were published in English.

The main keyword combination used was:

("early-onset colorectal cancer" OR "young-onset colorectal cancer" OR "early age onset colorectal cancer") AND ("risk factor" OR determinant OR exposure OR obesity OR "body mass index" OR diet OR alcohol OR smok OR diabetes OR "metabolic syndrome" OR antibiotic OR medication OR "family history" OR genetic OR "polygenic risk score")

Search syntax was adjusted to each database (quotation marks, Boolean operators, subject terms, truncation, and year filters). Results were exported in RIS or CSV format, merged in reference-management software, and checked for duplicates using DOI, PMID, title, first-author name, and publication year.

Article Selection and Methodological Quality Assessment

Selection was conducted through title and abstract screening, full-text assessment, and final inclusion (Table 2). At the first stage, articles were excluded if they did not address EOCRC, focused on treatment or prognosis, used precancerous lesions as outcomes, or were not primary studies; full-text decisions considered the age definition, cancer type, comparison group, availability of an extractable association estimate, and access to the complete article.

Table 2. Article inclusion and exclusion criteria

Aspect	Inclusion criteria	Exclusion criteria
Publication year	Published in 2021–2026	Published before 2021
Population	Diagnosis of invasive colorectal cancer before the age of 50 years	Age threshold extending to 50 years or using a threshold below 55 years without separate results for participants aged <50 years
Design	Cohort, case-control, nested case-control, registry analysis, GWAS, or Mendelian randomization	Review, meta-analysis, scoping review, editorial, commentary, protocol, case report, and conference abstract
Exposure	Factors suspected to be associated with EOCRC incidence	Prognostic factors, treatment, recurrence, mortality, stage, or diagnostic delay
Outcome	Invasive EOCRC with an extractable estimate of association	Adenoma, serrated polyp, neoplasia, or precursor lesions without an invasive-cancer outcome
Comparator	Group without EOCRC, without exposure, or a clearly defined reference category	Describes only EOCRC patients without a comparison group
Access	Full text available through an official website or public repository	Abstract only or full text unavailable

A total of 42 reports reached the full-text assessment stage. Fifteen reports were excluded: nine articles with precursor or neoplasia outcomes, three articles with incompatible age thresholds, one study without a comparison group or risk estimate, one study that only developed a prediction model, and one article whose full text could not be accessed. The final selection yielded 27 primary research articles. The selection process is shown in Table 3.

Table 3. Article selection process based on PRISMA 2020

Stage	Description	n
Identification	Databases and initial search results	118
	Duplicate records removed	8
Screening	Records after duplicates removed	110
	Records excluded at title and abstract screening	68
	Records retained for full-text review	42
Eligibility	Full-text reports excluded	15
	– Outcome limited to colorectal adenoma, serrated polyp, neoplasia, or another EOCRC precursor	9
	– Age threshold did not meet the definition of EOCRC diagnosed before 50 years	3
	– No appropriate comparison group or estimable risk association	1
	– Focused exclusively on risk prediction rather than an etiological association	1
	– Full text unavailable	1
	Full-text eligibility	27
Included	Final studies included	27

Methodological quality was assessed using the JBI Critical Appraisal Checklist adapted to cohort, case-control, and other analytical designs, covering participant criteria, comparison groups, validity of exposure and outcome measurement, control of confounding, adequacy of follow-up, and statistical analysis. Genetic studies were assessed based on case definition, control selection, control of population stratification, strength of genetic instruments, and sensitivity analyses. Tailoring appraisal instruments to each design helps prevent different sources of bias from being judged using identical criteria (Aromataris & Munn, 2020; Barker et al., 2023).

Data Extraction and Analysis

Data from the 27 articles were extracted using a structured worksheet containing author, publication year, country, data source, study design, sample size, age range, EOCRC definition, exposure type, comparison group, measure of association, confidence interval, adjustment variables, and main findings, and were rechecked against the original articles. Results reported by sex or tumor location were recorded separately without counting the article as a different study. The thematic synthesis classified risk factors into five groups: diet and lifestyle; obesity and metabolic disorders; antibiotic and medication use; birth, family, and early-life factors; and genetic and biological factors. Findings were compared according to direction and magnitude of association, precision of confidence intervals, number of EOCRC cases, control of confounding, and temporal consistency between exposure and diagnosis. Statistical pooling was not performed.

Bibliometric analysis was conducted using VOSviewer version 1.6.20. Bibliographic data were cleaned using a thesaurus file to merge synonymous terms (e.g., "young-onset colorectal cancer," "early onset CRC," and "EOCRC" into "early-onset colorectal cancer"; "BMI" into "body mass index"). Co-occurrence analysis used author keywords and important terms in titles and abstracts, with full counting and a minimum threshold of two occurrences. Network, overlay, and density visualizations were generated to display thematic groups, changes in research focus by average publication year, and terms with the highest occurrence and connectivity. The mapping followed the visualization-of-similarities principle used by VOSviewer to place more strongly related terms closer together (van Eck & Waltman, 2024).

