Association of body mass index with risk of early-onset colorectal cancer: systematic review and meta-analysis

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Abstract

Objectives: Incidence of colorectal cancer (CRC) in young adults has been increasing in recent decades in many countries for still widely unclear reasons. Suspected candidates include increasing prevalence of overweight and obesity, but specific evidence on their role for early-onset CRC (EOCRC) is sparse. We conducted a systematic review and meta-analysis to summarize available evidence on the association of body mass index (BMI) with EOCRC.

Methods: We systematically searched PubMed, Embase and Web of Science up to February 2021 for studies that evaluated the association of BMI (prior to diagnosis but not near diagnosis) with CRC risk and reported specific results for EOCRC. Results from studies with similar BMI groupings were summarized in meta-analyses using random-effects models.

Results: Twelve studies were eligible and included. Results of six studies were pooled in meta-analyses which yielded a higher risk of EOCRC for overweight and obesity (BMI $\geq$25kg/m$^2$) compared to normal weight (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.19-1.68). An increasing risk with increasing BMI was observed, with much higher risk for obesity (OR 1.88, 95% CI 1.40-2.54) than for overweight (OR 1.32, 95% CI 1.19-1.47).

Conclusions: Obesity is a strong risk factor for EOCRC, and its increasing prevalence in younger generations is likely to substantially contribute to the increase in EOCRC. Efforts to limit the obesity epidemic in adolescents and younger adults may be crucial for reducing CRC incidence in future generations of adults.
Keywords: early-onset colorectal cancer; body mass index; young adult; adolescence
**Introduction**

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide, with an estimated 1.8 million new cases in 2018.\(^1\) Results from multiple studies indicate that despite overall decline or stabilization of CRC incidence due to screening programs among persons aged 50 years or older in many high-income countries, the incidence of CRC has been increasing in persons <50 years in several countries such as the United States, the United Kingdom, Canada, Australia, New Zealand, France, Denmark, Sweden, Slovenia, and Japan.\(^2\)-\(^8\) The largest increase in early-onset CRC (EOCRC) incidence in Europe was observed in 20-39 year old people,\(^5\) who are not covered by screening programs. These patterns suggest a role of an unfavorable shift in prevalence of risk factors that might account for the increasing EOCRC incidence. However, the specific contributions of various risk factors are yet to be clarified.\(^9\)-\(^12\)

Excess body fatness, most commonly measured by increased body mass index (BMI), is an established risk factor for CRC.\(^13\)-\(^16\) However, existing evidence is largely based on studies on CRC at all ages. In many developed countries, only approximately 5 and 10\% of CRC cases occur below ages 50 and 55,\(^5,6,8\) respectively, and the role of body fatness for such EOCRC remains to be established. This is of particular importance given the increasing prevalence of overweight and obesity among children and adolescents in many countries in recent decades.\(^17\)-\(^19\) In this study, we aimed to conduct a systematic review and meta-analysis of epidemiological studies on the association of BMI (prior to diagnosis but not near diagnosis) with EOCRC risk.
Methods and Materials

The reporting of this systematic review follows the PRISMA statement. 20

Literature search

We conducted a systematic literature search in the PubMed, Embase and Web of Science databases. Because there are few studies which specifically focused on the association of BMI with EOCRC risk, we initially searched for all original epidemiological studies on BMI and CRC risk, which might have contained our target population of younger adults and which might have reported specific results for this group. A broad-range search up to 28th February, 2021 based on the search strategy published in the World Cancer Research Fund International Systematic Literature Review 21 was applied without language restrictions. Details of the search strategy are provided in the Supplementary Methods. Briefly, we used diagnosed colon or rectal cancer as outcome, included measurement terms related to body fatness and anthropometry, excluded non-human studies and obviously irrelevant publication types in the search strategy. Reference lists of relevant articles were also hand-searched for potentially eligible publications.

Study Eligibility

A clear definition of EOCRC has not been widely established. Many studies use 50 years as the threshold age for defining CRC in younger population because it is the starting age for CRC screening recommended in many countries’ screening guidelines. 22 In this systematic review, we defined all first time diagnoses of CRC in persons aged 55 years or younger as
having occurred in younger adults, which allowed to accommodate more eligible studies. We also conducted sensitivity analyses with a cut-off age of EOCRC at 50 years for reference. Studies were eligible to be included in this systematic review if they were published as original articles and reported effect estimate(s) (e.g. relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs)) for the association of BMI with CRC risk (colon, rectal, or colorectal cancer). Studies were excluded if they included participants older than age 55 years only or did not report specific results for younger populations. Our search included studies using various measures of body fatness, such as BMI, waist circumference, hip circumference or waist to hip ratio. However, because results from multiple studies meeting the further inclusion criteria were identified for BMI only, further analyses focused on studies using this metric. BMI assessments were obtained at different times and some studies did not state BMI assessment time clearly, so it is hard to make strict criteria for the time of BMI assessment. However, we made utmost efforts to ensure to exclusively focus on BMI measures might that not be affected by tumor progression or cancer treatment, based on information provided in the studies’ “methods”, “discussion” and “limitation” sections. BMI measures obtained after or near diagnosis of CRC, including BMI measures from cross-sectional studies (such as screening colonoscopy studies) were not considered. Studies were excluded if they reported results for CRC combined with other outcomes only or if their study populations overlapped with otherwise included study populations (see Figure 1, Supplementary Table 1).

