

Obesity is Associated With Increased Risk of Crohn's disease, but not Ulcerative Colitis: A Pooled Analysis of Five Prospective Cohort Studies



Simon S. M. Chan,^{*,‡} Ye Chen,[§] Kevin Casey,[§] Ola Olen,^{||,¶,#}
 Jonas F. Ludvigsson,^{**,#} Franck Carbonnel,^{§§,||||} Bas Oldenburg,^{¶¶}
 Marc J. Gunter,^{##} Anne Tjønneland,^{***,†††} Olof Grip,^{§§§} DEFINE-IBD Investigators,
 Paul Lochhead,^{§,|||||} Andrew T. Chan,^{§,|||||} Alicia Wolk,^{¶¶¶,###} and
 Hamed Khalili^{§,|||||,****}

^{*}Department of Gastroenterology, Norfolk and Norwich University Hospital NHS Trust, Norwich, United Kingdom; [‡]Department of Medicine, Bob Champion Research and Education Building, Norwich Medical School, University of East Anglia, Norwich, United Kingdom; [§]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ^{||}Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [¶]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [#]Department of Pediatric Gastroenterology and Nutrition, Sachs' Children and Youth Hospital, Stockholm, Sweden; ^{**}Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ^{##}Department of Paediatrics, Örebro University Hospital, Örebro, Sweden; ^{§§}Service de Gastroentérologie, Centre hospitalier Universitaire de Bicêtre, Assistance Publique Hôpitaux de Paris, Université Paris Saclay, Le Kremlin Bicêtre, France; ^{||||}INSERM U1018, Villejuif, France; ^{¶¶}Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, The Netherlands; ^{###}Section of Nutrition and Metabolism, International Agency for Research on Cancer - WHO, Lyon, France; ^{***}Danish Cancer Society Research Center, Copenhagen, Denmark; ^{†††}Department of Public Health, University of Copenhagen, Denmark; ^{§§§}Department of Gastroenterology, Skåne University Hospital, Malmö, Sweden; ^{|||||}Gastroenterology Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ^{¶¶¶}Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; ^{###}Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; ^{****}Broad Institute of MIT and Harvard, Cambridge, Massachusetts

BACKGROUND AND AIMS:

It is unclear whether obesity is associated with the development of inflammatory bowel disease despite compelling data from basic science studies. We therefore examined the association between obesity and risk of Crohn's disease (CD) and ulcerative colitis (UC).

METHODS:

We conducted pooled analyses of 5 prospective cohorts with validated anthropometric measurements for body mass index (BMI) and waist-hip ratio and other lifestyle factors. Diagnoses of CD and UC were confirmed through medical records or ascertained using validated definitions. We used Cox proportional hazards modeling to calculate pooled multivariable-adjusted HRs (aHRs) and 95% confidence intervals (CIs).

RESULTS:

Among 601,009 participants (age range, 18-98 years) with 10,110,018 person-years of follow-up, we confirmed 563 incident cases of CD and 1047 incident cases of UC. Obesity (baseline BMI ≥ 30 kg/m²) was associated with an increased risk of CD (pooled aHR, 1.34; 95% CI, 1.05-1.71, $I^2 = 0\%$) compared with normal BMI (18.5 to <25 kg/m²). Each 5 kg/m² increment in baseline BMI was associated with a 16% increase in risk of CD (pooled aHR, 1.16; 95% CI, 1.05-1.22; $I^2 = 0\%$). Similarly, with each 5 kg/m² increment in early adulthood BMI (age, 18-20 years), there was a 22% increase in risk of CD (pooled aHR, 1.22; 95% CI, 1.05-1.40; $I^2 = 13.6\%$). An increase in waist-hip ratio was associated with an increased risk of CD that did not reach statistical significance (pooled aHR across quartiles, 1.08; 95% CI, 0.97-1.19; $I^2 = 0\%$). No associations were observed between measures of obesity and risk of UC.

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; CD, Crohn's disease; HR, hazard ratios; IBD, inflammatory bowel disease; MV, multivariable; TNF, tumor necrosis factor; UC, ulcerative colitis; WHR, waist-hip ratio; WHO, World Health Organization.

© 2022 by the AGA Institute. Published by Elsevier, Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).
1542-3565

<https://doi.org/10.1016/j.cgh.2021.06.049>

CONCLUSIONS:

In an adult population, obesity as measured by BMI was associated with an increased risk of older-onset CD but not UC.

Keywords: Body Mass Index; Epidemiology; Inflammatory Bowel Diseases; Waist-Hip Ratio.

The global incidence of the inflammatory bowel diseases (IBDs), Crohn's disease (CD) and ulcerative colitis (UC), has increased especially in developing countries that have witnessed a dramatic Westernization of lifestyle.¹ Over a similar time frame, obesity is becoming increasingly prevalent worldwide,² and is one of the strongest risk factors for chronic disease morbidity and mortality.³ As a major environmental factor in the development of autoimmune diseases,⁴ obesity may contribute substantially to the etiopathogenesis of IBD, particularly in those with older-onset IBD, where, relative to those with younger disease onset, the overall contribution of the environment is significantly greater.⁵

Obesity is often linked to Westernized lifestyles such as physical inactivity and excess calorie consumption from meals high in refined grains and unhealthy fats. Adipocyte hypertrophy resulting from obesity generates a proinflammatory state through the secretion of inflammatory mediators including tumor necrosis factor (TNF)- α ⁶ and C-reactive protein.⁷ These are also elevated in patients with IBD, especially TNF- α , whose pathogenic role is antagonized by anti-TNF therapies. Obesity is further associated with increased markers of bowel inflammation based on fecal calprotectin measurements⁸ and intestinal permeability,⁹ biological hallmarks of IBD. Yet despite these compelling data, epidemiologic studies have failed to identify a consistent link between obesity and the risk of CD and UC.^{10,11} This is likely to be due to the significant limitations of previous studies that include retrospective design, sample size, and inability to control for confounding from other important lifestyle exposures and lack of detailed measures of obesity.

We therefore investigated the relationship between measures of obesity and risk of CD and UC while addressing the methodological limitations of prior studies through a pooled analysis of several well-established prospective cohorts. These robust population-based cohorts had detailed and validated data on measures of obesity and lifestyle data, offering us a unique opportunity to comprehensively examine the relationship between obesity and risk of older-onset IBD.

Methods

Study Populations

A pooled analysis of the primary data from 5 large prospective cohorts was conducted within the Dietary and Environmental Factors IN-IBD (DEFINe-IBD) study.

