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Adolescent body mass index and erythrocyte sedimentation rate in relation to colorectal cancer risk

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Abstract

Objective—Adult obesity and inflammation have been associated with risk of colorectal cancer (CRC); however, less is known about how adolescent body mass index (BMI) and inflammation, as measured by erythrocyte sedimentation rate (ESR), relate to CRC risk. We sought to evaluate these associations in a cohort of 239,658 Swedish men who underwent compulsory military enlistment examinations in late adolescence (ages 16–20 years).

Design—At the time of the conscription assessment (1969–1976), height and weight were measured and erythrocyte sedimentation rate was assayed. By linkage to the national cancer registry, these conscripts were followed for CRC through January 1, 2010. Over an average of 35 years of follow-up, 885 cases of CRC occurred, including 501 colon cancers and 384 rectal cancers. Cox regression was used to estimate adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs).

Results—Compared with normal weight (BMI: 18.5–<25 kg/m²) in late adolescence, upper overweight (BMI: 27.5–<30 kg/m²) was associated with a 2.08-fold higher risk of CRC (95% CI: 1.40, 3.07) and obesity (BMI: 30+ kg/m²) was associated with a 2.38-fold higher risk of CRC (95% CI: 1.51, 3.76) (p-trend:<0.001). Male adolescents with ESR(15+ mm/hr) had a 63% higher risk of CRC (HR: 1.63; 95% CI: 1.08, 2.45) than those with low ESR (<10 mm/hr) (p-trend: 0.006). Associations did not significantly differ by anatomic site.

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COMPETING INTERESTS:

Study authors have no conflict of interest to declare.

Conclusion—Late-adolescent BMI and inflammation, as measured by ESR, may be independently associated with future CRC risk. Further research is needed to better understand how early-life exposures relate to CRC.

Keywords

adolescent; erythrocyte sedimentation rate; body mass index; colorectal neoplasms; inflammation

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer among men worldwide,¹ and yet little is understood about how exposures over the life course relate to the aetiology of this disease. To date, epidemiologic research has largely focused on elucidating the role of adult exposures in the development of CRC, with few studies addressing the role of earlier-life exposures. Late adolescence marks the transition from childhood to adulthood and is a period of accelerated growth, especially among men; thus, this period may represent a critical window for exposure susceptibility among men. If adolescence does offer a critical period, measurement error with respect to the timing of exposure assessment may attenuate associations, especially with regard to risk factors that may change over the life-course, such as body mass index (BMI) and inflammation.

There is convincing evidence that adult BMI is positively associated with CRC risk,² with a recent meta-analysis reporting that each 5 kg/m² increase in adult BMI is associated with an 25% increase in risk of CRC among men, an association which is significantly stronger than that observed among women.³ Despite a large body of evidence linking adult BMI to CRC risk, comparatively few studies have evaluated the association between adolescent/young-adult BMI and CRC.^{4–16} While the literature suggests a positive association, these studies largely relied on participant recall of earlier-life BMI or have been small and unable to disaggregate overweight and obese adolescents. There are a number of putative mechanisms by which BMI may affect the risk of CRC, including effects on insulin, leptin, steroid hormones, and inflammation.⁶¹⁷¹⁸

Chronic inflammation in adulthood has also been implicated in the aetiology of CRC,¹⁹²⁰ with prospective studies observing significant associations between CRC and inflammatory biomarkers, such as C-reactive protein (CRP)²¹ and prostaglandin E2-metabolite (PGE-M).²² Further, persons with inflammatory bowel disease (IBD) experience increased risk of CRC²³²⁴ and use of the non-steroidal anti-inflammatory drug aspirin has been shown to reduce CRC risk and mortality.²⁵ Chronic inflammation is hypothesized to increase the risk of CRC through a number of mechanisms, including effects on oxidative stress and subsequent DNA damage, as well as through effects on cellular proliferation and apoptosis.⁶¹⁹²⁶²⁷ Although some evidence points to the involvement of inflammation early in colorectal carcinogenesis,^{1928–30} no prior studies have evaluated the association between markers of systemic inflammation in adolescence and risk of CRC.