**Data extraction and quality assessment**

Two authors (HJL and DB) extracted data from eligible studies independently from each
other. Descriptive characteristics of eligible studies including study design, publication year, country, race, sample size, number of cases, sex, age at recruitment, timing of BMI assessment, follow-up time, and age at CRC diagnosis were extracted. In addition, we extracted results on the association of BMI categories with CRC risk, estimated with RRs, ORs, or HRs as well as their 95% confidence intervals (CI) and covariates that were adjusted for. If reported in the same study, associations of BMI with CRC risk among older adults were also extracted for comparison. Risk of study bias assessment methods based on the Newcastle-Ottawa Scale (NOS)\textsuperscript{23} in a domain-based approach was used to comprehensively assess the degree of risk of bias in each of the studies. Studies that were at low risk of bias in all domains were considered as low risk of bias studies; studies with at least one unclear risk of bias domain (all other domain being at low risk) were considered as unclear risk of bias studies; studies with one or more domains at high risk of bias were classified as high risk of bias studies. Low, unclear or high risk of bias were color coded as green, yellow and red, respectively.

**Data synthesis**

Different effect estimates for CRC risk (RRs, ORs, and HRs) were reported in the included studies. Because the absolute risk of EOCRC is low, the three different measures were treated as equivalent risk measures. We log-transformed the extracted RRs, ORs, and HRs and estimated their standard errors indirectly.\textsuperscript{24} Then, the RR, OR and, HR estimates were pooled in both fixed and random effects models. Results from random effects models were finally chosen due to the small number of included studies and high heterogeneity in some of them.\textsuperscript{25}
Because meta-analyses included only 6 studies, risk of publication bias was not formally assessed (Supplementary Figure 5). Studies not suitable for meta-analysis were synthesized in a systematic fashion using systematic review without meta-analysis (SWiM) methods.

We used the World Health Organization’s BMI classification and performed meta-analyses in two ways due to heterogeneous categorizations of BMI in the included studies: (i) overweight and obesity (BMI ≥25kg/m²) combined compared with normal weight and (ii) overweight or obesity separately compared with normal weight. All analyses were performed with the R statistical software (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.3) and the R “meta” package (version 4.8-4). All p-values are two-sided, and the level of significance was set at 0.05.

Results

Literature search

Figure 1 shows the flow chart of the literature search. The literature search identified 17,878 records in the initial electronic database searches. After exclusion of duplicates and title and abstract screening, 229 articles were eligible for full-text review. Of these, twelve studies were eligible and included in this systematic review. Of the twelve included studies, six studies with similar BMI groupings were included in the meta-analysis. Results of studies that could not be included in the meta-analysis are synthesized in the Supplementary Figure 1.
**Study characteristics**

**Table 1** summarizes the basic characteristics of the studies which included eight cohort studies\(^{32, 35-41}\) and four case-control studies,\(^{30, 31, 33, 34}\) with a total of 242,561 CRC cases (32,275 cases aged ≤55 years). The by far largest number of EOCRC cases (n=16,090) was contributed by the study of Elangovan et al.,\(^{41}\) who analyzed data from a large US medical claims database. Publication years ranged from 1998 to 2020. Studies were from high income countries (United States, Israel, Italy, Sweden, and Switzerland) and one upper-middle-income country (China). The largest studies, and those with the highest EOCRC case numbers, were from the USA (75% of EOCRC cases). Regarding gender, one study conducted among military personnel included men only\(^{35}\); two studies investigated women only\(^{38, 40}\) and the remaining studies examined both sexes. Three studies included colon cancer cases only\(^{30, 32, 33}\) and the remainder (nine studies) included both colon and rectal cancer cases. BMI assessment was obtained at different times: For cohort studies, three studies\(^{32, 38, 40}\) used BMI during follow-up examination / questionnaire visits, three\(^{35, 36, 38}\) used BMI at late adolescence (also at baseline) and three\(^{37, 39, 41}\) used the same commercial database whose search criteria ensured that BMI was recorded prior to a diagnosis of CRC. For case-control studies, one\(^{30}\) study used BMI 2 years prior to interview, two studies\(^{31, 34}\) used BMI at age 30 years and Hou et al\(^{33}\) used “usual BMI” as BMI exposure before diagnosis. Covariates adjusted for in the studies varied and included age, sex, use of aspirin, smoking, alcohol intake, physical activity and family history of CRC and so on. Risk of bias assessment is summarized in **Supplementary Table 2**. Overall, the risk of bias of the eligible studies was rated as “Low”, “Unclear” and “High” in 3, 3, and 6 studies, respectively, with
higher risks of bias in the case-control studies than in the cohort studies.