DEFINe-IBD is an international consortium of cohort studies aimed at identifying environmental and lifestyle risk factors for IBD by analyzing harmonized individual-level data from multiple prospective cohorts using standardized criteria. The consortium includes the European Prospective Investigation into Cancer and Nutrition (EPIC), the Nurses' Health Study (NHS) and NHS II, the Cohort of Swedish Men (COSM), and the Swedish Mammography Cohort (SMC). An overview of the study populations, the design of each cohort and predefined inclusion criteria are given in the [Supplementary Methods](#). All cohorts provided their primary individual level data for analyses related to this study. At baseline, we excluded individuals with missing baseline anthropometric measurements needed to determine body mass index (BMI), those with BMI <18.5 kg/m² (due to the possibility of underlying disease), and participants diagnosed with IBD prior to start of follow-up in each cohort. We excluded incident cases of CD and UC diagnosed within the first 2 years of follow-up to minimize the possibility of reverse causation.

Each cohort's ethics committee approved participation in this study.

Exposure Assessment

Anthropometric measurements were obtained from baseline questionnaires to calculate BMI and waist-hip ratio (WHR) as measures of obesity. Where information on key variables including covariates (see below) were unavailable at baseline but were collected later, on subsequent questionnaires, the baseline was redefined as the later date. Therefore, baseline questionnaires were collected from EPIC participants from 1991 to 1997; NHS and NHS II participants in 1986 and 1993, respectively; and COSM and SMC participants in 1997. Self-reported weight in early adulthood (18–20 years) recorded in baseline questionnaires was used to calculate early adulthood BMI, assuming that participants' height in early adulthood would be the same as that recorded at baseline.¹² For additional details, see [Supplementary Figure 1](#) and [Supplementary Table 1](#).

Assessment of Covariates

Total physical activity, total energy intake, dietary fiber and fat intake were calculated from baseline questionnaires for each cohort as summarized in the [Supplementary Methods](#). Self-reported smoking status at baseline was recorded as current, past, or never.

Outcome Ascertainment

Case ascertainment for CD and UC have been described in detail for EPIC,¹⁰ NHS and NHS II,¹³ COSM, and SMC,^{14,15} and a summary of IBD case ascertainment for each cohort is given in the [Supplementary Methods](#).

Statistical Analysis

Measures of obesity were modeled categorically and continuously. For the categorical analysis, BMI was modeled using cut points proposed by the World Health Organization (WHO): 18.5 to <25 kg/m² (normal), 25 to <30 kg/m² (overweight), and ≥30 kg/m² (obese).¹⁶ We used BMI of 18.5 to <25 kg/m² as the referent category. Categorical analysis of WHR was modeled using the WHO definition of abdominal obesity (female >0.85, male >0.90)¹⁷ and as quartiles. Continuous analyses modeled per 5 kg/m² increase in BMI and for WHR per quartile and per unit increase.

We calculated person-time for each participant from the date of the baseline questionnaire until the date of CD or UC diagnosis, death from another cause, loss to follow-up, or end of follow-up, whichever came first. Minimally adjusted (age and sex) and multi-variable (MV)-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models for each cohort. Covariables were formatted to be consistently classified across all cohorts, and multiple imputations with chain equations were used to carry out 50 imputations for missing data (physical activity, n = 38,418 [6.4%]; smoking status, n = 6428 [1.0%]; total energy intake, n = 25,397 [4.2%]; total fiber intake, n = 25,397 [4.2%]; total fat intake, n = 25,397 [4.2%]). Where the outcome was CD, MV-adjusted HRs were adjusted for sex (male/female), smoking status (nonsmoker/ex-smoker/current smoker), total energy intake (kcal/day), physical activity (metabolic equivalent task hours/week modeled as quartiles according to cohort distribution), and dietary fiber (g/day). For UC, MV-adjusted HRs models were similar but were adjusted for dietary fat (g/day) instead of dietary fiber. These variables were selected based on their known associations with risk of CD or UC.^{18,19} For models in which baseline BMI was not the main exposure (ie, WHR or BMI in early adulthood), BMI was included as a covariable in the model to examine the independent associations of our secondary exposures. Lastly, models that examined the relationship between change in weight from early to middle adulthood and risk of CD and UC were additionally adjusted for height and early adulthood weight but not baseline BMI.

Cohort-specific Cox proportional HRs were pooled using a fixed effect meta-analysis.²⁰ Heterogeneity between studies was evaluated using the Q and I² statistic, I² > 50% indicated substantial heterogeneity. In addition, we conducted sensitivity analyses to evaluate

What You Need to Know

Background

Plausible biological mechanisms imply a role for obesity in the pathogenesis of inflammatory bowel disease, but the relationship between obesity and risk of Crohn's disease (CD) and ulcerative colitis (UC) is unclear.

Findings

In a pooled analysis of 5 prospective cohorts, obesity as defined by body mass index is associated with a significant risk of incident CD but not UC.

Implications for patient care

The growing burden of obesity may be an important contributor to the increasing incidence of CD worldwide with the effects of obesity potentially playing a stronger role in the etiopathogenesis of CD compared with UC.

whether associations between BMI and risk of CD and UC were modified by age at start of follow-up (<50 vs ≥50 years), sex (female vs male), and smoking status (never vs ever). Lastly, we also examined the association between BMI and risk of CD according to age of diagnosis (< 40 years, 40 to <60 years, ≥ 60 years). All *P*-values were 2-sided, and *P* < .05 was considered statistically significant.

We calculated the population attributable risk conferred by obesity as defined by BMI (≥30 kg/m²) to estimate the percentage of IBD cases that may have been preventable if participants had maintained a normal BMI, assuming a causal relationship between BMI and IBD.

Stata 16.1/MP (StataCorp LLC, College Station, TX) and SAS 9.4 (SAS Institute Inc, Cary, NC) were used for analyses of individual cohorts and pooling of estimates.

Results

Following exclusions, our pooled cohort included 601,009 participants from 9 countries, and 71% were female. Over 10,110,018 person-years of follow-up with a mean follow-up of 16 years, we identified 563 incident cases of CD (incidence rate, 6 cases/100,000 person-years) and 1047 incident cases of UC (incidence rate, 10 cases/100,000 person-years). [Table 1](#) reports the baseline characteristics of participants categorized by BMI. Compared with participants in the lowest category of BMI, those in the highest category had higher WHR, were less physically active, and more likely to be smokers.