It is important that we understand the role of exposures in childhood and adolescence in the development of CRC, both to enhance our understanding of the aetiology of this disease and to shed light on potential points of intervention. We therefore sought to evaluate the

associations between late-adolescent BMI and inflammation, assessed by erythrocyte sedimentation rate (ESR), and risk of CRC in a cohort of Swedish men.

MATERIALS AND METHODS

Study Population

Our study population was drawn from a cohort of men who underwent a compulsory conscription assessment for the Swedish military between 1969 and 1976, a time during which conscription was mandatory for male Swedish citizens. Conscription took place in late adolescence, at a mean age of 18 years. Prior to conscription, men completed extensive standardized physical and psychological examinations. At this time, height and weight were measured, blood was drawn, and information was recorded in the Swedish Military Conscription Register. Only men with severe disability or chronic disease were exempt from conscription, leaving more than 96% of the male population eligible.

Due to errors in personal identification number, female sex, or uncertain vital status at the end of study, 2,564 persons included in the Swedish Military Conscription Register were excluded from our study. As has been done previously in this cohort,^{31–33} 225 men were further excluded due to improbable measures at conscription assessment, including: height less than 144 cm (n=39), BMI below 15 (n=134), weight above 178 kg (n=9), systolic blood pressure below 50 or above 230 mmHg (n=33), and diastolic blood pressure below 30 or above 135 mmHg (n=12). Of the remaining 281,409 men, we further restricted this study to 249,488 men conscribed in late-adolescence (known age at conscription: 16–20, inclusive), and then we excluded men with any of the following reported or noted at conscription: a history of IBD (ulcerative colitis or Crohn's disease; n=246), an ill-defined health problem (n=22), extreme weakness (n=137), or history of CRC (n=3). After these exclusions, men were excluded if missing exposures of interest, BMI (n=4,144) or ESR (n=4,905), and/or any covariates (n=9,321), resulting in a final sample size of 239,658 men born between 1952 and 1956.

Exposure Assessment

Height and weight were measured by trained personnel at the time of the conscription examination, from which BMI (kg/m^2) was calculated. This variable was categorized as follows: underweight (BMI:<18.5; ranging from BMI:15-<18.5), normal weight (BMI:18.5-<25), lower overweight (BMI:25-<27.5), upper overweight (BMI:27.5-<30), and obese (BMI:30+; ranging from 30-<55). The traditional overweight group (BMI:25-<30) was divided into lower and upper overweight, as has been done elsewhere,^{34,35} given concern about potential heterogeneity within this group.

Our measure of inflammation, ESR, is a non-specific marker of inflammation,^{36,37} which rises and falls slowly, and is therefore suitable for tracking inflammation among patients with chronic conditions.^{38,39} Assessed using venous blood samples collected at examination, ESR corresponds to the distance that a column of anti-coagulated blood falls over a one-hour period, and was measured using the Westergren method.³⁶ As has been done previously,³¹ ESR was categorized into the following groups: low inflammation (ESR:<10 mm/hr;

ranging from 1–10 mm/hr), moderate inflammation (ESR: >10 – <15 mm/hr), and high inflammation (ESR: ≥ 15 mm/hr; ranging from 15–89 mm/hr), with the threshold between “moderate” and “high” ESR groups corresponding to the clinical cut-point for normal ESR among men in this age group.³⁷³⁹ As described in the Statistical Analysis section below, analyses involving ESR were adjusted for erythrocyte volume fraction (EVF), as is standard in analyses of ESR.

Outcome Assessment

Participants were followed for incident, malignant CRC from the time of conscription examination until January 1, 2010. CRC diagnoses were identified by linkage to the Swedish Cancer Registry using international classification of disease (ICD)-7 codes 153 and 154 (n=885 CRC cases). This national cancer registry, established in 1958, has been estimated to have a completeness exceeding 95–97% for common cancer types.⁴⁰⁴¹ In secondary analyses, we further restricted our outcome definition to known adenocarcinomas of the colorectum (n=797), including 451 and 346 adenocarcinomas of the colon and rectum, respectively.