RESULT AND DISCUSSION

Distribution of Articles by Year, Region, and Study Design

A total of 27 primary articles published between 2021 and 2026 were analyzed to describe publication trends, study locations, study designs, and groups of risk factors examined (Table 4).

Table 4. Frequency distribution of included articles (n = 27)

Characteristic	Category: n (%)
Publication year	2021: 6 (22.2%); 2022: 6 (22.2%); 2023: 7 (25.9%); 2024: 4 (14.8%); 2025: 2 (7.4%); 2026: 2 (7.4%)
Main region	United States: 9 (33.3%); South Korea: 4 (14.8%); United Kingdom: 4 (14.8%); Sweden: 3 (11.1%); Germany: 2 (7.4%); Multinational: 2 (7.4%); Canada: 1 (3.7%); China: 1 (3.7%); United Kingdom–China: 1 (3.7%)
Main risk factor	Diet and lifestyle behavior: 8 (29.6%); Metabolic and anthropometric factors: 6 (22.2%); Antibiotic use: 5 (18.5%); Early-life characteristics: 3 (11.1%); Genetic factors and biological aging: 2 (7.4%); Combined risk factors: 2 (7.4%); Autoimmune and inflammatory diseases: 1 (3.7%)
Total	All articles: 27 (100.0%)

The largest number of publications appeared in 2023, with seven articles (25.9%). Nineteen of the 27 articles (70.4%) were published during 2021–2023. The United States was the most common study region, while South Korea and the United Kingdom each contributed four articles. Diet and lifestyle factors were studied most frequently, followed by metabolic factors and antibiotic use.

Characteristics of Included Articles

The included articles were examined to ensure that all studies provided primary data on factors associated with early-onset colorectal cancer (EOCRC). Table 5 presents all 27 included articles according to author, region, design, sample size, sample age, main findings, and JBI quality rating.

Sample sizes ranged from 516 participants in the EOCRC analysis by Sandhu et al. (2025) to more than 26 million in Danial et al. (2022). Three articles used an early-onset

threshold below 55 years (Chen et al., 2022; Li et al., 2023; Luo et al., 2024); their findings are retained but not directly equated with studies defining EOCRC as diagnosis before the age of 50 years.

Article Quality Assessment Using JBI

JBI checklists of 10 items (case-control), 11 items (cohort), and eight items (analytical cross-sectional) were applied according to study design, and quality was categorized as high ($\geq 80\%$ of applicable items met), moderate (60–79%), or low ($< 60\%$).

Twenty-four articles were categorized as high quality and three as moderate quality, with none of low quality (Table 5); all articles were therefore included, while sample size, age thresholds, exposure measurement, and confounding control were considered when comparing findings.

Table 5. Characteristics, main findings, and methodological quality of the 27 included articles

Author (year); region	Design	Sample	Sample age	Main findings	JBI quality
Archambault et al. (2021); Multinational	Pooled case-control study	7,816 (3,767 cases; 4,049 controls)	EOCRC group < 50 years; comparator ≥ 50 years	Red meat consumption, lower education, absence of regular NSAID use, alcohol abstinence, and heavy alcohol consumption were associated with increased risk	9/10 (High)
Cao et al. (2023); Sweden	Population-based nationwide case-control study	2,744 (564 cases; 2,180 controls)	18–49 years	No association was found in the overall sample, but risk increased among women with OR 1.62	9/10 (High)
Chang et al. (2021); Canada	Population-based case-control study	428 (175 cases; 253 controls)	20–49 years	Family history, sedentary behavior ≥ 10 hours/day, sugar-sweetened beverages, and a Western diet increased risk	8/10 (High)
Chang et al. (2024); South Korea	Nationwide population-based cohort study	3,340,635 participants; 7,492 developed EOCRC	20–49 years	Persistent hypertriglyceridemia increased risk, particularly for early-onset rectal cancer	10/11 (High)
Chao et al. (2026); United States	Nested case-control study	3,089 (295 cases; 2,794 controls)	15–49 years	Overall antibiotic use was not associated with EOCRC; broad-spectrum use > 90 days suggested increased colon-cancer risk	9/10 (High)
Chen et al. (2021); United States	Nested case-control study	45,505 (4,673 cases; 40,832 controls)	18–49 years for the EOCRC group	Metabolic syndrome increased risk by 25%; risk increased with the number of metabolic disorders	9/10 (High)
Chen et al. (2022); Germany	Population-based case-control study	9,235 (5,104 cases; 4,131 controls)	Early-onset group < 55 years; late-onset group ≥ 55 years	High alcohol consumption increased early-onset cancer risk with OR 1.80, but the age threshold used was < 55 years	8/10 (High)
Danial et al. (2022); United States	Retrospective population-based study	26,919,960 (13,800 cases; 26,906,160 comparators)	20–49 years	Family history, inflammatory bowel disease, obesity, diabetes, alcohol, smoking, and hyperlipidemia were associated with young-onset colorectal cancer	6/8 (Moderate)