For baseline BMI, we observed an increased risk of CD in those who were obese (BMI ≥30 kg/m²) in our minimally adjusted model (HR, 1.27; 95% CI, 0.97–1.68; I² = 0%) when compared with participants in the lowest

Table 1. Baseline Characteristics of Participants in Each Cohort According to Extreme Categories of BMI at Baseline

	EPIC		NHS		NHS II		COSM		SMC	
	BMI, kg/m ²									
	18.5 to <25 (n = 154,465)	≥30 (n = 47,401)	18.5 to <25 (n = 44,847)	≥30 (n = 11,995)	18.5 to <25 (n = 59,481)	≥30 (n = 17,784)	18.5 to <25 (n = 18,820)	≥30 (n = 4351)	18.5 to <25 (n = 20,459)	≥30 (n = 4087)
Age at recruitment, years	50.0 (11.2)	54.1 (8.7)	52.6 (7.2)	53.4 (7.0)	38.4 (4.6)	39.6 (4.5)	60.2 (10.0)	59.7 (9.0)	61.3 (9.4)	62.3 (8.5)
Female sex, %	73	62	100	100	100	100	0	0	100	100
BMI, kg/m ²	22.5 (1.6)	33.3 (3.3)	22.3 (1.6)	34.3 (4.2)	22.0 (1.7)	35.5 (5.1)	23.1 (1.4)	32.6 (2.7)	22.5 (1.6)	33.0 (3.2)
Waist to hip ratio	0.80 (0.08)	0.90 (0.10)	0.77 (0.17)	0.83 (0.11)	0.77 (0.07)	0.83 (0.09)	0.92 (0.06)	1.00 (0.09)	0.80 (0.09)	0.86 (0.10)
Smoking, %										
Never	49	48	43	48	66	65	39	29	51	56
Former	27	32	34	37	23	24	34	46	22	25
Current	24	20	24	15	11	11	26	25	25	18
Physical activity, MET-hr/wk	35.1 (26.9)	29.9 (26.0)	16.0 (22.8)	9.8 (15.8)	22.9 (28.6)	15.2 (20.8)	41.8 (4.8)	40.7 (5.2)	42.6 (4.7)	41.6 (5.1)
Energy intake, kcal/day	2109 (656)	2111 (733)	1754 (518)	1806 (549)	1776 (537)	1842 (571)	2699 (281)	2611 (1030)	1756 (555)	1713 (632)
Total fat intake, g	81 (31)	82 (34)	63 (23)	68 (24)	61 (22)	68 (24)	94 (36)	90 (42)	63 (24)	60 (26)
Total fiber intake, g	24 (8)	23 (8)	20 (8)	20 (8)	19 (8)	18 (8)	32 (13)	30 (15)	23 (9)	22 (10)

Note: All nonpercentage values presented as mean with standard deviation.

BMI, Body mass index; CoSM, Cohort of Swedish Men; EPIC, European Prospective Cohort Investigation into Cancer and Nutrition; MET, metabolic equivalent task; NHS, Nurses' Health Study; SMC, Swedish Mammography Cohort.

Table 2. Risk of Crohn's Disease According to BMI at Baseline

	BMI at Baseline, kg/m ²			HR (95% CI) per 5 kg/m ² increase in BMI
	18.5 to <25	25 to <30	≥30	
EPIC				
Person-years of follow-up	2,229,220	1,701,427	642,078	–
No. of cases	57	46	22	–
Age- and sex-adjusted HR (95% CI)	1.00	1.10 (0.74–1.63)	1.37 (0.84–2.23)	1.10 (0.90–1.34)
Multivariable-adjusted HR (95% CI) ^a	1.00	1.12 (0.75–1.66)	1.43 (0.89–2.31)	1.16 (0.95–1.40)
NHS				
Person-years of follow-up	1,137,959	572,120	282,393	–
No. of cases	82	48	22	–
Age- and sex-adjusted HR (95% CI)	1.00	1.14 (0.80–1.63)	1.06 (0.66–1.70)	1.10 (0.90–1.28)
Multivariable-adjusted HR (95% CI) ^a	1.00	1.16 (0.81–1.67)	1.09 (0.67–1.75)	1.10 (0.95–1.28)
NHS II				
Person-years of follow-up	1,302,853	517,841	375,603	–
No. of cases	82	31	31	–
Age- and sex-adjusted HR (95% CI)	1.00	1.22 (0.70–2.14)	1.04 (0.50–2.13)	1.10 (0.86–1.34)
Multivariable-adjusted HR (95% CI) ^a	1.00	0.97 (0.64–1.47)	1.35 (0.89–2.06)	1.16 (0.95–1.34)
COSM				
Person-years of follow-up	310,259	330,221	69,958	–
No. of cases	40	34	12	–
Age- and sex-adjusted HR (95% CI)	1.00	0.80 (0.51–1.26)	1.33 (0.70–2.53)	1.05 (0.77–1.47)
Multivariable-adjusted HR (95% CI) ^a	1.00	0.79 (0.50–1.26)	1.27 (0.66–2.44)	1.05 (0.77–1.40)
SMC				
Person-years of follow-up	351,461	217,609	69,016	–
No. of cases	29	16	11	–
Age- and sex-adjusted HR (95% CI)	1.00	0.93 (0.51–1.72)	2.01 (1.00–4.03)	1.22 (0.90–1.61)
Multivariable-adjusted HR (95% CI) ^a	1.00	0.94 (0.51–1.73)	2.00 (0.99–4.03)	1.22 (0.90–1.61)
Pooled age- and sex-adjusted HR (95% CI)	1.00	1.04 (0.85–1.28)	1.27 (0.97–1.68)	1.10 (1.00–1.22)
Pooled multivariable HR (95% CI)	1.00	1.01 (0.83–1.23)	1.34 (1.05–1.71)	1.16 (1.05–1.22)

BMI, Body mass index; CI, confidence interval; CoSM, Cohort of Swedish Men; EPIC, European Prospective Cohort Investigation into Cancer and Nutrition; HR, hazard ratio; NHS, Nurses' Health Study; SMC, Swedish Mammography Cohort.

^aAdjusted for age at baseline (continuous), sex, smoking status (never/former/current), physical activity (quartiles), energy intake (continuous), dietary fiber (continuous). I^2 values for highest category of BMI and per 5 kg/m² increment in BMI for pooled analyses = 0%.

category of BMI (BMI 18.5 to <25 kg/m²) (Table 2), and for each 5 kg/m² increase in baseline BMI, a statistically significant 10% increase in risk of CD (HR, 1.10; 95% CI, 1.00–1.22; $I^2 = 0\%$). These associations were not altered after adjusting for known and potential risk factors for CD including smoking, physical activity, and dietary fiber intake. Compared with participants in the lowest category of BMI, the MV-adjusted HR of CD for participants with BMI ≥30 kg/m² was 1.34 (95% CI, 1.05–1.71; $I^2 = 0\%$). Similarly, for every 5 kg/m² increase in baseline BMI, we observed a 16% increase in risk of CD (MV-adjusted HR, 1.16; 95% CI, 1.05–1.22). We observed no heterogeneity in the association between the highest category of BMI (≥30 kg/m²) or per 5 kg/m² increment in BMI and risk of CD across the 5 cohorts ($Q_{\text{statistic}} = 2.11$; $I^2 = 0\%$; $P = .71$ and $Q_{\text{statistic}} = 0.85$; $I^2 = 0\%$; $P = .93$, respectively). We used data on worldwide prevalence of BMI ≥30 kg/m² from the WHO Global Health Observatory to estimate the population attributable risk for older-onset CD. In Western Europe and the United States, the prevalence of obesity increased from 15% to

29% at the mid-point of the study (~2005) to 20% to 36% towards the end of the study period (~2016), conferring an adjusted population attributable risk ranging from 5% to 11%, assuming a causal relationship between BMI and CD.