Statistical Analysis

Cox proportional hazards regression models were used to evaluate the associations of interest, with calendar year the time metric of analysis. The proportional hazards assumption of the Cox models was checked using the Schoenfeld residual method, with no evidence of violation found. ESR and BMI were modeled using categorical variables; p-values for linear trend were calculated by alternatively modeling the exposures as single grouped-linear variables. Participants were followed until the earliest of the following: date of CRC diagnosis, date of death, date of emigration, or January 1, 2010. Date of emigration and vital status were determined using the Total Population Register.

Covariates were selected from available registry data on the basis of potential association with both exposure and outcome. Multivariable models were adjusted for the following covariates: age at conscription, EVF, household crowding health status; systolic blood pressure, diastolic blood pressure, muscular strength, physical working capacity, and cognitive function. Analyses of BMI were further adjusted for ESR, while analyses of ESR were further adjusted for BMI. Childhood household crowding was calculated by dividing the number of persons living in a given household at the time of the 1960 Swedish census by the number of habitable rooms. Conscripts' health status was determined by a detailed medical assessment, at which time physicians collected detailed medical history and classified men by the severity of health problem(s), with the most common diagnoses including: personality disorder, cardiovascular, and respiratory diseases. Resting recumbent blood pressure was measured using a sphygmomanometer. Participants' muscular strength was evaluated by performance on three isometric muscle strength tests and physical working capacity was assessed using a cycle ergonomic test. Lastly, a single cognitive function score was calculated from a written assessment testing conscripts' aptitude in the following areas: linguistic understanding, spatial recognition, general knowledge, and ability to follow mechanical instruction.

Associations were also examined for tumour subsite-specific differences. When examining the association between ESR or BMI and cancers of either the colon or rectum, Cox regression was used and cancers of the subsite not under study were censored at the date of diagnosis. A case-only logistic model was used to assess the statistical significance of subsite-specific differences.

Given the possibility that some men could have had subclinical IBD at conscription, we conducted a sensitivity analysis in which we further excluded men receiving inpatient care for ulcerative colitis or Crohn's disease in the 10-year period after baseline. In this sensitivity analysis, we delayed the start of follow-up until the end of this 10-year period, leaving 234,555 men for analysis.

All analyses were conducted in Stata, version 12.0 (College Station, TX). This study has been deemed exempt by the Regional Ethical Review Board in Uppsala, Sweden, and the Institutional Review Board at the Harvard School of Public Health.

RESULTS

This study included 239,658 men followed for a total of 8,469,469 million person-years. Over an average of 35 years of follow-up, 885 diagnoses of CRC occurred, including 501 diagnoses of colon cancer and 384 diagnoses of rectal cancer. The mean age at conscription was 18.5 years, with most men assessed for conscription at ages 18 (49.1%) or 19 (46.5%) years. As noted in Table 1, this cohort was largely healthy at conscription, with most reporting either no medical issues (44.3%) or no serious medical problem (39.7%). The mean systolic blood pressure was 127.6 mmHg and the mean diastolic blood pressure was 71.7 mmHg. Nearly 12% of the study population was underweight at the time of conscription, while almost 81% were normal weight; 5% fell into the lower overweight group, 1.5% fell into the upper overweight group, and nearly 1% were obese. Most (96.3%) men in the cohort had a normal ESR at conscription, while 2.0% had a moderate ESR and 1.7% had a high ESR. In this population, BMI was associated with ESR (Supplementary Table 1): at the mean EVF in the population (46.4%), 4.1% of underweight individuals were classified as having moderate/high inflammation (ESR 10+), as compared to 3.6% of normal weight individuals, 4.0% of lower overweight individuals, 6.0% of upper overweight individuals, and 7.7% of obese individuals. Other factors were less strongly associated with ESR, as shown in Supplementary Table 1.