Author (year); region	Design	Sample	Sample age	Main findings	JB quality
Hur et al. (2021); United States	Prospective cohort study	95,464 women; 109 developed EOCRC	25–42 years at cohort entry; diagnosis <50 years	Consumption ≥ 2 servings/day more than doubled the risk, with RR 2.18	10/11 (High)
Jiang et al. (2023); United Kingdom	UK Biobank cohort analysis	113,256 participants; 165 EOCRC cases and 719 early-onset adenoma cases	40–69 years at recruitment; diagnosis <50 years	Early-life antibiotic exposure increased EOCRC risk with OR 1.48	8/11 (Moder ate)
Jin et al. (2022); South Korea	Nationwide population- based cohort study	5,672,153 participants; 8,320 developed EOCRC	20–49 years	Metabolic syndrome increased risk and showed a dose–response pattern according to the number of components	10/11 (High)
Jin et al. (2023); South Korea	Nationwide population- based cohort study	5,666,576 participants; 8,314 developed EOCRC	20–49 years	Moderate and heavy alcohol consumption increased risk, particularly in the distal colon and rectum	10/11 (High)
Kane et al. (2025); United States	Population- based nested case-control study	6,070 (1,359 cases; 4,711 controls)	18–49 years	No convincing association was found between antibiotic use and EOCRC, with OR 1.04	9/10 (High)
Kim et al. (2021); United States	Prospective cohort study	94,205 women; 111 developed EOCRC	25–42 years at cohort entry; diagnosis <50 years	Vitamin D intake ≥ 450 IU/day was associated with lower risk, with HR 0.49	10/11 (High)
Laskar et al. (2024); Multinational	Genome-wide association study and Mendelian randomization analysis	72,005 (6,176 cases; 65,829 controls)	Cases diagnosed before the age of 50 years	Two new loci were identified; MUTYH variants and body-size and metabolic factors supported EOCRC susceptibility	8/8 (High)
Li et al. (2023); Germany	Population- based case- control study	1,511 (724 cases; 787 controls)	Early-onset group <55 years	Current smokers had higher risk with OR 1.57, but the early-onset threshold used was <55 years	8/10 (High)
Li et al. (2022); United States	Nested case- control study	58,105 (6,001 cases; 52,104 controls)	18–49 years	Diabetes increased risk, particularly when uncontrolled or accompanied by complications	9/10 (High)
Lundqvist et al. (2023); Sweden	Nationwide nested case- control study	18,382 (2,626 cases; 15,756 controls)	<50 years; mean age 42.5 years	Metabolic disease increased risk 1.82-fold and inflammatory bowel disease increased risk 5.98-fold	9/10 (High)
Luo et al. (2024); United Kingdom– China	Prospective cohort and Mendelian randomization study	547,377 participants, including 374,568 UK Biobank participants and 172,809 Kailuan Cohort participants	UK Biobank 40–69 years; Kailuan Cohort >18 years; early onset defined as <55 years	Glucose >7.0 mmol/L was more strongly associated with early-onset cancer in the UK Biobank, with HR 1.61	10/11 (High)
McDowell et al. (2022); United Kingdom	Case-control study using a national clinical database	2,335 (445 cases; 1,890 controls)	<50 years for the EOCRC group	Antibiotic use was associated with early-onset colon cancer with OR 1.49, but not with rectal cancer	9/10 (High)

Author (year); region	Design	Sample	Sample age	Main findings	JB1 quality
Nguyen et al. (2022); Sweden	Population-based case-control study	15,197 (2,557 cases; 12,640 controls)	18–49 years	Overall antibiotic use was not associated with EOCRC; broad-spectrum antibiotics showed a weak increase in risk	9/10 (High)
Pan et al. (2023); China	Prospective cohort study	88,055 (222 cases; 87,833 comparators)	30–49 years in the EOCRC analysis	Alcohol, hypertension, diabetes, high BMI, fish consumption, and family history of cancer increased risk	9/11 (High)
Peeri et al. (2024); United Kingdom	Cross-sectional analysis within a prospective cohort	166,650 (212 cases; 166,438 comparators)	40–69 years at recruitment; diagnosis <50 years	Having two or more older biological siblings increased risk with OR 1.46	6/8 (Moderate)
Sandhu et al. (2025); United Kingdom	Case-control analysis within a prospective cohort	31,164 participants across all analyses; the EOCRC group included 86 cases and 430 controls	40–69 years at recruitment; diagnosis <50 years	Polygenic risk score increased risk; each one-year acceleration in PhenoAge increased the odds of EOCRC by 7%	8/10 (High)
Siddique et al. (2026); United States	Population-based nested case-control study	62,271 (1,221 cases; 61,050 controls)	0–39 years	Male sex, Hispanic ethnicity, high birth weight in females, and paternal age ≥ 35 years were associated with risk	9/10 (High)
Song et al. (2023); South Korea	Nationwide population-based cohort study	3,340,635 participants; 7,492 developed EOCRC	20–49 years	Persistent general and abdominal obesity increased risk, with HR 1.09 and 1.18	10/11 (High)
Yue et al. (2021); United States	Prospective cohort study	94,217 women; 332 developed colorectal cancer during follow-up	26–45 years at baseline; diagnosis <50 years	Patterns that increased hyperinsulinemia were more strongly associated with EOCRC, with HR 1.86	10/11 (High)