In contrast to CD, we did not observe an association between those who were overweight (BMI 25 to <30 kg/m²) or obese (BMI ≥30 kg/m²) and risk of UC in our minimally adjusted or MV-adjusted models (Table 3). For every 5 kg/m² increase in BMI, the minimally adjusted HR for UC was 1.00 (95% CI, 0.95–1.10), and the MV-adjusted HR was 1.00 (95% CI, 0.90–1.05). We observed no heterogeneity across cohorts in the association between the highest category of BMI (≥30 kg/m²) or per 5 kg/m² increment in BMI and risk of UC across the 5 cohorts ($Q_{\text{statistic}} = 3.29$; $I^2 = 0\%$; $P = .51$ and $Q_{\text{statistic}} = 1.25$; $I^2 = 0\%$; $P = .87$, respectively).

We explored whether the association between baseline BMI and risk of CD and UC was consistent across several subgroups defined by sex, age, and smoking (Figure 1) and observed no evidence of effect

Table 3. Risk of Ulcerative Colitis According to BMI at Baseline

	BMI at baseline, kg/m^2			HR (95% CI) per 5 kg/m^2 increase in BMI
	18.5 to <25	25 to <30	≥ 30	
EPIC				
Person-years of follow-up	2,229,220	1,701,427	642,078	–
No. of cases	148	135	53	–
Age- and sex-adjusted HR (95% CI)	1.00	1.01 (0.80–1.29)	1.10 (0.81–1.43)	1.10 (0.90–1.34)
Multivariable-adjusted HR (95% CI) ^a	1.00	1.02 (0.81–1.30)	1.13 (0.82–1.55)	1.05 (0.95–1.22)
NHS				
Person-years of follow-up	1 137 959	572 120	282 393	–
No. of cases	98	43	20	–
Age- and sex-adjusted HR (95% CI)	1.00	0.88 (0.62–1.26)	0.85 (0.52–1.37)	0.95 (0.82–1.16)
Multivariable-adjusted HR (95% CI) ^a	1.00	0.87 (0.61–1.25)	0.83 (0.51–1.35)	0.95 (0.82–1.16)
NHS II				
Person-years of follow-up	1 302 853	517 841	375 603	–
No. of cases	120	47	30	–
Age- and sex-adjusted HR (95% CI)	1.00	1.20 (0.75–1.90)	0.91 (0.49–1.69)	1.10 (0.90–1.28)
Multivariable-adjusted HR (95% CI) ^a	1.00	0.95 (0.68–1.33)	0.81 (0.54–1.23)	0.95 (0.86–1.10)
COSM				
Person-years of follow-up	310 259	330 221	69 958	–
No. of cases	86	126	14	–
Age- and sex-adjusted HR (95% CI)	1.00	1.38 (1.05–1.82)	0.72 (0.41–1.26)	1.00 (0.83–1.22)
Multivariable-adjusted HR (95% CI) ^a	1.00	1.34 (1.02–1.76)	0.68 (0.39–1.20)	0.95 (0.77–1.03)
SMC				
Person-years of follow-up	351 461	217 609	69 016	–
No. of cases	77	39	11	–
Age- and sex-adjusted HR (95% CI)	1.00	0.89 (0.60–1.31)	0.79 (0.42–1.48)	0.95 (0.77–1.22)
Multivariable-adjusted HR (95% CI) ^a	1.00	0.90 (0.61–1.33)	0.76 (0.40–1.44)	0.95 (0.77–1.22)
Pooled age- and sex-adjusted HR (95% CI)	1.00	1.07 (0.93–1.24)	0.92 (0.74–1.14)	1.00 (0.95–1.10)
Pooled multivariable HR (95% CI)	1.00	1.03 (0.91–1.19)	0.88 (0.72–1.08)	1.00 (0.90–1.05)

BMI, Body mass index; CI, confidence interval; CoSM, Cohort of Swedish Men; EPIC, European Prospective Cohort Investigation into Cancer and Nutrition; HR, hazard ratio; NHS, Nurses' Health Study; SMC, Swedish Mammography Cohort.

^aAdjusted for age at baseline (continuous), sex, smoking status (never/former/current), physical activity (quartiles), energy intake (continuous), dietary fat (continuous). I^2 values for highest category of BMI and per 5 kg/m^2 increment in BMI for pooled analyses = 0%.

modification (all $P_{interaction} \geq .44$). We considered the possibility that the association between obesity and risk of CD may differ according to age of diagnosis, and therefore evaluated the associations according to different categories of age of diagnosis (18 to <40, 40 to <60, and ≥ 60 years). Compared with participants in the lowest category of BMI, participants with BMI ≥ 30 kg/m^2 had MV-adjusted HRs of 1.35 (95% CI, 0.92–1.99; $Q_{statistic} = 6.68$; $I^2 = 40\%$; $P = .12$) and 1.66 (95% CI, 1.12–2.30; $Q_{statistic} = 4.57$; $I^2 = 12\%$; $P = .33$) for diagnosis of CD during middle age (40 to <60 years) and older age (≥ 60 years), respectively. We could not examine the association with younger-onset CD (18 to <40 years), given limited numbers of cases in all the cohorts. Conducting an analysis limiting our cohort to participants with above average physical activity level in each cohort, we observed a 22% increase in risk of CD with every 5 kg/m^2 increase in BMI (MV-adjusted HR, 1.22; 95% CI, 1.10–1.40) and no increase in risk of UC (MV-adjusted HR, 1.00; 95% CI, 0.90–1.16).

