Childhood body mass index and risk of inflammatory bowel disease in adulthood: a population-based cohort study

Camilla B. Jensen, PhD[1], Lars H. Ängquist, PhD[1], Michael A. Mendall, MD[2], Thorkild I. A. Sørensen, MD, DMSc[3,4], Jennifer L. Baker, PhD[1,4] and Tine Jess, MD, DMSc[1,5]

BACKGROUND: **The increasing incidence of inflammatory bowel disease (IBD) in western countries has led to the hypothesis that obesity-related inflammation could play a role in the etiology of IBD. However, this hypothesis lacks confirmation in studies of individuals prior to the typical onset of IBD in young adulthood.**

METHODS: **In a cohort of 316,799 individuals from the Copenhagen School Health Records Register (CSHRR), we examined whether BMI at ages 7 through 13 years was associated with later IBD. Linking the CSHRR to the Danish National Patient Register, we identified cases of Crohn's disease (CD) and ulcerative colitis (UC) diagnosed during follow-up. Cox regression was used to estimate the hazard ratios (HR) with 95% confidence intervals.**

RESULTS: **During 10 million person-years of follow-up, 1500 individuals were diagnosed with CD and 2732 with UC. At all examined ages, a 1 unit increase in BMI *z*-score was associated with a significantly decreased risk of UC (HRs = 0.9) and with a significantly increased risk of CD when diagnosed before age 30 (HRs = 1.2). We observed no associations between changes in BMI *z*-score between 7 and 13 years and later risk of CD or UC.**

CONCLUSION: **We found a direct association between childhood BMI and CD diagnosed before 30 years of age, and an inverse association between childhood BMI and UC irrespective of age. Our results support the previous hypotheses of obesity being a risk factor for CD, and suggest that childhood underweight might be a risk factor for UC.**

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INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic debilitating disorders requiring lifelong medical treatment and often also surgery. The incidence of IBD is increasing, particularly in early adulthood (16–25 years) [1].

The etiology of IBD is largely unknown, but genetics, environment, immunology, and infections may be of importance. In recent years, the increasing incidence of IBD in western countries has led to the hypothesis that overweight, obesity, and obesity-related inflammation play a role in the etiology of IBD. In a study based on the "Nurses' Health Study II," obesity at age 18 years was associated with increased risk of CD but not of UC [2]. Likewise, results from a case–control study showed that obesity was cross-sectionally associated with risk of CD but not UC [3]. This study also reported a cross-sectional association between underweight at time of diagnosis and risk of CD, but this was possibly due to reverse causation. Increased risk of CD was also suggested for both under- and overweight women in a study of the "Danish National Birth Cohort," and again no associations were found for UC [4]. The European Prospective Investigation into Cancer and Nutrition study (EPIC) including more than half a million participants failed

[1]Centre for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Capital Region, Copenhagen,, Denmark. [2]Gastroenterology, Croydon University Hospital, Surrey, UK. [3]Department of Public Health, Section of Epidemiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. [4]The Novo Nordisk Foundation Centre for Basic Metabolic Research, Section on Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. [5]Department of Clinical Medicine, University of Aalborg, Aalborg, Denmark. **Correspondence:** C.B.J. (email: camilla.bjoern.jensen@regionh.dk)

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to find any association between BMI and IBD [5]. Considering that the peak onset of IBD occurs in early adulthood, it is a disadvantage of all above-mentioned studies that results were based on BMI in adult populations, which might induce bias due to reverse causation due to altered BMI after the development of the diseases.

Using the unique Copenhagen School Health Records Register (CSHRR) of 372,636 children with linkage to the National Patient Register (NPR), we investigated if BMI at ages 7 through 13 years was associated with later risk of IBD.

METHODS

Study population

The study population was selected from the CSHRR, which is an ongoing register that includes measures of height and weight for all school children in the Copenhagen municipality [6]. Until 1983, children had yearly measures of height and weight from 7 through 13 years of age as part of the mandatory school health examination. From 1984, children were measured at school entry and exit, and more frequently if the child had special needs. Height and weight were measured with high precision by school physicians and nurses and filled into the child's personal health record. Currently, the register includes 372,636 computerized records of children born between 1930 and 1989.

Childhood BMI was calculated as weight divided by height-squared (kg/m^2) and transformed into z-scores using the LMS method [7, 8]. The z-scores were based on an internal age- and sex-specific reference population of children born between 1955 and 1960, where the obesity prevalence was low and stable. Next, z-scores were interpolated or extrapolated within a $\pm$12-month period to estimate BMI z-scores at precisely 7 through 13 years of age. Z-scores <-4.5 or >4.5 were considered extreme values and excluded. Body size categorization was based on BMI z-scores and the CDC definitions (underweight: BMI z-score ≤ -1.64; normal weight: $-1.64 <$ BMI z-score < 1.04; overweight: $1.04 \leq$ BMI z-score < 1.64; obesity: BMI z-score ≥ 1.64) [9].