Thematic Mapping through Network Visualization

Keyword co-occurrence analysis was used to identify the structure of relationships among topics. Node size represents term frequency, lines indicate co-occurrence relationships, and colors distinguish thematic groups. The mapping produced 10 clusters, with early-onset colorectal cancer, colorectal cancer, risk factors, and cancer epidemiology as the main nodes (Figure 1). The keywords and linked evidence of each cluster are summarized in Table 6.

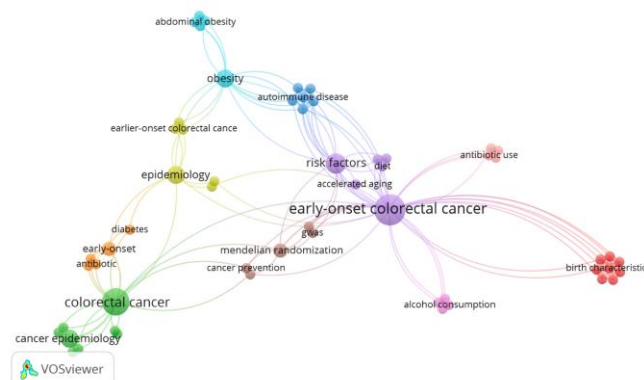


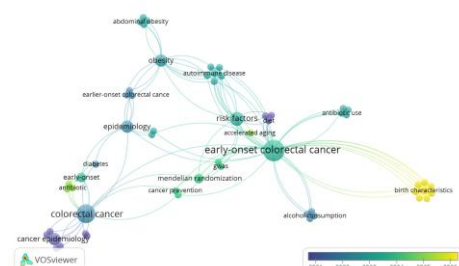
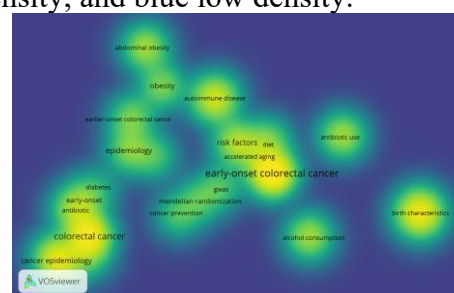
Figure 1. Network visualization of early-onset colorectal cancer risk factors

Table 6. Keyword clusters identified by VOSviewer network visualization

Cluster	Main keywords	Linked articles
1	Birth characteristics, birthweight, colorectal cancer risk factors, early-life exposures, Hispanic ethnicity, parental characteristics, paternal age, sex differences	Cao et al., 2023; Siddique et al., 2026; Peeri et al., 2024
2	Cancer epidemiology, colorectal adenoma, colorectal cancer, dietary–colon cancer, dietary and lifestyle pattern, gastrointestinal cancer, vitamin D, young women	Archambault et al., 2021; Hur et al., 2021; Kim et al., 2021; Yue et al., 2021
3	Autoimmune disease, diabetes mellitus, hyperlipidemia, hypertension, inflammatory bowel disease, metabolic disease	Chen et al., 2021; Li et al., 2022; Lundqvist et al., 2023; Pan et al., 2023
4	China Kadoorie Biobank, earlier-onset colorectal cancer, epidemiology, metabolic syndrome, screening, waist circumference	Jin et al., 2022; Chang et al., 2024; Song et al., 2023
5	Accelerated aging, diet, early-onset colorectal cancer, risk factors, sedentary behavior, sugary drinks	Chang et al., 2021; Sandhu et al., 2025; Archambault et al., 2021
6	Abdominal obesity, cohort study, early onset colorectal ca, obesity, obesity change	Song et al., 2023; Pan et al., 2023
7	Adenocarcinoma, antibiotic, diabetes, early-onset, young	McDowell et al., 2022; Nguyen et al., 2022; Kane et al., 2025; Chao et al., 2026
8	Cancer prevention, genetics, glucose, GWAS, Mendelian randomization	Laskar et al., 2024; Luo et al., 2024; Sandhu et al., 2025
9	Alcohol consumption, genetic risk equivalent, late-onset colorectal cancer, polygenic risk score	Chen et al., 2022; Jin et al., 2023; Li et al., 2023
10	Antibiotic use, early-life factors, FUT2 gene, polygenic risk	Jiang et al., 2023; Chao et al., 2026; Laskar et al., 2024

Topic Development and Density through Overlay and Density Visualization

Overlay visualization was used to show temporal changes in keyword occurrence (Figure 2), in which purple and blue indicate topics appearing more frequently in the early period, green the middle period, and yellow more recent topics. Density visualization was used to identify areas with the highest keyword concentration (Figure 3), in which yellow indicates terms with high frequency and connectivity, green moderate density, and blue low density.