Information on BMI in early adulthood (age 18–20 years) was available in just over two-thirds of participants, and we further explored the association between early adulthood BMI and risk of CD and UC. In those with an early adulthood BMI ≥ 25 kg/m^2 (ie, overweight), the minimally adjusted HR of developing CD later in life was 1.52 (95% CI, 1.15–1.99; $I^2 = 0\%$) when compared with participants with an early adulthood BMI <25 kg/m^2 . This estimate was not materially altered in MV-adjusted analysis (HR, 1.48; 95% CI, 1.12–1.95; $I^2 = 0\%$). Similarly, we observed a 22% increase in risk of CD with every 5 kg/m^2 increase in early adulthood BMI (MV-adjusted HR, 1.22; 95% CI, 1.05–1.40; $I^2 = 0\%$). No associations were found between early adulthood BMI and risk of UC in minimally and MV-adjusted HRs of developing UC later in life. For every 5 kg/m^2 increase in early adulthood BMI, the MV-adjusted HR for UC was 1.05 (95% CI, 0.90–1.22; $I^2 = 0\%$). We also examined the association between weight change from early adulthood (age 18–20 years) and mid-life (baseline in each cohort) and observed no significant associations with risk of CD

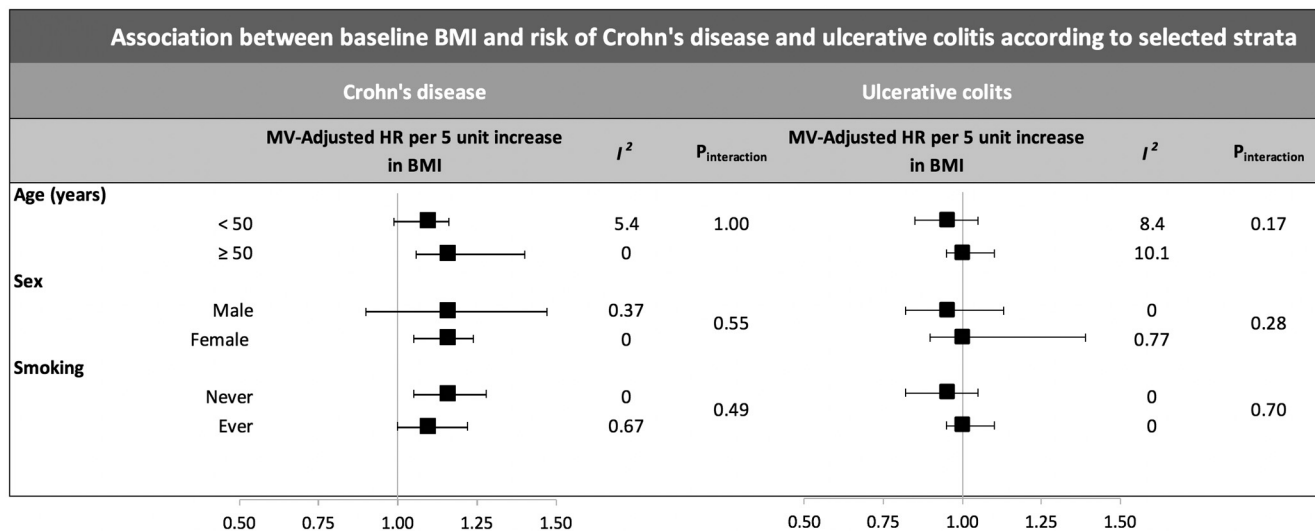


Figure 1. Association between baseline BMI and risk of CD (*left*) and UC (*right*) according to selected strata. HR, hazard ratio; MV, multivariable.

or UC (Supplementary Table 2). However, in joint analysis of early adulthood BMI and weight change from early adulthood to midlife, the highest risk of CD was observed in participants with early adult BMI ≥ 25 kg/m² and the largest category of weight gain (≥ 10 kg) (Figure 2). Compared with participants with BMI < 25 kg/m² and no changes in weight (< 2 kg), the MV-adjusted HR of CD among those with BMI ≥ 25 kg/m² and ≥ 10 kg change in weight was 2.14 (95% CI, 1.43–3.22; $I^2 = 38\%$).

Finally, we evaluated the association between abdominal obesity and risk of CD and UC (Table 4). Compared with participants in the lowest quartile of WHR, the MV-adjusted HR for the second, third, and highest quartile of WHR were associated with a non-statistically significant increased risk of CD (continuous HR per WHR quartile, 1.08; 95% CI, 0.98–1.19) and were unaffected by additional adjustments for baseline BMI (continuous HR per WHR quartile, 1.08; 95% CI, 0.97–1.19). Similarly, assessing WHR as a continuous variable or based on the WHO WHR classification of abdominal obesity showed a non-statistically significant increased risk of CD in both these models (HR, 1.02; 95% CI, 0.97–1.07 and HR, 1.09; 95% CI, 0.85–1.40, respectively). No associations between WHR and risk of UC were observed in any of our models.

Discussion

In a pooled analysis of over 600,000 participants in 5 prospective cohorts of predominantly middle-aged men and women from 9 Western countries, we showed that obesity, as measured by BMI, is associated with an increased risk of CD. Similarly, we found that BMI in early adulthood is associated with an increased risk of subsequently developing CD. These findings were

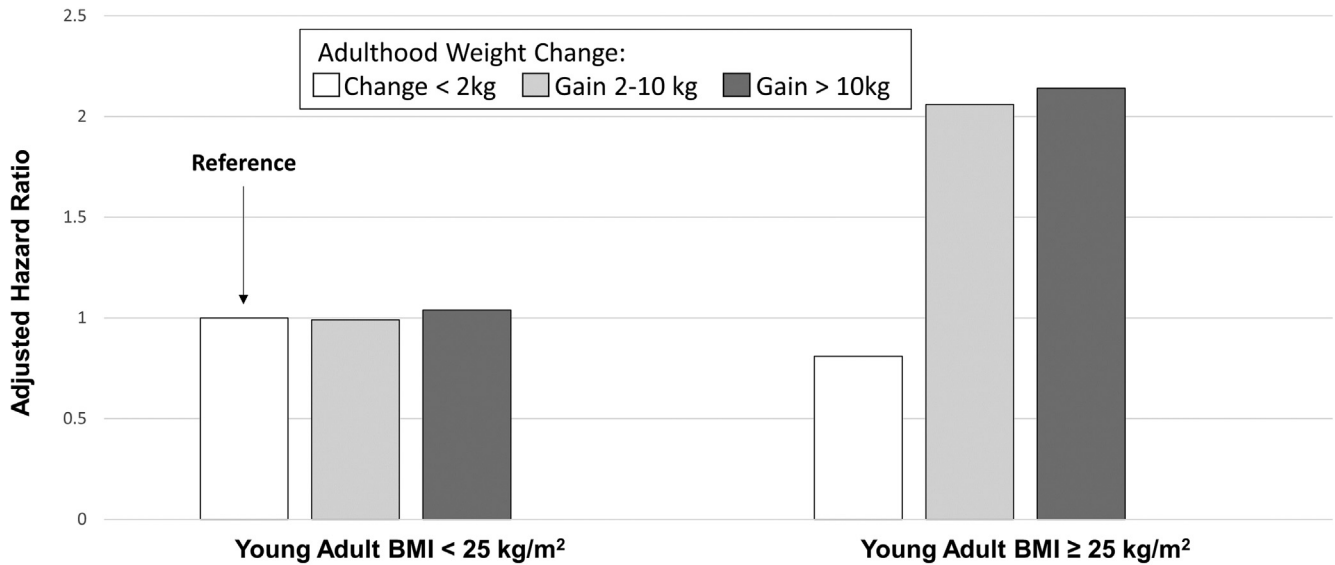
consistent across multiple sensitivity and subgroup analyses, after accounting for unhealthy lifestyles associated with and after adjusting for dietary risk factors for IBD. Abdominal obesity, as measured by WHR, was associated with a non-statistically significant increased risk of CD. No associations were seen between any of these anthropometric measures and UC.