Data linkage

Since April 1968, all Danish citizens alive and residing in Denmark or born in Denmark after that date have been assigned a personal identification number by the Danish Civil Registration System [10]. The personal identification number was used to obtain vital statistics and to link the CSHRR to the nationwide NPR for obtaining diagnoses of IBD [11]. The NPR contains all in- and outpatient hospital contacts since 1 January 1977 and all ambulatory outpatient contacts since 1995. Diagnoses are based on the ICD coding system (versions 8 and 10). Incident cases of IBD were identified based on the first occurrence of the ICD-8 codes 563.00 through 563.09 for CD and 563.19 and 569.04 for UC, and the ICD-10 codes K50 for CD and K51 for UC. IBD diagnoses based on the NPR are almost complete and of high validity [12].

Ethics

An access and linkage permission was obtained from the Danish Data Protection Agency (j.no.: 2012-58-0004). This type of research based on pre-existing routinely collected data does not require ethical permission in Denmark.

Statistical analysis

Cox proportional hazards regression was used to examine the association between BMI z-scores at each age and the risk of CD and UC, respectively. BMI z-scores were modeled as continuous variables and as categorical variables of underweight, normal weight, overweight, and obese. Changes in BMI z-score were modeled as continuous variables (e.g., change from 7 to 10 years = BMI z-score at 10 years—BMI z-score at 7 years) and as categorical variables of loss, no change, and gain in body size (e.g., smaller, same, or larger body size at age 7 and 10 years). Age was used as the underlying time scale, and analyses were adjusted for birth year while allowing the baseline hazard to vary over combinations of 5-year birth cohorts and sex.

The associations were checked for non-linearity by using a linear spline with three knots and likelihood ratio tests showed no indications of non-linearity.

Proportional hazards were checked by testing if associations between BMI at each age and UC and CD, respectively, differed within categories of age at risk, i.e., the underlying time scale, using likelihood ratio tests. Based on the Montreal classification [13], we chose $</\geq$40 years at IBD diagnosis as the cut point. Violations of the proportional hazards assumption were detected in the association between BMI z-score (treated continuously) and CD. Stratification of the analyses into the two groups of $</\geq$40 years at IBD diagnosis did not solve the problems with non-proportional hazards in the younger group and we moved the cut point to $</\geq$30 years. The proportional hazard assumption was then met in both groups and the results for BMI and CD were therefore presented for diagnosis before 30 years and after.

Children were included in as many analyses as possible according to availability of data, i.e., a child with information on BMI at 7, 10, and 13 years was included in analyses of the association between BMI z-scores at 7, 10, and 13 years and the risk of CD and UC, respectively.

We performed sensitivity analyses using alternative IBD definitions to reduce the risk of ascertainment bias. First, we defined IBD based on two separate encounters rather than one as in the main analyses, and second we excluded IBD diagnoses made before 1997 when only inpatient contacts were registered plus a couple of years to avoid prevalent cases.

Analyses taking appendicitis into account were performed to exclude potential confounding (diagnosis based on simultaneous reporting of appendicitis (ICD-8: 540, 54199; ICD-10: DK35-DK37) and appendectomy (1977–1995: 43000, 43001; 1996–2011: KJEA00, KJEA01, KJEA10)).

All analyses were performed using Stata 14.

RESULTS

Within the total population of 372,636 boys and girls in the CSHRR, 42,802 children were excluded because they did not have a personal identification number, mainly because of death and emigration before the establishment of the civil registration

system (Fig. 1). Further, 6906 children emigrated, died, or were lost to follow up prior to the 1 January 1977, when the NPR was established, or before they turned 15 years. Seventy-two children were diagnosed with IBD before they turned 15 years, 6048 children had missing information of BMI at all ages, and 9 children had extreme values of BMI. Hence, the final study population consisted of 316,799 children.

The follow-up period lasted up to 39 years from 1 January 1977 to the 31 December 2015 and included approximately 10 million person-years of follow-up. During this period, 4232 individuals were diagnosed with IBD including 634 men and 866 women diagnosed with CD and 1249 men and 1483 women diagnosed with UC (Table 1).

For CD, mean (SD) age at diagnosis was 43.2 (16.6) years for men and 45.8 (17.3) years for women, and for UC, mean (SD) age at diagnosis was 47.4 (16.6) years for men and 48.5 (15.9) years for women (Table 1). As expected, incidence rates by age at diagnosis revealed two peaks for both CD and UC: the first incidence peak was in the interval 20–30 years (2.2 cases of CD per 10,000 person-years and 2.8 cases of UC per 10,000 person-years) and the second was in the interval 65–75 years (2.9 cases of CD per 10,000 person-years and 6.0 cases of UC per 10,000 person-years).