**Figure 2.** Overlay visualization of early-onset colorectal cancer risk factors**Figure 3.** Density visualization of early-onset colorectal cancer risk factors

Early publications in 2021–2022 centered on cancer epidemiology, colorectal cancer, alcohol consumption, diabetes, and diet; topics in 2023–2024 shifted toward obesity, autoimmune disease, antibiotic use, GWAS, Mendelian randomization, and accelerated biological aging; and birth characteristics, birth weight, paternal age, ethnicity, and sex differences became newer research directions in 2025–2026, reflecting a transition toward early-life exposures and biological and genetic factors.

The highest density was found for early-onset colorectal cancer, colorectal cancer, cancer epidemiology, and birth characteristics; moderate density for risk factors, diet, autoimmune disease, obesity, and antibiotic use; and lower density for alcohol consumption, glucose,

GWAS, and Mendelian randomization, indicating that integration of genetic factors, glucose, antibiotics, and biological aging is still developing.

Diet and Lifestyle Factors

Table 7. Synthesis of diet and lifestyle factors in relation to EOCRC risk

Factor	Description	Source
Red meat and fiber	Higher red meat consumption increases EOCRC risk; low fiber intake is more strongly associated with rectal cancer; a Western dietary pattern shows a positive association.	Archambault et al. (2021); Chang et al. (2021)
Sugar-sweetened beverages	≥7 beverages/week: OR 2.99 (Canada); ≥2 servings/day among women: RR 2.18; each additional serving/day at ages 13–18 years increased risk by 32%.	Chang et al. (2021); Hur et al. (2021)
Hyperinsulinemic dietary and lifestyle pattern	Patterns that increase insulin response are associated with higher EOCRC risk, linking diet quality, sedentary behavior, adiposity, and insulin metabolism.	Yue et al. (2021); Chang et al. (2021); Archambault et al. (2021)
Vitamin D	Intake ≥450 IU/day: HR 0.49 vs. <300 IU/day; the protective direction comes mainly from a female cohort.	Kim et al. (2021); Sandhu et al. (2025)
Alcohol consumption	Moderate and heavy consumption increase risk, particularly in the distal colon and rectum; increased risk also among abstainers and heavy drinkers; association remained after accounting for polygenic risk (one article used a <55-year threshold).	Archambault et al. (2021); Chen et al. (2022); Jin et al. (2023); Pan et al. (2023)
Smoking	Current smoking: OR 1.57 (<55-year threshold); positive association with tobacco use in a United States registry.	Li et al. (2023); Danial et al. (2022)
Sedentary behavior	Sedentary time ≥10 hours/day: OR 1.93 vs. <5 hours/day; related to a hyperinsulinemic lifestyle pattern.	Chang et al. (2021); Yue et al. (2021)
Fish consumption	Higher fish consumption: HR 1.64 in a Chinese cohort; found in only one population.	Pan et al. (2023)

Alcohol consumption was the most consistent behavioral factor, with positive associations in multinational, German, South Korean, and Chinese populations; sugar-sweetened beverages produced notably large associations, and higher vitamin D intake was the clearest protective factor, mainly in female cohorts (Table 7).

Metabolic Disorders and Adiposity

Table 8. Synthesis of metabolic disorders and adiposity in relation to EOCRC risk

Factor	Description	Source
Metabolic syndrome	Increases EOCRC risk by approximately 20–25%; risk rises with the number of components and varies by tumor location.	Chen et al. (2021); Jin et al. (2022)
Type 2 diabetes mellitus	OR 1.24; larger in uncontrolled or complicated diabetes; also a risk factor in a Chinese cohort and a United States registry.	Li et al. (2022); Pan et al. (2023); Danial et al. (2022)
Blood glucose	Glucose >7.0 mmol/L: HR 1.61 for early-onset cancer in the UK Biobank (<55-year threshold).	Luo et al. (2024)
Hypertriglyceridemia	Persistent hypertriglyceridemia: HR 1.097 with a dose–response relationship; clearest for rectal cancer and among participants with diabetes.	Chang et al. (2024); Danial et al. (2022)
General obesity	Persistent obesity: HR 1.09; higher BMI associated with risk in a Chinese cohort; higher obesity prevalence in a United States registry.	Song et al. (2023); Pan et al. (2023); Danial et al. (2022)
Abdominal obesity	Persistent abdominal obesity: HR 1.18, stronger than general obesity; adds risk information beyond BMI.	Song et al. (2023); Jin et al. (2022)
Hypertension	HR 1.99 in a Chinese cohort; a metabolic component contributing to cumulative risk.	Pan et al. (2023); Chen et al. (2021); Jin et al. (2022)
Metabolic disease	History of metabolic disease: HR 1.82 in the Swedish registry, persisting after adjustment for demographics and comorbidities.	Lundqvist et al. (2023); Chen et al. (2021)

Factor	Description	Source
Metabolic factors and biological age	Not all metabolic variables differed between cases and controls; accelerated PhenoAge remained associated after adjustment for metabolic indicators.	Sandhu et al. (2025)

Metabolic disorders showed a relatively consistent direction of association: uncontrolled or complicated diabetes produced larger associations than controlled diabetes, abdominal obesity a stronger association than general obesity, and tumor location influenced associations with hypertriglyceridemia and metabolic syndrome (Table 8).