Several biologically plausible mechanisms support our findings for an association between obesity and risk of CD. First, obesity causes adipocyte hypertrophy and dysfunction, leading to the secretion of many adipokines and pro-inflammatory mediators that are elevated in those with active CD.²¹ Second, levels of intestinal inflammation and permeability are associated with obesity^{8,9,22} and may facilitate bacterial translocation and loss of immune tolerance in the gastrointestinal tract. Third, CD is associated with ‘creeping’ of mesenteric fat, which is associated with fibrosis and structuring.²³ Lastly, obesity has been linked to alterations in the gut microbiome.²⁴ We speculate these mechanisms are likely to have a greater role in the etiopathogenesis of CD compared with UC.

To our knowledge, this is the largest prospective adult cohort study to examine the relationship between different measures of obesity and risk of CD with the opportunity to adjust for multiple lifestyle and dietary exposures. Few studies have previously investigated the associations between obesity and IBD, and both null^{10,25} and positive associations^{11,26–28} have been reported. Reasons for the inconsistencies in these associations may be due to differences in study design, small sample size (≤ 100 cases), inability to control for risk factors such as smoking, limited number of cases for higher categories of obesity, and different definitions of obesity.

Our findings are supported by prior work from the NHS II cohort,¹¹ part of this pooled analysis, which

A. Crohn's Disease



B. Ulcerative colitis

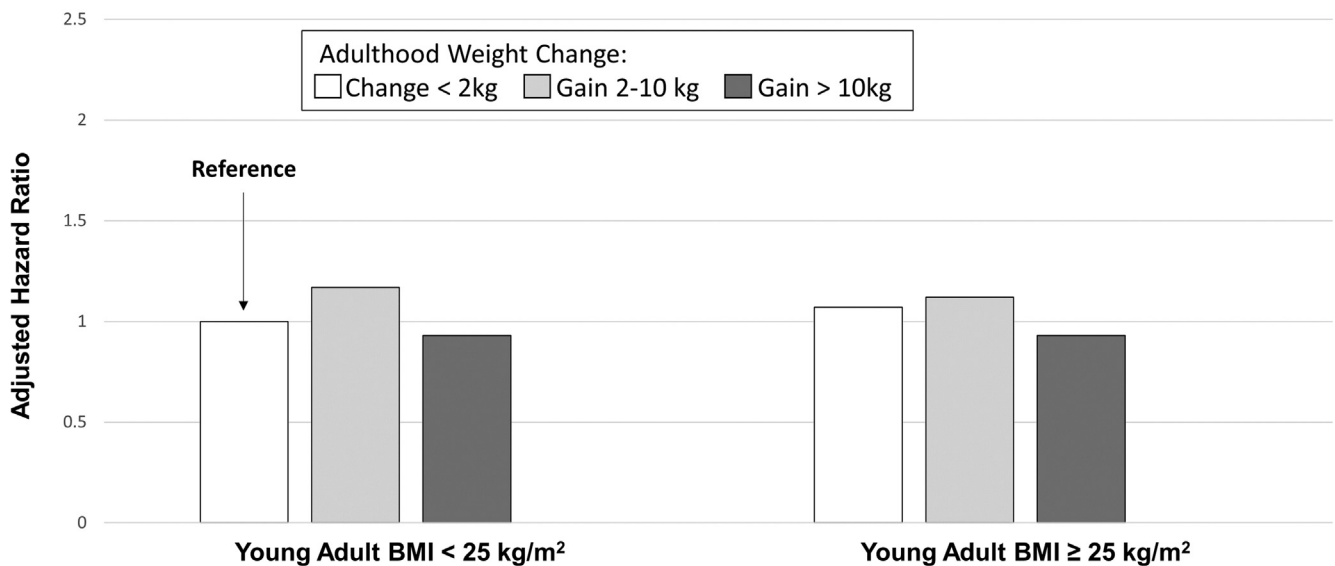


Figure 2. Multivariable-adjusted risk of incident CD (A) and UC (B) according to early adult BMI and weight change since early adulthood. Each column shows the multivariable-adjusted hazard ratio for the joint association of BMI and weight gain and risk of CD and UC. Models were adjusted for variables listed in Tables 2 and 3. Pooled estimates were derived using fixed-effect meta-analyses.

previously reported that obesity defined by BMI at baseline was associated with increased risk of CD. Interestingly, in this study, obesity defined by BMI at baseline in EPIC-IBD showed a positive association with CD, albeit not statistically significant. This is in contrast to previous data from EPIC-IBD, which found no associations between BMI and CD¹⁰ and may be due to the analysis of EPIC-IBD as a full cohort, rather than the previous nested case-control design and additional follow-up time, affording greater statistical power. In addition, our observation that BMI in early adulthood is

associated with increased risk of later-onset CD is supported by a study that reported obesity in childhood (age 8–13 years) is associated with CD before the age of 30 years.²⁹

Because BMI in middle-aged and older populations may not sufficiently represent the changes in fat distribution that are associated with age, we used WHR to assess the role of abdominal obesity and observed a non-statistically significant increased risk for CD. To date, only a single study has found an association with WHR and IBD,¹¹ and based on the findings from our study with

Table 4. Risk of Crohn's Disease and Ulcerative Colitis Based on WHR (Quartiles) and on WHO Classification of WHR at Baseline