**BMI and risk of CRC among younger adults**

Associations of BMI with CRC risk among younger adults (≤55 years) are shown in **Table 2**. Overall, nine \(^{30,31,33,35-39,41}\) out of the twelve included studies found a positive association between overweight or obesity with increased EOCRC risk. All studies that used BMI at late adolescence also found a positive association with EOCRC risk. The strongest association with an OR of 2.88 (95% CI 2.74-3.04) was reported for obese compared to normal weight participants in the very large study by Syed et al\(^ {39}\) which was based on a claims database from the US. Among the studies showing results by sex, associations of obesity with EOCRC risk seemed to be diverse. For example, in the cohort study by Levi et al\(^ {36}\), the HR for obesity was 1.88 among men and 1.53 among women, but confidence intervals of sex-specific estimates were wide and overlapping. Similar patterns were reported in the case-control study by Russo et al\(^ {31}\) with odds ratios of 1.77 and 1.29 for the highest versus lowest quintile of BMI at age 30 among men and women, respectively. Conversely, Caan\(^ {30}\) and Hou\(^ {33}\) found stronger risk elevations of EOCRC for the upper quintiles of BMI among women. Elangovan et al\(^ {41}\) found a stronger association of obesity with EOCRC risk for women in in age group 20-39 and for men in age group 40-49.

**Figure 2** shows results of the meta-analysis of the association of overweight and obesity combined versus normal weight with EOCRC risk. Overweight and obesity (BMI ≥25kg/m\(^ 2\)) were associated with a 42% increased risk of CRC compared to normal weight (OR 1.42, 95% CI 1.19-1.68). Tests for heterogeneity indicated a low degree of heterogeneity (\(I^2=0\%,\)
p-heterogeneity=0.60) across the four studies. When taking 50 as the cut-off age for EOCRC, the OR was 1.38 (95% CI 1.08-1.76) (See Supplementary Figure 2).

Figure 3 and 4 show separate meta-analyses of the associations of overweight versus normal weight and obesity versus normal weight with EOCRC risk. A substantially stronger excess risk was observed for obesity (OR 1.88, 95% CI 1.40-2.54) than for overweight (OR 1.32, 95% CI 1.19-1.47). Sensitivity analyses with a cut-off age of 50 years showed very similar results (See Supplementary Figure 3 and 4).

Comparisons of associations of BMI with risk of CRC among younger and older adults

Among studies that reported and compared associations of BMI with CRC risk in younger (≤55 years) and older (>55 years) age,30-33,40,41 Caan et al30 found the association of BMI with CRC risk in men to be stronger in the younger population than in those aged 70-79 years, but associations were mostly comparable to those aged 55-69 years, except for the 4th and 5th quintiles of BMI where a higher risk of CRC was observed in the 55-69 years age group (Table 2). However, in the study by Russo et al31 the association of BMI with CRC risk was comparable in both younger and older populations. Moore et al32 found stronger associations of overweight and obesity with increased CRC risk in participants aged ≥55 than in younger participants. Hou et al33 found increased CRC risk for BMI levels in the 5th quintile in both younger (<55 years) men and women, while a similar association was only observed in older (≥55 years) men. Dash et al40 found no associations of BMI with CRC risk, neither in younger (<50 years) nor in older (≥50 years) participants. Elangovan et al41 found stronger associations of obesity with increased CRC risk in participants aged <50 years than in older
Discussion

The prevalence of overweight and obesity in adolescents and younger adults is high and increasing in many countries, especially in high-income countries.\textsuperscript{17-19} Because the incidence of CRC is also increasing in younger adults in many countries,\textsuperscript{2-8} investigating the potential role of BMI as a risk factor for EOCRC is highly relevant. We conducted a systematic review and meta-analysis to synthesize available evidence on the association of BMI with CRC risk in the younger population.

Results from our meta-analysis indicate that overweight and obese younger adults have approximately 32\% and 88\% higher risk of developing CRC than those with normal weight, respectively. These results are consistent and comparable in magnitude with those from studies that evaluated BMI and risk of CRC at all ages, the vast majority of which occurs at older ages.\textsuperscript{42-44} With respect to sex-specific associations, no consistent pattern regarding the differences in the association of BMI with EOCRC were observed. Previous studies had shown a stronger association of BMI with CRC risk for men than for women in the older population.\textsuperscript{15, 45, 46} In the study by Elangovan et al\textsuperscript{41} which was based on a large US medical claims database and included the largest number of EOCRC cases, CRC patients diagnosed in the 20–39 year age group were predominantly women. This may be due to younger women being more connected with healthcare system for cervical screening or pregnancies examinations, and thus having higher chances of earlier diagnosis than men.
Besides potential detection bias by sex and possible socioeconomic factors in studies using medical claims database, these studies also used partly overlapping study populations. Glover et al\(^{37}\), Syed et al\(^{39}\) and Elangovan et al\(^{41}\) used the same medical claims database (Explorys, IBM Watson Health). In addition, certain patients may have been counted multiple times if they received healthcare at multiple institutions that utilize the Explorys database\(^{37}\). Syed et al\(^{39}\) who reported the highest OR for obesity of 2.88 (95% CI 2.74-3.04) did not perform a true regression analysis due to an aggregated de-identified data set and did not exclude subjects with inflammatory bowel disease and family history of malignant neoplasm of digestive organs, which the other two studies did. Due to their specific limitations results from medical claims databases need to be interpreted with due caution.