In fully-adjusted models (Model 2, Table 2), we observed that underweight men experienced a non-statistically significant 14% lower risk of CRC than normal weight men (HR:0.86; 95% CI:0.68–1.08), while lower overweight men experienced a non-statistically significant 1.15-fold higher risk (HR:1.15; 95% CI:0.85–1.55), upper overweight men experienced a statistically significant 2.08-fold higher risk (HR:2.08; 95% CI:1.40–3.07), and obese men experienced a statistically significant 2.38-fold higher risk (HR:2.38; 95% CI:1.51–3.76) (p-trend:<0.001). In a sensitivity analysis dividing the normal weight group into lower normal weight (BMI 18.5–<22) and upper normal weight (BMI 22–<25), with lower normal weight as the reference, a similar trend was observed: underweight (HR:0.88; 95% CI:0.70–1.11), upper normal weight (HR:1.16; 95% CI:0.98–1.37), lower overweight (HR:1.22; 95% CI:

0.90–1.65), upper overweight (HR:2.21; 95% CI:1.48–3.28), and obese (HR:2.54; 95% CI:1.60–4.63) (p-trend:<0.001). Furthermore, results between BMI and CRC were comparable after delaying the start of follow-up by 10-years and excluding men receiving inpatient care for IBD during this period (Model 3, Table 2). The association between BMI and CRC did not change when models were alternatively not adjusted for ESR and EVF (results not shown). Results for BMI did not differ by subsite (p-difference:0.29), with the trend statistically significant for cancers of both the colon (p-trend:<0.001) and rectum (p-trend:0.047).

With full multivariable adjustment (Model 2, Table 2), moderate ESR (ESR 10–<15) was associated with a non-significant 40% increased risk of CRC compared to normal ESR (ESR <10) (HR:1.40; 95% CI:0.93–2.10), while high ESR (ESR 15+) was associated with a significant 63% increased risk of CRC (HR:1.63; 95% CI:1.08–2.45) (p-trend:0.006). Results attenuated slightly upon exclusion of the first 10 years of follow-up and persons seeking inpatient care for IBD in this time (Model 3, Table 2): in this sensitivity analysis, moderate ESR was associated with non-significant 38% higher risk of CRC (HR:1.38; 95% CI:0.91–2.10) and high ESR was associated with non-significant 48% higher risk of CRC (HR:1.48; 95% CI:0.95–2.29), and the trend remained statistically significant (p-trend:0.03). To address potential concern that the association between ESR and CRC could reflect illness present at the time of baseline, we restricted our models to 106,113 men with no documented illness at conscription, and the effect estimates remained unchanged (albeit with less statistical power): men with moderate ESR experienced a non-significant 50% higher risk of CRC than men with low ESR (HR:1.50; 95% CI:0.80–2.82), while men with high a non-significant ESR experienced 68% higher risk of CRC (HR:1.68; 95% CI:0.86–3.28) (p-trend:0.056). When examining inflammation associations by subsite, we observed a statistically significant association between ESR and colon cancer (p-trend:0.01), but the association between ESR and rectal cancer was not significant (p-trend:0.23); the association did not significantly differ by subsite (p-difference:0.49).

In sensitivity analyses in which the outcome was alternatively defined as colorectal adenocarcinoma, the association remained statistically significant for both BMI (HR obese vs normal weight:2.70; 95% CI:1.70–4.27; p-trend:<0.001) and ESR (HR high vs low:1.72; 95% CI:1.13–2.62; p-trend:0.005).

DISCUSSION

In this cohort of Swedish men, late-adolescent BMI and inflammation, as measured by ESR, were associated with risk of subsequent CRC, suggesting that BMI and inflammation in adolescence may play a role in the development of CRC. The BMI-CRC association (evident for both upper overweight and obese adolescents) was independent of ESR, indicating that adolescent BMI may affect CRC risk through mechanisms other than inflammation, as measured by ESR.

Our results noting a positive association between adolescent/early-adult BMI and CRC align with much^{4–79–1214–16} but not all⁸¹³ of the literature. However, most prior studies have relied on self-reported recall of early life weight^{6714–16} or have been limited by small

numbers of events.⁴⁵⁸⁹¹²¹³ To date, few large studies have addressed this question using measured adolescent BMI, and these studies indicate a strong association between adolescent BMI and CRC.¹⁰¹¹ In a study of Israeli male conscripts followed for CRC for approximately 18 years, men with BMI in the top quintile experienced 69% higher risk of colon cancer than men in the lowest quintile (HR:1.69; 95% CI:1.24–2.29).¹¹ As was the case in our study, few Israeli conscripts were overweight or obese at baseline; consequently, the top quintile in this study was defined by a BMI approximately $>24 \text{ kg/m}^2$, mixing some normal weight men with overweight and obese individuals. When disaggregating the overweight/obese group in our study, we observed a clear gradient, with highest risk of CRC among upper overweight and obese adolescents. Also, it should be considered that in studies such as our own and the Israeli study, in which upper overweight and obesity were uncommon at the time of exposure assessment, it is plausible that high BMI represents something different than is represented in populations in which this exposure is more common, potentially affecting the generalizability of these results.