	WHR at baseline						Per unit increase	
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per quartile increase	Non-obese ^a		Obese ^a
Crohn's disease								
Pooled age- and sex-adjusted HR (95% CI)	1.00	1.20 (0.89–1.63)	1.30 (0.95–1.77)	1.38 (1.00–1.90)	1.10 (1.00–1.22)	1.00	1.19 (0.93–1.53)	1.27 (0.68–2.40)
Pooled MV-adjusted HR (95% CI) ^b	1.00	1.13 (0.84–1.51)	1.22 (0.90–1.66)	1.28 (0.93–1.77)	1.08 (0.98–1.19)	1.00	1.14 (0.89–1.47)	1.33 (0.56–3.16)
Pooled MV-adjusted HR (95% CI) ^c	1.00	1.12 (0.84–1.50)	1.19 (0.88–1.62)	1.23 (0.88–1.71)	1.08 (0.97–1.19)	1.00	1.09 (0.85–1.40)	1.02 (0.97–1.07)
Ulcerative colitis								
Pooled age- and sex-adjusted HR (95% CI)	1.00	1.09 (0.90–1.33)	0.93 (0.74–1.14)	1.04 (0.82–1.32)	0.99 (0.92–1.07)	1.00	1.09 (0.92–1.30)	1.21 (0.85–1.74)
Pooled MV-adjusted HR (95% CI) ^b	1.00	1.12 (0.91–1.36)	0.93 (0.75–1.15)	0.98 (0.77–1.24)	0.97 (0.91–1.05)	1.00	1.05 (0.89–1.25)	1.21 (0.83–1.76)
Pooled MV-adjusted HR (95% CI) ^c	1.00	1.10 (0.87–1.30)	0.91 (0.73–1.12)	0.98 (0.77–1.25)	0.97 (0.90–1.04)	1.00	1.04 (0.87–1.25)	1.01 (0.97–1.06)

Note: ^aI² values for highest category of WHR, and as continuous variable for pooled analyses = 0%.

CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; UC, ulcerative colitis; WHO, World Health Organization; WHR, waist to hip ratio.

^aNon-obese WHR = female ≤ 0.85, male ≤ 0.90; Obese WHR = female > 0.85, male > 0.90.

^bModels adjusted for age at baseline (continuous), sex, smoking status (never/former/current), physical activity (quartiles), energy intake (continuous), dietary fiber (continuous) for CD only.

^cModels adjusted for age at baseline (continuous), BMI (3 categories: 18.5 to <25, 25 to <30, ≥30 kg/m²), sex, smoking status (never/former/current), physical activity (quartiles), energy intake (continuous), dietary fiber (continuous) for CD only, dietary fat (continuous) for UC only.

a significantly larger sample size, any associations between WHR and the risk of CD or UC are likely to be very modest.

There are several strengths to our study. First, the prospective design avoids the potential selection and recall biases of retrospective case-control studies. Second, accurate and validated measures for weight, height, and waist and hip circumference ensured that recorded and self-reported anthropometric measures were valid and reproducible. Third, the diversity of included studies, large sample size, and long follow-up period ensured that our estimates are generalizable to similar populations. Fourth, the availability of detailed and validated information on smoking, physical activity, and dietary fiber and fat intakes allowed us to control for several risk factors that may have impacted our associations. Fifth, all diagnoses of CD and UC were either confirmed through medical records or ascertained using validated definitions, minimizing the risk of outcome misclassification. Finally, by pooling individual-level data, we were able to harmonize the exposures, covariates, outcomes, and analytic modeling, leading to little heterogeneity and decreased variability in effect estimates that can often be found in standard meta-analyses of the published literature.

We acknowledge several limitations. First, our study participants were predominantly Western middle-aged men and women, and so our findings may not be generalizable to a non-Western or younger population at risk of IBD. That said, environmental exposures may play a greater role in IBD development of older-onset disease.⁵ Second, our study was reliant mainly on anthropometric measures recorded at a single point in middle age. The lack of repeated anthropometric measures in all cohorts over follow-up time meant that we were unable to assess the time point during the life-course at which obesity becomes a critical factor for risk of developing CD. However, we did have data on early adulthood BMI in the majority of our participants and found similar associations to those with BMI at baseline. Finally, although we were able to account for several confounding factors, we further acknowledge that our observed associations are unable to demonstrate causality and may be related to residual confounding for factors such as early life exposures, which we are unable to adjust for. However, our results remained consistent after adjusting for known confounders and were consistent in several subgroups.

Conclusions

Our data implies that the growing burden of obesity is likely contributing to the increasing incidence of CD worldwide. Together with previous observations that obesity modulates immune responses,²¹ intestinal permeability,^{9,22} and alterations in the gut microbiota,²⁴ such pathways may play a more important role in the

etiopathogenesis of CD compared with UC. Future work should consider examining the precise mechanisms through which obesity may influence the etiopathogenesis of CD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://doi.org/10.1016/j.cgh.2021.06.049>.

References

- Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;390:2769–2778.
- NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* 2016;387:1377–1396.
- Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363:2211–2219.
- Versini M, Jeandel PY, Rosenthal E, et al. Obesity in autoimmune diseases: not a passive bystander. *Autoimmun Rev* 2014;13(9):981–1000.
- Ruel J, Ruane D, Mehandru S, et al. IBD across the age spectrum: is it the same disease? *Nat Rev Gastroenterol Hepatol* 2014;11:88–98.
- Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor- α in human obesity and insulin resistance. *J Clin Invest* 1995;95:2409–2415.
- Greenfield JR, Samaras K, Jenkins AB, et al. Obesity is an important determinant of baseline serum C-reactive protein concentration in monozygotic twins, independent of genetic influences. *Circulation* 2004;109:3022–3028.
- Poullis A, Foster R, Shetty A, et al. Bowel inflammation as measured by fecal calprotectin: a link between lifestyle factors and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2004;13:279–284.
- Moreno-Navarrete JM, Sabater M, Ortega F, et al. Circulating zonulin, a marker of intestinal permeability, is increased in association with obesity-associated insulin resistance. *PLoS One* 2012;7:e37160.
- Chan SS, Luben R, Olsen A, et al. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). *Am J Gastroenterol* 2013;108:575–582.
- Khalili H, Ananthakrishnan AN, Konijeti GG, et al. Measures of obesity and risk of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2015;21:361–368.
- Mouratidou N, Malmborg P, Sachs MC, et al. Adult height in patients with childhood-onset inflammatory bowel disease: a nationwide population-based cohort study. *Aliment Pharmacol Ther* 2020;51:789–800.
- Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. *Ann Intern Med* 2012;156:350–359.
- Jakobsson GL, Sternegard E, Olen O, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). *Scand J Gastroenterol* 2017;52:216–221.
- Khalili H, Hakansson N, Chan SS, et al. No association between consumption of sweetened beverages and risk of later-onset Crohn's disease or ulcerative colitis. *Clin Gastroenterol Hepatol* 2019;17:123–129.
- World Health Organization. Physical status: the use of and interpretation of anthropometry, report of a WHO expert committee. Geneva: World Health Organization, 1995.
- World Health Organization. Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008. Geneva: World Health Organization; 2011.
- Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. *Gut* 2014;63:776–784.
- Ananthakrishnan AN, Khalili H, Konijeti GG, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology* 2013;145:970–977.
- Smith-Warner SA, Spiegelman D, Ritz J, et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. *Am J Epidemiol* 2006;163:1053–1064.
- Zulian A, Canello R, Micheletto G, et al. Visceral adipocytes: old actors in obesity and new protagonists in Crohn's disease? *Gut* 2012;61:86–94.
- Gummesson A, Carlsson LM, Storlien LH, et al. Intestinal permeability is associated with visceral adiposity in healthy women. *Obesity (Silver Spring)* 2011;19:2280–2282.
- Buning C, von Kraft C, Hermsdorf M, et al. Visceral adipose tissue in patients with Crohn's disease correlates with disease activity, inflammatory markers, and outcome. *Inflamm Bowel Dis* 2015;21:2590–2597.
- Ley RE, Backhed F, Turnbaugh P, et al. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005;102:11070–11075.
- Melinder C, Hiyoshi A, Hussein O, et al. Physical fitness in adolescence and subsequent inflammatory bowel disease risk. *Clin Transl Gastroenterol* 2015;6:e121.
- Harpsoe MC, Basit S, Andersson M, et al. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. *Int J Epidemiol* 2014;43:843–855.
- Mendall M, Harpsoe MC, Kumar D, et al. Relation of body mass index to risk of developing inflammatory bowel disease amongst women in the Danish National Birth Cohort. *PLoS One* 2018;13:e0190600.
- Mendall MA, Gunasekera AV, John BJ, et al. Is obesity a risk factor for Crohn's disease? *Dig Dis Sci* 2011;56:837–844.
- Jensen CB, Angquist LH, Mendall MA, et al. Childhood body mass index and risk of inflammatory bowel disease in adulthood: a population-based cohort study. *Am J Gastroenterol* 2018;113:694–701.