All three cohort studies using BMI at late adolescence as BMI exposure found a positive association with EO CRC risk\(^{35,36,38}\). Adolescent BMI is strongly correlated with adult BMI\(^{47}\), and obesity in adolescence has been shown to be a risk factor of several cancers\(^{48,49}\), possibly by creating a pro-carcinogenic environment via various mechanisms such as changes in insulin and other hormones, insulin-like growth factors, and adipokine secretion. Cumulative exposure to an obesogenic environment might drive pro-cancerous pathophysiological processes\(^{50}\).

The results of sensitivity analyses with a cut-off age of 50 are very close to the results obtained with a cut-off age of 55, which indicates that the observed associations are robust against variations of definitions of EOCRC. However, results by Hou et al\(^{33}\) suggest that menopause status might affect the association of higher BMI and colon cancer risk. In their
study, higher BMI was associated with an increased risk of CRC in pre-menopausal women <55 years of age (OR for highest versus lowest quintile 1.9, 95% CI 1.1–4.9) and a decreased risk of CRC among post-menopausal women (OR 0.6, 95% CI 0.5–0.9). Future studies should pay attention to a potential role of menopausal status.

The cohort study by Dash et al\textsuperscript{40} was restricted to African-American women and did not find a significant association between BMI and CRC, neither in younger nor in older women. However, the cohort included a large proportion of women who reported a colonoscopy or sigmoidoscopy during the follow-up period from 1997 to 2011 which may have altered the natural history and subsequent risk of CRC to some extent. In other studies conducted in the US that included both women and men of different ethnicities including African-Americans, BMI was positively associated with EOCRC\textsuperscript{37,39,51}.

Several studies looked at the association of other indicators of obesity with EOCRC risk. Moore et al\textsuperscript{32} found that a larger waist circumference (≥99.1cm and 101.6cm for women and men, respectively) was independently associated with a two-fold increased risk of colon cancer and a particularly strong association was found among sedentary subjects (RR=4.4 for middle-aged adults; RR=3.0 for older adults). Caan et al\textsuperscript{30} found that after controlling for BMI, waist to hip ratio (WHR) was not associated with colon cancer in men but was associated with a slight risk increase in women. Russo et al\textsuperscript{31} found that WHR was positively associated with EOCRC risk independent of BMI (OR for ≥ 0.90 vs. ≤0.81 = 1.6; 95% CI 1.2–2.1). Further research is required to more precisely define the specific role of excessive weight and abdominal obesity for EOCRC risk among men and women.
Several studies that did not meet our inclusion criteria as they looked at different outcomes, such as combined outcomes of CRC and adenoma, also reported positive associations between body fatness and risk of colorectal neoplasms at young ages.\textsuperscript{52-54} For example, in the study by J. Y. Kim et al,\textsuperscript{53} overweight (BMI $\geq$25 kg/m\(^2\)) was associated with increased risk of advanced colorectal neoplasia (defined as an adenoma $\geq$10 mm in diameter, adenoma with any component of villous histology, high-grade dysplasia, or invasive cancer) in adults $<$ 50 years of age (OR 1.23, 95\%CI 1.03-1.47). N. H. Kim et al\textsuperscript{54} also found both overweight (BMI $\geq$25 kg/m\(^2\)) and abdominal obesity (waist circumference: males $\geq$90 cm, females $\geq$80 cm) to be independent risk factors for both colorectal neoplasia (defined as cancer or any adenoma) and advanced colorectal neoplasia in young adults aged 20-39 years. Juo et al\textsuperscript{55} found obesity (BMI $>$ 30 kg/m\(^2\)) to be associated with a reduction in age at diagnosis of CRC by 4.56 $\pm$ 0.18 years; an even stronger reduction in age at diagnosis (7.75 $\pm$ 0.30 years) was observed for morbid obesity (BMI $>$ 40 kg/m\(^2\)).

In contrast to the global increase in overweight and obesity, the prevalence of other lifestyle related risk factors of CRC, such as smoking and alcohol consumption, has decreased in many high-income countries in recent years.\textsuperscript{56, 57} This suggests that the increasing trend of overweight and obesity and their potential consequences, such as increasing prevalence of early diabetes,\textsuperscript{58} or factors associated with overweight and obesity, such as a sedentary lifestyle and specific nutritional habits might play a key role in the increasing EOCRC incidence rates. As overweight and obesity are associated with numerous other adverse health outcomes, efforts to curb the obesity epidemic will be paramount far beyond CRC prevention.
Our systematic review focused on relative risk estimates. For guiding clinical decision making, absolute estimates may even be more relevant. Although none of the included studies reported absolute risk estimates, the relative risk estimates could be combined with external data, such as cancer registry data, to derive absolute risk estimates, which might also be most relevant for modeling the impact of specific prevention strategies.