Furthermore, although men in our study were followed for an average of 35 years, they were not followed into late adulthood (average age at end of follow-up=53.9), and the aetiology of these early-to-mid-life CRC diagnoses may differ from those occurring later in adulthood. In fact, the strong association observed between adolescent obesity and early-to-mid-life CRC, coupled with the increasing prevalence of adolescent obesity,⁴² may shed light on the increase in CRC incidence among young adults in the United States.⁴³

Our observation of a positive association between adolescent inflammation and CRC risk cannot be compared directly with other studies, as our study is the first to report on this association among healthy individuals. We can, however, place our results in the context of the vast literature on adult inflammation and CRC, which also suggests a positive association between inflammation and CRC risk. A recent meta-analysis of the systemic inflammatory biomarker CRP in relation to CRC risk concluded that a one-unit change in the natural logarithm of CRP was associated with a significant 12% increase in CRC risk.²¹ A strong dose-response relationship has also been observed between PGE-M and CRC, with Chinese women in the upper PGE-M quartile experiencing a 5.6-fold higher risk of CRC than women in the lowest quartile (95% CI:2.4–13.5).²² Candidate gene studies further support the hypothesis that inflammation may be important to the development of CRC.^{44–47} The putative role of inflammation in colorectal carcinogenesis is further corroborated by the fact that aspirin, an anti-inflammatory, has been shown to reduce CRC risk and mortality.²⁵ While no other studies have directly addressed the association between early-life inflammation and CRC risk, evidence supports the role of inflammation early in carcinogenesis. A study using data from the National Health and Nutrition Examination Survey (NHANES) observed a strong dose-response relationship between CRP levels and CRC mortality approximately 14 years later,²⁸ suggesting that inflammation may act early in colorectal carcinogenesis. Moreover, prospective studies have linked high levels of PGE-M to risk of clinically-meaningful adenoma.²⁹³⁰ Nevertheless, while there is much evidence to support the association between inflammation in adults and CRC, not all studies are in agreement.^{2148–50} Some evidence suggests that the apparent association between adult CRP and CRC is driven by subclinical CRC present at blood draw.⁵⁰ Furthermore, a recent study observed no association between circulating CRP and colonic inflammation, as measured on

colonic biopsy,⁴⁸ and study authors suggested that observed associations between CRP and CRC may be attributable to residual confounding by obesity.

It should also be considered that study-specific conclusions may vary by inflammatory biomarker, and ESR may not generalize to other inflammatory biomarkers. Most studies addressing the association between adult inflammation and CRC risk have defined inflammation using circulating concentrations of CRP, interleukin-6 (IL-6), tumor necrosis factor receptors, or by urinary concentration of PGE-M.²¹²²²⁸⁵¹ Little is known about how ESR relates to CRC risk among healthy individuals, despite the utility of ESR as a measure of inflammation, its use in tracking inflammation among IBD patients, and its prospective association with CRC risk among IBD patients.²³²⁴³⁷³⁸

Given that IBD is associated with both ESR and CRC, it is possible that our observed association reflects subclinical IBD present at the time of conscription assessment. To address this concern, we excluded men known to be diagnosed with IBD before conscription assessment, and conducted a sensitivity analysis further excluding those seeking inpatient care for IBD in the first 10 years of follow-up. Although our results for the ESR-CRC association attenuated somewhat in this sensitivity analysis, the trend remained significant, indicating that even if some of the association is accounted for by subclinical IBD at conscription, it does not appear to account for the entirety of the association. Further, the number of IBD diagnoses identified over this 10-year period (n=465) is consistent with the expected number over this period based on an incidence rate of 18 diagnoses/100,000 person-years.⁵² Even so, we cannot exclude the possibility that subclinical IBD may be influencing observed associations between ESR and CRC.