Antibiotic Exposure

Table 9. Synthesis of antibiotic use in relation to EOCRC risk

Factor	Description	Source
Oral antibiotics and tumor location	Associated with early-onset colon cancer (OR 1.49) but not rectal cancer; trend toward increased colon-cancer risk after prolonged broad-spectrum use.	McDowell et al. (2022); Chao et al. (2026)
Antibiotics overall	OR close to one with no significant association in two United States healthcare systems and a Swedish registry.	Nguyen et al. (2022); Kane et al. (2025); Chao et al. (2026)
Broad-spectrum antibiotics	Weak increase in risk in the Swedish registry; cumulative use >90 days 10–14.9 years before diagnosis: OR 2.04 for colon cancer but not EOCRC overall.	Nguyen et al. (2022); Chao et al. (2026)
Early-life antibiotics	Repeated or long-term use at age ≤19 years: OR 1.48 for EOCRC and OR 1.40 for early-onset adenoma.	Jiang et al. (2023); Kane et al. (2025)
Duration and timing of exposure	Short-term adulthood exposure tended not to be associated, whereas longer and earlier exposure showed stronger associations.	McDowell et al. (2022); Nguyen et al. (2022); Jiang et al. (2023); Kane et al. (2025); Chao et al. (2026)

Antibiotic use in adulthood generally did not increase risk, whereas repeated early-life exposure and prolonged cumulative broad-spectrum exposure showed positive associations, more consistently for colon than rectal cancer (Table 9).

Genetic Susceptibility

Table 10. Synthesis of genetic susceptibility in relation to EOCRC risk

Genetic factor	Description	Source
Loci 1p34.1 and 4p15.33	Two new loci associated with EOCRC in large-scale genomic analysis.	Laskar et al. (2024)
MUTYH variant	OR 1.80; among the largest genetic associations in EOCRC analysis.	Laskar et al. (2024)
Polygenic risk score	OR 1.53 in the UK Biobank; remained a predictor after adjustment for age, sex, body composition, behavior, and biological factors.	Sandhu et al. (2025); Laskar et al. (2024)
Polygenic risk and alcohol consumption	No significant interaction; high alcohol consumption remained independently associated (<55-year threshold).	Chen et al. (2022); Laskar et al. (2024)
FUT2 gene and antibiotics	The association between early-life antibiotics and early-onset adenoma was stronger in certain FUT2 genotypes.	Jiang et al. (2023); Chao et al. (2026)
Genetic instruments for glucose	Mendelian randomization assessed a possible causal glucose–colorectal cancer relationship; stronger observational association with early-onset cancer (<55-year threshold).	Luo et al. (2024); Laskar et al. (2024)

Genetic susceptibility acts as an independent factor and may modify environmental associations: a high polygenic risk score increases risk, alcohol remains associated after accounting for polygenic risk, and FUT2 findings point to interactions among genetic factors, gut microbiota, and antibiotic exposure (Table 10).

Biological Aging

Table 11. Synthesis of biological aging in relation to EOCRC risk

Indicator	Description	Source
PhenoAge acceleration	Each one-year acceleration increased the odds of EOCRC by 7%; better model fit than chronological age alone.	Sandhu et al. (2025)
Telomere length	No significant difference between EOCRC cases and controls.	Sandhu et al. (2025)
Homeostatic dysregulation	Weaker association than PhenoAge; more prominent in late-onset colorectal cancer.	Sandhu et al. (2025)
PhenoAge and polygenic risk	Combined model indicates complementary risk information from biological aging and genetic predisposition.	Sandhu et al. (2025); Laskar et al. (2024)

PhenoAge was the most informative biological-aging indicator, but direct evidence comes from only one article with 86 EOCRC cases, so consistency across populations cannot yet be assessed (Table 11).

Early-Life and Family Characteristics

Table 12. Synthesis of early-life and family characteristics in relation to EOCRC risk

Factor	Description	Source
Cesarean delivery	No overall association (OR 1.28); OR 1.62 among women and no significant association among men.	Cao et al. (2023); Siddique et al. (2026)
Older biological siblings	Two or more older siblings: OR 1.46, persisting after adjustment for household income and family history.	Peeri et al. (2024); Siddique et al. (2026)
Sex and ethnicity	Male sex: OR 1.34; Hispanic ethnicity associated with higher risk than non-Hispanic White ethnicity.	Siddique et al. (2026); Danial et al. (2022)
Maternal birthplace	Mother born outside the United States: OR 0.85.	Siddique et al. (2026)
Birth weight	Each 500-g increase among females: OR 1.10; no significant association among males.	Siddique et al. (2026); Cao et al. (2023)
Paternal age	Paternal age ≥ 35 years: OR 1.56 among female offspring; maternal age not similarly associated.	Siddique et al. (2026)
Family history	Increased risk in Canadian, United States, and Chinese populations; largest in the United States registry.	Chang et al. (2021); Danial et al. (2022); Pan et al. (2023)
Parity	Parity ≥ 3 : OR 0.29 vs. nulliparous women.	Chang et al. (2021)

Early-life evidence differed by sex, with cesarean delivery, birth weight, and paternal age more pronounced among females, while family history was consistent across more than one study region (Table 12).