Reprint requests

Address reprint requests to: Simon S. M. Chan, Department of Gastroenterology, Norfolk and Norwich University Hospital NHS Trust, Norwich, NR4 7UY, United Kingdom. e-mail: simon.chan@uea.ac.uk.

Acknowledgments

The authors thank all EPIC, NHS, NHSII, COSM, and SMC participants for their contribution to the study. EPIC-Norfolk are grateful to all the participants who have been part of the project and to the many members of the study teams at the University of Cambridge who have enabled this research. The authors acknowledge the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts as the home of the Nurses' Health Studies.

The DEFINE-IBD study data cannot be deposited publicly as these collaborative data originate from multiple research institutions across 8 European countries and the United States with different legal frameworks. Information on submitting applications to access the data from the cohorts used in this study are as follows: COSM and SMC (<https://www.simpler4health.se/researchers> and <https://www.simpler4health.se/researchers/cohorts>), EPIC (<https://epic.iarc.fr/access/index.php>), NHS and NHSII (<https://www.nurseshealthstudy.org/researchers>).

CRedit Authorship Contributions

Simon S. M. Chan, MB BChir, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Supporting; Investigation: Equal; Methodology: Equal; Writing – original draft: Lead; Writing – review & editing: Equal)

Ye Chen, MS (Formal analysis: Lead; Writing – review & editing: Supporting)

Kevin Casey, MS (Formal analysis: Supporting; Writing – review & editing: Supporting)

Ola Olen, MD, PhD (Writing – review & editing: Supporting)

Jonas F. Ludvigsson, MD, PhD (Data curation: Equal; Writing – review & editing: Supporting)

Franck Carbonnel, MD, PhD (Writing – review & editing: Supporting)

Bas Oldenburg, MD, PhD (Writing – review & editing: Supporting)

Marc J. Gunter, PhD (Data curation: Equal; Writing – review & editing: Supporting)

Anne Tjønneland, PhD (Data curation: Equal; Writing – review & editing: Supporting)

Olof Grip, MD, PhD (Writing – review & editing: Supporting)

Paul Lochhead, MB ChB, PhD (Writing – review & editing: Supporting)

Andrew T. Chan, MD, MPH (Writing – review & editing: Supporting)

Alicia Wolk, DMSc (Data curation: Equal; Writing – review & editing: Supporting)

Hamed Khalili, MD, MPH (Conceptualization: Equal; Data curation: Equal; Investigation: Equal; Methodology: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal)

DEFINE-IBD Investigators: *EPIC-IBD* - Pilar Amian, Aurelio Barricarte, Manuela M Bergmann, Marie-Christine Boutron-Ruault, Amanda Cross, Andrew R Hart, Rudolf Kaaks, Tim Key, María Dolores Chirlaque López, Robert Luben,

Giovanna Masala, Jonas Manjer, Anja Olsen, Kim Overvad, Domenico Palli, Elio Riboli, Maria José Sánchez, Rosario Tumino, Roel Vermeulen, W. M. Monique Verschuren, and Nick Wareham. *NHS-IBD* - Ashwin Ananthakrishnan, Kristin Burke, Emily Walsh Lopes, and James Richter

Conflicts of interest

These authors disclose the following: Simon S. M. Chan has received travel grants from Abbvie and Takeda. Karolinska Institutet has received investigator-initiated study grants and fees for lectures and consulting performed by Ola Olén for Janssen, Pfizer, Ferring, and Takeda. Jonas F. Ludvigsson coordinates a study on behalf of the Swedish Inflammatory Bowel Disease quality register (SWIBREG) that has received funding from Janssen Corporation. Andrew T. Chan serves as a consultant for Janssen Pharmaceuticals, Pfizer Inc, and Bayer Pharma AG, and Boehringer Ingelheim for work unrelated to the topic of this manuscript. Hamed Khalili receives grant funding from Takeda and Pfizer. He has also received consulting fees from AbbVie and Takeda. The remaining authors disclose no conflicts.

Funding

This work is supported by senior research grants by the US Crohn's and Colitis Foundation to HK, AW, and ATC.

The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by the Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Éducation Nationale, and Institut National de la Santé et de la Recherche Médicale (Inserm), (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum, and Federal Ministry of Education and Research (Germany); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare, and Sports, Netherlands Cancer Registry, LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund, and Statistics Netherlands (the Netherlands); Health Research Fund, Instituto de Salud Carlos III, regional governments of Andalucía, Basque Country, Murcia, and Navarra, and the Catalan Institute of Oncology (Spain); Swedish Cancer Society, Swedish Scientific Council, and county councils of Skåne and Västergötten (Sweden); Medical Research Council (MR/N003284/1, MC-PC_13048 and MC-UU_12015/1 to EPIC-Norfolk (DOI [10.22025/2019.10.105.00004](https://doi.org/10.22025/2019.10.105.00004)), Medical Research Council (MR/M012190/1) and Cancer Research UK (C8221/A29017) to EPIC-Oxford (UK). The funders had no role in the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

The NHS and NHSII are supported by grants (UM1 CA186107, U01 CA176726) from the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.