We observed that the association with BMI did not statistically differ by subsite. Specifically, obese adolescents experienced substantially increased risk of both colon and rectal cancer, and upper overweight individuals experienced significantly increased risk of colon cancer only. Like our study, some meta-analyses suggest that the association between BMI and CRC is statistically significant for both subsites,⁵³⁵⁴ especially among men.⁵⁴ However, others report that the association between BMI and CRC may be stronger for cancers of the colon than the rectum.³¹¹ ESR was statistically significant with cancers of the colon, but not with rectal cancers, although the association did not statistically differ by subsite. This may be expected, given that the association between CRP and CRC appears to be stronger for cancers of the colon than rectum.²¹ It should be considered, though, that power to detect associations within a given subsite was limited by the small number of cases occurring in the highest levels of exposure, especially for rectal cancer.

To further address biologic heterogeneity within CRC, we conducted a sensitivity analysis with the outcome alternatively defined by colorectal adenocarcinoma. Results from this analysis were not appreciably different from our overall analysis; however, given small numbers of non-adenocarcinomas, we were unable to formally evaluate differences by histologic type. Even so, it is still possible that there are histologic, and therefore etiologic, differences between the cases in this study and those observed in older adult populations.

While it is possible that our results reflect an association between adolescent BMI and inflammation and CRC, alternative explanations must be considered. Importantly, we were unable to account for later-life measures of BMI and inflammation, and it is possible that our results reflect an association between older adult exposure and CRC risk. We are therefore unable to comment on whether the strong association between adolescent BMI and colorectal cancer could be mitigated by weight loss during adulthood. It is also possible that adolescent BMI is reflecting childhood energy intake, as severe energy restriction in early life has been associated with lower CRC risk,⁵⁵ perhaps via persistent epigenetic changes.⁵⁶ Lastly, BMI and inflammation in adolescence are likely associated with exposure in both childhood and adulthood, and it is plausible that it is the total duration of exposure to high BMI or inflammation which confers increased risk, rather than exposure at a specific period in the life course. Further, BMI may not be the ideal measure of adiposity in this period of growth⁵⁷ and additional studies are needed to address how other measures of adolescent adiposity relate to CRC risk.

It is also possible that our results reflect known CRC risk factors such as smoking. However, as ESR is not strongly associated with smoking,⁵⁸ it is unlikely that smoking is acting as a strong confounder. Further, the association between smoking and CRC (especially colon cancer) is relatively weak,⁵⁹ and is unlikely to explain the strong associations observed. It is also possible that BMI and/or ESR may be marking unmeasured dietary factors, as we are unable to address the role of diet in this large registry-based study. Lastly, results should not be generalized to women, especially since the associations between BMI and inflammation and CRC appear to be weaker among women than men.³⁶²¹

Even with these limitations, it is important to recognize the unique strengths of this study. In this large population-based national cohort of Swedish men, we were able to evaluate the association between adolescent exposures and CRC risk, leveraging data from existing national registry data. This data source has enabled the evaluation of the association between adolescent inflammation and CRC risk, a question not been previously evaluated. Further, adolescent BMI was measured and not subject to measurement error in recall. Lastly, we were able to adjust analyses of BMI for ESR, with results suggesting that the association between adolescent BMI and CRC may be independent of ESR, and may be instead mediated by other posited factors, such as insulin, leptin, or steroid hormones.⁶¹⁷¹⁸ However, it is also possible that adolescent BMI may affect CRC through an inflammatory pathway not reflected by ESR.

In conclusion, our study suggests a graded association between adolescent inflammation, as measured by ESR, and CRC, and an even stronger association between adolescent BMI and CRC risk. These results suggest that BMI and inflammation, as measured by ESR, in early life may be important to the development of CRC. With additional follow-up, and therefore statistical power, future studies may address how adolescent inflammation and BMI interact to affect CRC risk, and further work may seek to address how these factors, independently and jointly, relate to CRC mortality. Further research is needed to better disentangle BMI and inflammation from associated exposures, and similarly, from exposure at other points in the life-course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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SUMMARY BOX**What is already known about this subject?**

- Obesity and chronic inflammation have been implicated in the aetiology of colorectal cancer.
- While much research has been conducted on adult BMI and inflammation, relatively few studies have evaluated the role of adolescent BMI in CRC and none have evaluated the association between adolescent inflammation and risk of CRC.