Inflammatory and Autoimmune Diseases

Table 13. Synthesis of inflammatory and autoimmune diseases in relation to EOCRC risk

Condition	Description	Source
Inflammatory bowel disease	HR 5.98, the largest association in the article corpus; Crohn disease and ulcerative colitis also associated in a United States registry.	Lundqvist et al. (2023); Danial et al. (2022)
Inflammatory bowel disease with metabolic disease	HR 3.65, lower than for IBD without a metabolic condition.	Lundqvist et al. (2023); Chen et al. (2021)
Non-IBD autoimmune disease	No statistically significant association.	Lundqvist et al. (2023)
Crohn disease	Associated with young-onset colorectal cancer in population-registry data.	Danial et al. (2022); Lundqvist et al. (2023)
Ulcerative colitis	Positive association with young-onset colorectal cancer, consistent with the Swedish registry.	Danial et al. (2022); Lundqvist et al. (2023)

Inflammatory bowel disease produced a larger association than metabolic, dietary, and lifestyle factors, whereas autoimmune diseases not involving intestinal inflammation did not,

positioning chronic colonic inflammation as a more consistent risk factor than autoimmune status in general (Table 13).

Metabolic and Inflammatory Disorders as Risk Factors for EOCRC

The synthesis of 27 articles showed that metabolic disorders were the group of factors most consistently associated with EOCRC. General and abdominal obesity, metabolic syndrome, type 2 diabetes mellitus, hyperglycemia, hypertriglyceridemia, and hypertension reflect disrupted energy homeostasis beginning during the productive years of life. Obesity is associated with early-onset colorectal adenocarcinoma, whereas diabetes, hypertension, and dyslipidemia do not always show independent associations after other factors are controlled (Schumacher et al., 2021), which helps explain differences in the strength of associations among metabolic components.

Excess body weight in early adulthood provides a longer period during which insulin resistance, altered adipokines, oxidative stress, and low-grade inflammation can affect the colonic epithelium. Both overweight and obesity increase EOCRC risk, with a greater magnitude for obesity (Li et al., 2021), and body mass index at ages 20 and 30 years and 10 years before diagnosis remains relevant (Li et al., 2022), consistent with the role of abdominal obesity as a marker of metabolically active visceral fat.

Insulin resistance promotes hyperinsulinemia and insulin-like growth factor signaling, which enhance proliferation and inhibit apoptosis of epithelial cells (Samuel et al., 2025), and obesity may alter the microbiota, intestinal permeability, bile-acid metabolism, and inflammatory mediators. The strong association with inflammatory bowel disease, but not with other autoimmune diseases, suggests that the location and duration of intestinal inflammation matter more than autoimmunity in general, and recent evidence places obesity, metabolic syndrome, hypertension, triglycerides, and inflammatory bowel disease among the factors most frequently associated with EOCRC (Hua et al., 2023).

Dietary Patterns and Behavior as Risk Factors for EOCRC

Sugar-sweetened beverages, alcohol, pro-inflammatory or hyperinsulinemic dietary patterns, smoking, and sedentary behavior tend to increase risk, whereas vitamin D shows a protective direction, supporting the theory of cumulative exposure beginning in adolescence through increased body weight, glycemic load, inflammation, and altered colonic metabolism. Western dietary patterns, sugar-sweetened beverages, red or processed meat, and pro-inflammatory diets are recurring dietary exposures in EOCRC and its precursors (Carroll et al., 2022), and alcohol, unhealthy dietary patterns, and sedentary behavior are associated with EOCRC, although the magnitude varies according to how exposures are measured (O'Sullivan et al., 2022).

Sugar-sweetened beverages combine a rapidly absorbed sugar load with increased adiposity when consumed continuously; intake of simple sugars and sugar-sweetened beverages during adolescence has been associated with high-risk adenomas before the age of 50 years, particularly in the rectum (Joh et al., 2021). Alcohol adds exposure to acetaldehyde and oxidative stress, while smoking delivers carcinogens to the colorectal mucosa, so these relationships are better understood as an accumulation of mutually reinforcing exposures.

High consumption of ultra-processed foods is associated with colorectal cancer in men, particularly distal colon cancer (Wang et al., 2022), and with conventional adenomas and serrated lesions (Hang et al., 2023). Additives, low fiber, high energy density, and altered food matrices may affect the intestinal barrier and microbiota (Whelan et al., 2024), while poor diet quality, adiposity, and chronic psychosocial stress may converge on inflammation and insulin resistance (Oliveira et al., 2024). The protective direction of vitamin D should be interpreted cautiously because vitamin D levels also reflect outdoor activity, adiposity, diet, and health status.