**Strengths and limitations**

To our knowledge, our study is the first to summarize the evidence for the association of BMI with EOCRC risk in a systematic review and meta-analysis. The study included a comprehensive literature search following the search strategy by the *World Cancer Research Fund*. Nevertheless, despite screening an overall very large number of studies assessing the association of overweight and obesity with CRC risk at all ages, only a relatively small number of studies that explicitly reported on subgroup analyses for EOCRC could be included. The diversity of study populations, study designs and measures of overweight of eligible studies are both a strength and a limitation of our analysis.

A number of important limitations require careful consideration. Diverse timing of BMI assessment, different inclusion and exclusion criteria of and different covariate adjustment limit comparability of results from the various studies. Due to diverse categorization of BMI, our meta-analysis had to be restricted to six studies that used comparable BMI categories. Also, given the limited number of studies and information available from these studies, we could not perform dose-response meta-analyses. The study by Levi et al\textsuperscript{36} whose study populations were mostly Jews contributed the largest weight in the “overweight vs. normal”
meta-analysis (Figure 3). This might affect generalizability of our estimates if the magnitude of the association of overweight with EOCRC risk differs by ethnicity.

Although we tried to minimize bias by strict inclusion and exclusion criteria, the findings may still be affected by a number of potential biases. For example, obese people could have been offered colonoscopy earlier due to their increased risk of CRC which might have led to earlier detection and apparently increased risk of EOCRC. Conversely, more frequent offers of colonoscopy to obese people due to their increased risk may have reduced such risk due to polypectomy which might have led to apparently reduced risk of EOCRC. Some studies have also reported less use of colonoscopy by obese people,\textsuperscript{59,60} making it hard to predict if, and to what extent such differences in colonoscopy use might have affected the results.

A most crucial issue for further research on BMI and EOCRC is the proper timing of BMI measurement. Studies with measurement of BMI at, shortly before or after CRC diagnosis are at very high risk of reverse causality, given that disease associated weight loss is well known for CRC patients. Ascertainment of BMI years before diagnosis in case-control studies and exclusion of early years of follow-up in cohort studies are paramount to minimize bias from reverse causality.

**Conclusions**

In this first systematic review and meta-analysis on the association of BMI and CRC risk in younger adults, both overweight and obesity were strongly associated with increased risk of CRC. The magnitude of the association of BMI with CRC risk for younger adults seems to be
comparable with the association previously reported for all ages or specifically for older adults, suggesting that higher BMI might also be an important risk factor for EOCRC. Along with the observation of a major increase in prevalence of overweight and obesity, our findings support suggestions of their major role in increasing incidence of EOCRC. Interventions aimed at preventing and enhancing management of obesity in adolescents and younger adults, which are crucial for the prevention of many other adverse health outcomes, might also play a key role for reducing CRC incidence in younger and older adults and should be a public health priority.
References


Table 1. Characteristics of the included studies

A. Cohort studies:

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Population selection</th>
<th>Country</th>
<th>Race</th>
<th>Sex</th>
<th>Age at diagnosis of EO CRC</th>
<th>N (Total (Cases))</th>
<th>Recruitment age (time)</th>
<th>BMI assessment time</th>
<th>Follow-up time</th>
<th>Cases confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, 2019[38]</td>
<td>Female nurses (NHSII cohort)</td>
<td>USA</td>
<td>mainly white women</td>
<td>F</td>
<td>45y [d]</td>
<td>85,256 (114)</td>
<td>25-42 y (1989- )</td>
<td>BMI at the last biennial questionnaire [b]; BMI at 18y [b]</td>
<td>13.9y, 1989-2011</td>
<td>CRC cases registered in medical records</td>
</tr>
<tr>
<td>First author, year</td>
<td>Population selection</td>
<td>Country</td>
<td>Race</td>
<td>Sex</td>
<td>Age at diagnosis of EOCRC</td>
<td>N_total (N_cases)</td>
<td>Recruitment age (time)</td>
<td>BMI assessment time</td>
<td>Follow-up time</td>
<td>Cases confirmation</td>
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<tr>
<td>Elangovan, 2020[41]</td>
<td>Population-based, commercial database (Explorys Inc)</td>
<td>USA</td>
<td>Caucasian, African American</td>
<td>All</td>
<td>&lt;50y</td>
<td>37,483,140 (162,150) ≤50y: 13,901,770 (16,090)</td>
<td>≥20 y 2015-2020</td>
<td>BMI before diagnosis (inferred from text)</td>
<td>5y, 2015-2020</td>
<td>CRC cases registered in Electronic health record data from 26 major integrated healthcare systems</td>
</tr>
</tbody>
</table>
## B. Case-control studies:

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Population selection</th>
<th>Country</th>
<th>Race</th>
<th>Sex</th>
<th>Age at diagnosis of EOCRC</th>
<th>N&lt;sub&gt;total&lt;/sub&gt; (n&lt;sub&gt;case&lt;/sub&gt;)</th>
<th>Recruitment age (time)</th>
<th>BMI assessment time</th>
<th>Cases confirmation</th>
<th>Matching of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caan, 1998&lt;sup&gt;[30]&lt;/sup&gt;</td>
<td>Hospital based</td>
<td>USA</td>
<td>91% white non-Hispanic</td>
<td>All</td>
<td>30-54y</td>
<td>4,383 (1,983) &lt;55y: 750 (334)</td>
<td>30-79y</td>
<td>BMI 2y prior to interview&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hospital cases</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Russo, 1998&lt;sup&gt;[31]&lt;/sup&gt;</td>
<td>Hospital based</td>
<td>Italy</td>
<td>Caucasian</td>
<td>All</td>
<td>≤55y</td>
<td>6,079 (1,943) &lt;50y: 1,337 (262)</td>
<td>19-74y</td>
<td>≤55y: BMI at 30y&lt;sup&gt;b&lt;/sup&gt; &gt;55y: BMI at 50y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>First histologically confirmed in hospital</td>
<td>Not matched</td>
</tr>
<tr>
<td>Hou, 2006&lt;sup&gt;[33]&lt;/sup&gt;</td>
<td>Population based</td>
<td>China</td>
<td>Chinese</td>
<td>All</td>
<td>&lt;55y</td>
<td>2,483 (931) &lt;55y: 853 (304)</td>
<td>30-74</td>
<td>Usual BMI</td>
<td>Histopathology (95%) and other methods (5%)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Rosato, 2013&lt;sup&gt;[34]&lt;/sup&gt;</td>
<td>Hospital based</td>
<td>Italy &amp; Switzerland</td>
<td>Caucasian</td>
<td>All</td>
<td>40&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤45y: 1,690 (329)</td>
<td>19-45y</td>
<td>BMI at age 30y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>First histologically confirmed in hospital</td>
<td>Age</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI: body mass index; BWHS: Black Women’s Health Study; EOCRC: early-onset colorectal cancer; NHSII: Nurses’ Health Study II  
<sup>a</sup> BMI calculated from quantitatively measured weight; <sup>b</sup> BMI calculated from self-reported weight; <sup>c</sup> median age; <sup>d</sup> mean age
Table 2. Association between BMI and risk of early-onset CRC (continues on next page)

<table>
<thead>
<tr>
<th>First author, year</th>
<th>BMI assessment</th>
<th>BMI ref. (kg/m²)</th>
<th>BMI (kg/m²)</th>
<th>Results</th>
<th>Comparison with older people</th>
<th>Covariates adjusted for</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore, 2004[32]</td>
<td>Mean of two BMI measures at biennial examination visits a</td>
<td>18.5-24.9</td>
<td>25.0-29.9:</td>
<td>30–54y: 1.30 (0.91-1.80) c</td>
<td>55–79y: 1.80 (1.20-2.60) c</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 30:</td>
<td>30–54y: 1.50 (0.92-2.50)</td>
<td>55–79y: 2.40 (1.50-3.90)</td>
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</tr>
<tr>
<td>Kantor, 2016[35]</td>
<td>Late adolescence BMI a</td>
<td>18.5-24.9</td>
<td>&lt;18.5:</td>
<td>0.86 (0.68-1.08) e</td>
<td>NA</td>
<td>√</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>25–27.5:</td>
<td>1.15 (0.85-1.55)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>27.6–29.9:</td>
<td>2.08 (1.40-3.07)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>≥ 30:</td>
<td>2.38 (1.51-3.76)</td>
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<tr>
<td>Levi, 2017[36]</td>
<td>Late adolescence BMI a</td>
<td>18.5-24.9</td>
<td>&lt;18.5:</td>
<td>All: 0.98 (0.88-1.10) e</td>
<td>NA</td>
<td>✓ ✓</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>25–29.9:</td>
<td>M:1.04 (0.91-1.19)</td>
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<tr>
<td></td>
<td></td>
<td>≥ 30:</td>
<td>F: 0.87 (0.71-1.08)</td>
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<tr>
<td>Glover, 2019[37]</td>
<td>BMI before diagnosis a</td>
<td>18.5-24.9</td>
<td>≥ 30:</td>
<td>1.82 (1.62-2.04) d</td>
<td>NA</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>o</td>
</tr>
<tr>
<td>Liu, 2019[38]</td>
<td>BMI at the last biennial questionnaire b</td>
<td>18.5-22.9</td>
<td>23.0-24.9:</td>
<td>1.33 (0.75-2.36) c</td>
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<td>✓ ✓ ✓ ✓ ✓</td>
<td>r,o,p, q,i</td>
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<td>25–29.9:</td>
<td>1.37 (0.81-2.30)</td>
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<tr>
<td></td>
<td></td>
<td>≥ 30:</td>
<td>1.93 (1.15-3.25)</td>
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<tr>
<td>Syed, 2019[39]</td>
<td>BMI before diagnosis a</td>
<td>18.5-24.9</td>
<td>≥ 30:</td>
<td>2.88 (2.74-3.04) d</td>
<td>NA</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>l,s</td>
</tr>
<tr>
<td>Dash, 2020[40]</td>
<td>BMI at the last biennial questionnaire b</td>
<td>18.5-24.9</td>
<td>25.0-29.9:</td>
<td>&lt; 50y: 1.46 (0.89-2.38) d</td>
<td>≥ 50y: 0.84 (0.61-1.16) d</td>
<td>✓ ✓ ✓ ✓ ✓</td>
<td>h, p, j, r, q</td>
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<tr>
<td></td>
<td></td>
<td>≥ 30:</td>
<td>&lt; 50y: 0.97 (0.55-1.71)</td>
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</table>