What are the new findings?

- In this cohort of Swedish men, as compared to normal weight adolescents (BMI 18.5-<25), upper overweight adolescents (BMI 27.5-<30) experienced a 2.08-fold higher risk of CRC, while obese adolescents (BMI 30+) experienced a 2.38-fold higher risk of CRC.
- Late-adolescent inflammation, as measured by erythrocyte sedimentation rate, was associated with increased risk of colorectal cancer: adolescents with high erythrocyte sedimentation rate experienced a 63% higher risk of colorectal cancer than adolescents with normal erythrocyte sedimentation rate.

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

- Future work is needed to better understand the role of life-course inflammation and BMI in the development of CRC.
- Elucidating the role of life-course exposures in colorectal cancer aetiology can improve our understanding of this disease, and can inform preventive strategies.

Table 1

Characteristics of the Study Population and Colorectal Cancer Cases

	Total Cohort N=239,658 N (%)	Colorectal Cancer Cases N=885 N (%)
Age at Conscription (years)		
Mean $\pm$ SD	18.5 $\pm$ 0.58	18.6 $\pm$ 0.59
Household Crowding (Persons per Room)		
<1	15,361 (6.41)	58 (6.55)
1	30,361 (12.7)	109 (12.3)
>1 –2	141,945 (59.2)	526 (59.4)
>2–3	36,735 (15.3)	130 (14.7)
>3	15,256 (6.37)	62 (7.01)
Disease at Conscription		
No diagnosis	106,113 (44.3)	384 (43.4)
No serious health problem	95,218 (39.7)	350 (39.6)
Fairly significant health problem	18,042 (7.53)	67 (7.57)
Significant health problem	20,285 (8.46)	84 (9.49)
Systolic Blood Pressure		
Mean $\pm$ SD	127.6 $\pm$ 11.1	127.0 $\pm$ 11.4
Diastolic Blood Pressure		
Mean $\pm$ SD	71.7 $\pm$ 8.6	72.0 $\pm$ 8.7
Muscular Strength		
Weakest (1–3)	32,146 (13.4)	137 (15.5)
Moderate (4–6)	155,861 (65.0)	547 (61.8)
Strongest (7–9)	51,651 (21.6)	201 (22.7)
Physical Working Capacity		
Lowest (1–3)	13,083 (5.46)	54 (6.10)
Moderate (4–6)	119,161 (49.7)	461 (52.1)
Highest (7–9)	107,414 (44.8)	370 (41.8)
Cognitive Function		
Lowest (1–3)	48,714 (20.3)	187 (21.1)
Moderate (4–6)	126,137 (52.6)	443 (50.1)
Highest (7–9)	64,807 (27.0)	255 (28.8)
Body Mass Index (kg/m ²)		
Underweight (<18.5)	27,906 (11.6)	92 (10.4)
Normal weight (18.5–<25)	193,828 (80.9)	698 (78.9)
Lower Overweight (25–<27.5)	11,866 (4.95)	48 (5.42)
Upper Overweight (27.5–<30)	3,694 (1.54)	27 (3.05)
Obese (30+)	2,364 (0.99)	20 (2.26)
Erythrocyte Sedimentation Rate (mm/hr)		
<10	230,706 (96.3)	837 (94.6)

	Total Cohort N=239,658 N (%)	Colorectal Cancer Cases N=885 N (%)
10-<15	4,801 (2.00)	24 (2.71)
15+	4,151 (1.73)	24 (2.71)

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Table 2

Association Between Late Adolescent Body Mass Index (BMI), Erythrocyte Sedimentation Rate (ESR) and Colorectal Cancer, Overall and by Subsite