Antibiotic Exposure and Dysbiosis in EOCRC Risk

The association between antibiotics and EOCRC depends on timing of exposure, duration, drug spectrum, and tumor location. General use in adulthood does not always increase risk, whereas prolonged or repeated use, particularly of broad-spectrum antibiotics and early in life, is more often associated with colon than rectal cancer. A similar site-specific pattern appears in Swedish nationwide data, with increased risk primarily in the proximal colon after more frequent antibiotic use (Lu et al., 2022), and the relationship with colorectal neoplasia is influenced by cumulative dose and tumor subsite. Antibiotics should therefore not be treated as a simple binary factor of ever versus never use.

The most plausible biological explanation is dysbiosis following antimicrobial pressure: reduced short-chain-fatty-acid-producing bacteria, expansion of opportunistic organisms, altered bile-acid metabolism, and weakened intercellular junctions may prolong mucosal contact with pro-inflammatory or genotoxic metabolites (Ahmad Kendong et al., 2021). The microbiota profile in EOCRC differs from that in late-onset cancer (Abdullah et al., 2021), and metagenomic and metabolomic analyses show distinct microbial phenotypes and metabolites in EOCRC (Kong et al., 2023).

The microbiota is also a point of convergence among antibiotics, diet, obesity, and inflammation, as low-fiber diets, ultra-processed foods, environmental exposures, and medications can shift gut ecology toward a state that supports carcinogenesis at a younger age (Dai et al., 2024). Because antibiotic use may also reflect infection, healthcare utilization, or illnesses preceding diagnosis, its association cannot yet be regarded as a single causal relationship.

Genetic and Early-Life Factors in EOCRC

Family history remains an important clinical marker, but not all EOCRC can be explained by high-penetrance hereditary syndromes. Hereditary and familial components account for only a proportion of cases, so the rising incidence of sporadic disease requires explanations involving low-risk genes and non-genetic exposures (Daca Alvarez et al., 2021), while a non-syndromic family history still offers opportunities for prevention through identification of relatives and earlier screening.

Somatic profiles of EOCRC and average-onset cancer share many similarities, although differences exist in the frequency of certain pathways and clinicopathological characteristics (Cercek et al., 2021). Pathogenic germline variants are slightly more frequent in EOCRC, yet the similarity of mutation profiles between age groups indicates that the genome alone does not explain the shift toward younger age at incidence (Storandt et al., 2025). This is consistent with the synthesis findings on polygenic risk scores: genetic effects become more meaningful when interpreted alongside alcohol, glucose, obesity, antibiotics, or early-life factors.

Birth characteristics, birth weight, paternal age, mode of delivery, and number of biological siblings can be understood through the developmental origins of health and disease framework, as markers of prenatal, hormonal, immunological, microbial, and social conditions that shape long-term susceptibility rather than direct causes. Accelerated biological aging strengthens this explanation because unhealthy lifestyles can leave DNA methylation changes and physiological dysregulation that are more strongly associated with early-onset cancer (Sun et al., 2025). Overall, four interrelated pathways were identified: metabolic–inflammatory, diet–behavior, antibiotic–microbiota, and genetic–early-life pathways.

CONCLUSION

The synthesis of 27 studies indicated that early-onset colorectal cancer (EOCRC) risk was associated with interrelated metabolic, inflammatory, dietary, behavioral, microbiome-related, genetic, and early-life factors. General and abdominal obesity, metabolic syndrome, glucose abnormalities, hypertriglyceridemia, inflammatory bowel disease, alcohol

consumption, sugar-sweetened beverage intake, unhealthy dietary patterns, sedentary behavior, and family history of colorectal cancer emerged as the most consistently reported risk factors. In contrast, associations with antibiotic exposure varied according to age at exposure, duration of use, antibiotic spectrum, and tumor subsite, while birth-related and parental characteristics appeared to represent potential markers of early-life susceptibility rather than established causal factors. These findings suggested that EOCRC prevention and early detection strategies should incorporate multifactorial risk assessment alongside established age-based screening recommendations. Relevant factors included family history, inflammatory bowel disease, abdominal obesity, metabolic disorders, dietary habits, alcohol consumption, smoking, physical activity, and antibiotic exposure. Preventive strategies could also emphasize weight management, improved dietary quality, reduced consumption of sugar-sweetened beverages and alcohol, regular physical activity, and appropriate antibiotic use. However, the review was limited by heterogeneity in EOCRC definitions, exposure assessments, participant age ranges, tumor subsites, and study populations. Future research should prioritize prospective cohort studies incorporating early-life exposure histories, longitudinal metabolic assessments, gut microbiome profiling, and genetic susceptibility data. The development and external validation of EOCRC-specific risk prediction models could further support individualized risk stratification and inform evidence-based screening strategies beyond chronological age alone.

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