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<table>
<thead>
<tr>
<th>First author, year</th>
<th>BMI assessment</th>
<th>BMI ref. (kg/m²)</th>
<th>BMI (kg/m²)</th>
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<th>Comparison with older people</th>
<th>Covariates adjusted for</th>
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<tr>
<td></td>
<td>BMI before diagnosis</td>
<td>18.5-24.9</td>
<td>≥30:</td>
<td>RR/OR/HR (95% CI)</td>
<td>20-39: M:1.92 (1.85-1.99)</td>
<td>50-74: M:1.44 (1.41-1.48)</td>
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<td>F: 2.22 (1.84-2.43)</td>
<td>F: 1.71 (1.68-1.75)</td>
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<td>40-49: M:1.96 (1.87-2.06)</td>
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<td></td>
<td>F: 1.49 (1.41-1.57)</td>
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Age Sex ASP ALC SMK PA FH Other

Elangovan, 2020 [41]
Table 2. Association between BMI and risk of early-onset CRC (continued)

<table>
<thead>
<tr>
<th>First author, year</th>
<th>BMI assessment</th>
<th>BMI ref. (kg/m²)</th>
<th>Results</th>
<th>Comparison with older people</th>
<th>Covariates adjusted for</th>
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<tr>
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<td></td>
<td>BMI (kg/m²)</td>
<td>RR/OR/HR (95% CI)</td>
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<td>Age Sex ASP ALC SMK PA FH Other</td>
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<td>√</td>
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<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
<td>h, j</td>
<td></td>
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<tr>
<td>Caan, 1998[30]</td>
<td>BMI 2y prior to interview b</td>
<td>Q1f,1</td>
<td>30-54y:</td>
<td>M: 1.30 (0.65-2.59) d</td>
<td>M: 1.38 (0.88-2.16) d</td>
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<td></td>
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<td></td>
<td>55-69y:</td>
<td>M: 1.55 (0.79-3.07)</td>
<td>M: 1.49 (0.96-2.30)</td>
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<td>70-79y:</td>
<td>M: 1.67 (0.83-3.36)</td>
<td>M: 2.26 (1.50-3.41)</td>
</tr>
<tr>
<td>Russo, 1998[31]</td>
<td>≤55y: BMI at 30y b; &gt;55y: BMI at 50y b</td>
<td>Q1f,2</td>
<td>Q2: 20.4-22.5:</td>
<td>M: 1.63 (0.84-3.16)</td>
<td>M: 2.62 (1.73-3.95)</td>
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<td></td>
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<td>Q2: 22.5-24.3:</td>
<td>M: 1.33 (1.00-1.78)</td>
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<td>Q3: 22.6-23.9:</td>
<td>M: 1.35 (1.01-1.80)</td>
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<td></td>
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<td>Q4: 24-25.6:</td>
<td>M: 1.72 (1.30-2.28)</td>
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<td>Q4: 26-28.1:</td>
<td>M: 1.21 (0.91-1.60)</td>
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<td></td>
<td></td>
<td>Q5: &gt;25.6:</td>
<td>M: 1.77 (1.33-2.36)</td>
</tr>
<tr>
<td>Hou, 2006[33]</td>
<td>Usual BMI b</td>
<td>Q1f,3</td>
<td>&lt;55y:</td>
<td>M: 1.1 (0.7-2.5) d</td>
<td>M: 1.0 (0.6-1.5) d</td>
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<td></td>
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<td>Q2: 20.4-22.5:</td>
<td>M: 0.8 (0.4-1.5)</td>
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<td>Q3: 22.6-23.9:</td>
<td>M: 1.1 (0.9-2.9)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Q4: 24-25.6:</td>
<td>M: 1.6 (1.1-3.1)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Q5: &gt;25.6:</td>
<td>M: 1.6 (1.1-3.1)</td>
</tr>
<tr>
<td>First author, year</td>
<td>BMI assessment</td>
<td>BMI ref. (kg/m²)</td>
<td>BMI (kg/m²)</td>
<td>Results RR/OR/HR (95% CI)</td>
<td>Comparison with older people</td>
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<tr>
<td>Rosato, 2013&lt;sup&gt;114&lt;/sup&gt;</td>
<td>BMI at age 30y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;20</td>
<td>20-24.9:</td>
<td>1.15 (0.65-2.02)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥25:</td>
<td></td>
<td>0.91 (0.48-1.73)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI: Body Mass Index; CI: Confidence interval; CRC: colorectal cancer; NA, Not applicable.<br><sup>a</sup> BMI calculated from quantitatively measured weight. <sup>b</sup> BMI calculated from self-reported weight. <sup>c</sup> Relative risk ratio (RR). <sup>d</sup> Odds ratio (OR). <sup>e</sup> Hazard ratio (HR).<br><sup>f_1</sup> Q1 means Quintile 1, data not shown in original text. <sup>f_2</sup> Q1 means Quintile 1. Cases ≤55y, Q1<20.4 kg/m². Cases >55y, Q1<22.5 kg/m². Q1<19.2, Q2 19.2–20.3, Q3 20.4–21.3, Q4 21.4–22.8 and Q5 > 22.8 for men; and Q1 < 19.0, Q2 19.1–20.5, Q3 20.6–21.9, Q4 22.0–23.6 and Q5 > 23.6 (kg/m²) for women.<br><sup>g</sup> ASP: use of aspirin; ALC: alcohol intake; SMK: smoking; PA: physical activity; FH: family history; Others (h=educational level, i=year of interview or recruitment, j=caloric intake, k=country of origin, l=socioeconomic status, m=perception about health status, n= erythrocyte sedimentation rate, o=diabetes, p=uptake of colonoscopy, q=menopausal status and hormonal use, r=dietary fiber, s=symptoms and comorbidities, t=red meat intake, u=the number of pregnancies and years of menstruation, v= hypertension or hyperlipidemia).
Figure legends