Body Mass Index (kg/m ²)	Cohort N N (%)	Case N N (%)	Model 1 ^a HR (95% CI)	Model 2 ^b HR (95% CI)	Model 3 ^{b,c} HR (95% CI)	Subsite-Stratified ^{d,g}	
						Colon Cancer ^{b,d} HR (95% CI)	Rectal Cancer ^{b,e} HR (95% CI)
Underweight (<18.5)	27,906 (11.6)	92 (10.4)	0.91 (0.74, 1.14)	0.86 (0.68, 1.08)	0.87 (0.69, 1.10)	0.82 (0.60, 1.12)	0.90 (0.64, 1.26)
Normal Weight (18.5-25)	193,828 (80.9)	698 (78.9)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (ref)
Lower Overweight (25-27.5)	11,866 (4.95)	48 (5.42)	1.12 (0.84, 1.50)	1.15 (0.85, 1.55)	1.13 (0.83, 1.54)	1.23 (0.84, 1.81)	1.04 (0.65, 1.67)
Upper Overweight (27.5-30)	3,694 (1.54)	27 (3.05)	2.03 (1.38, 2.98)	2.08 (1.40, 3.07)	2.19 (1.48, 3.24)	2.59 (1.62, 4.15)	1.41 (0.69, 2.87)
Obese (30+)	2,364 (0.99)	20 (2.26)	2.38 (1.53, 3.72)	2.38 (1.51, 3.76)	2.50 (1.58, 3.95)	2.55 (1.41, 4.61)	2.17 (1.05, 4.46)
			<i>P-trend: <0.001</i>	<i>P-trend: <0.001</i>	<i>P-trend: <0.001</i>	<i>P-trend: <0.001</i>	<i>P-trend: 0.047</i>
Erythrocyte Sedimentation Rate (mm/hr)							
Low (<10)	230,706 (96.3)	837 (94.6)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (ref)
Moderate (10-15)	4,801 (2.00)	24 (2.71)	1.43 (0.95, 2.16)	1.40 (0.93, 2.10)	1.38 (0.91, 2.10)	1.11 (0.61, 2.03)	1.78 (1.02, 3.12)
High (15+)	4,151 (1.73)	24 (2.71)	1.66 (1.10, 2.50)	1.63 (1.08, 2.45)	1.48 (0.95, 2.29)	1.99 (1.22, 3.25)	1.12 (0.53, 2.39)
			<i>P-trend: 0.004</i>	<i>P-trend: 0.006</i>	<i>P-trend: 0.03</i>	<i>P-trend: 0.01</i>	<i>P-trend: 0.23</i>

ABBREVIATIONS: 95% CI (95% Confidence Interval); HR (Hazard Ratio)

^aModel adjusted for age at conscription (continuous; years); analysis of ESR further adjusted for EVF (continuous)^bModel adjusted for age at conscription (continuous; years), ESR (categorical: mm/hr: <10, 10-15, 15+, with <10 as the reference), EVF (continuous), BMI (categorical: kg/m² <18.5, 18.5-25, 25-27.5, 27.5-30, 30+, with 18.5-25 as the reference), household crowding (categorical; persons per room: <1; 1; >1-2; >2-3; >3, with >1-2 as the reference), health status (categorical: no diagnosis; no serious health problem; fairly significant health problem; significant health problem; very significant health problem, with no diagnosis as the reference); systolic blood pressure (continuous; mmHg); diastolic blood pressure (continuous; mmHg); muscular strength (continuous; 9-point scale ranging from strongest to weakest); physical working capacity (categorical: low, moderate, high, with high as the reference); cognitive function (categorical: low, moderate, high, with low as the reference)^cExcludes the first 10 years of follow-up, as well as all persons diagnosed with ulcerative colitis or Crohn's disease in this 10-year period.^d501 colon cancer cases included in the analyses (473 among ESR 1-10, 11 among persons with ESR 11-14, and 17 among ESR 15-89); of the 501 colon cancer cases, 49 were underweight, 392 were normal weight, 29 were lower overweight, 19 were upper overweight, and 12 were obese^e384 rectal cancer cases included in the analyses (364 among ESR 1-10, 13 among persons with ESR 11-14, and 7 among ESR 15-89); of the 384 rectal cancer cases, 43 were underweight, 306 were normal weight, 19 were lower overweight, 8 were upper overweight, and 8 were obese^fp-difference: 0.49 comparing association between erythrocyte sedimentation rate and colon cancer versus rectal cancer^gp-difference: 0.29 comparing association between body mass index and colon cancer versus rectal cancer