**Figure 1.** Flow chart showing selection of eligible studies
  
  a Outcomes combined colorectal cancer and polys/neoplasia/adenomas together
  
  b See Supplementary Table 1

**Figure 2.** Association of BMI (overweight and obese vs. normal weight) with colorectal cancer risk in younger adults (<55 years)

Abbreviations: BMI: Body Mass Index. CI: Confidence interval. OR: Odds Ratio.
Note: BMI Categories: normal weight, 18.5-24.9 kg/m² (reference); overweight and obese, ≥25 kg/m².

**Figure 3.** Association of BMI with colorectal cancer risk in younger adults (<55 years): Overweight vs. normal weight.

Abbreviations: BMI: Body Mass Index. CI: Confidence interval. OR: Odds Ratio.
Note: BMI Categories: normal weight, 18.5-24.9 kg/m² (reference); overweight, 25-29.9 kg/m².

**Figure 4.** Association of BMI with colorectal cancer risk in younger adults (<55 years): Obese vs. normal weight.

Abbreviations: BMI: Body Mass Index. CI: Confidence interval. OR: Odds Ratio.
Note: BMI Categories: normal weight, 18.5-24.9 kg/m² (reference); obese ≥30 kg/m².

Legends of Supplementary Tables and Figures

**Supplementary Table 1.** Excluded studies with reasons for exclusions.

**Supplementary Table 2.**

**Supplementary Table 2A.** Results of risk of bias assessment for cohort studies

**Supplementary Table 2B.** Results of risk of bias assessment for case-control studies

**Supplementary Methods.** Search strategy used in PubMed, Emerge and Web of Science (search period up to 28th February 2021, no language restriction)

**Supplementary Figures:**

**Supplementary Figure 1.** Synthesis of results of studies that could not be included in meta-analysis.

Abbreviations: BMI: body mass index; ref: reference category of BMI; CI: confidence interval; Q: quintile; M: male; F: female

**Supplementary Figure 2.** Association of BMI (overweight and obese vs. normal weight) with colorectal cancer risk in younger adults (<50 years)

Abbreviations: BMI: Body Mass Index. CI: Confidence interval. OR: Odds Ratio.
Note: BMI Categories: normal weight, 18.5-24.9 kg/m² (reference); overweight and obese, ≥25 kg/m².
Supplementary Figure 3. Association of BMI with colorectal cancer risk in younger adults (<50 years): Overweight vs. normal weight
Abbreviations: BMI: Body Mass Index. CI: Confidence interval. OR: Odds Ratio.
Note: BMI Categories: normal weight, 18.5-24.9 kg/m^2 (reference); overweight, 25-29.9 kg/m^2.

Supplementary Figure 4. Association of BMI with colorectal cancer risk in younger adults (<50 years): Obese vs. normal weight
Abbreviations: BMI: Body Mass Index. CI: Confidence interval. OR: Odds Ratio.
Note: BMI Categories: normal weight, 18.5-24.9 kg/m^2 (reference); obese ≥30 kg/m^2.

Supplementary Figure 5. Funnel plots for evaluating potential publication bias