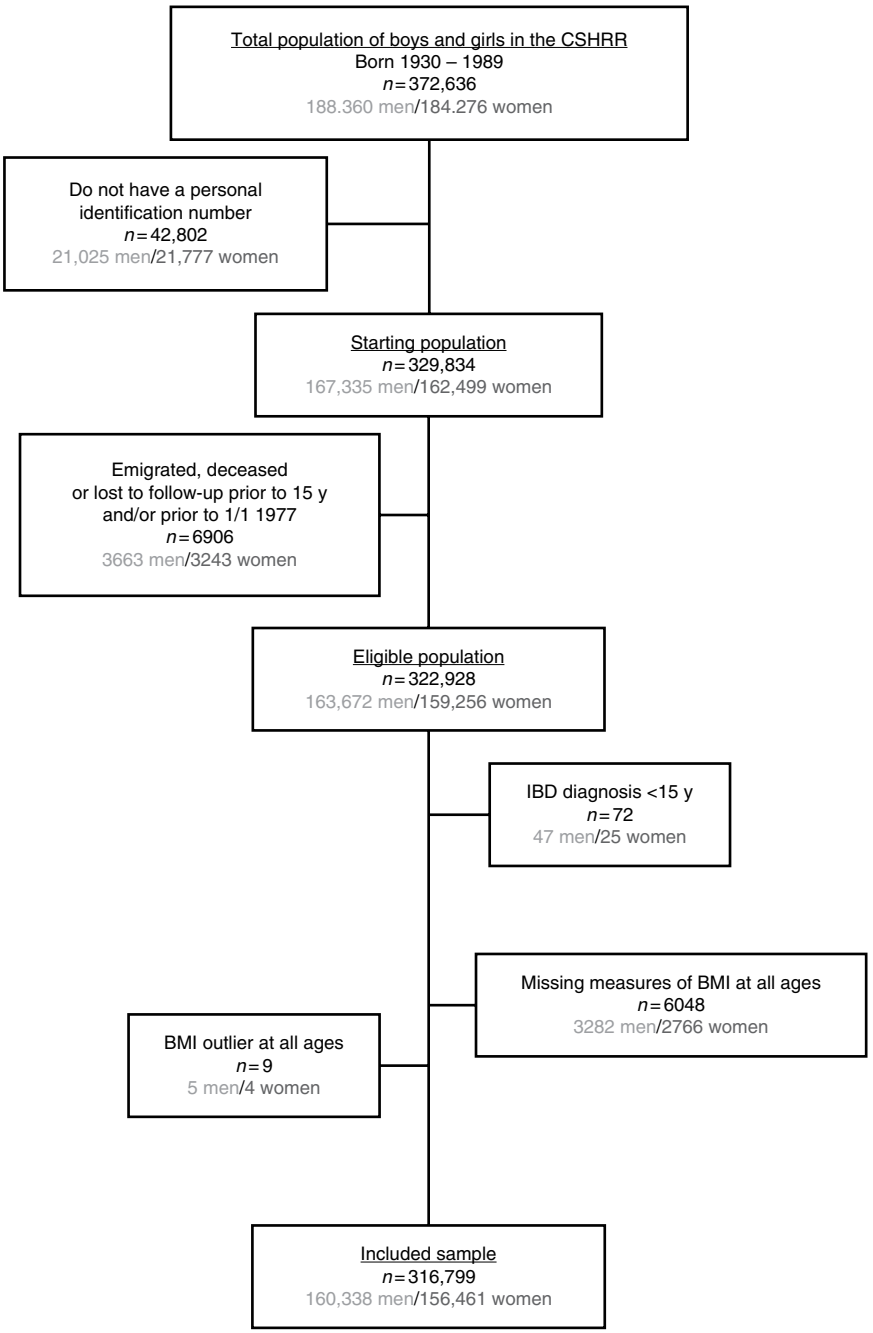

Fig. 1 Flow chart of the study population

Table 1 Descriptive statistics of the 316,799 study participants presented separately for boys and girls

Characteristic	Boys	Girls
n	160,338	156,461
IBD cases (*n*)		
Crohn's disease	634	866
Ulcerative colitis	1,249	1,483
Age at diagnosis, years (mean (SD))		
Crohn's disease	43.2 (16.6)	45.8 (17.3)
Ulcerative colitis	47.4 (16.6)	48.5 (15.9)
BMI, kg/m^2 (mean (SD)) at ages, years		
7	15.5 (1.3)	15.4 (1.4)
8	15.9 (1.4)	15.8 (1.6)
9	16.3 (1.6)	16.3 (1.8)
10	16.7 (1.7)	16.7 (2.0)
11	17.1 (1.9)	17.2 (2.1)
12	17.6 (2.1)	17.2 (2.1)
13	18.2 (2.2)	18.7 (2.5)
Body size[a] at 7 years, *n* (%)		
Underweight	6785 (5)	6348 (4)
Normal weight	123,996 (83)	120,862 (83)
Overweight	12,605 (8)	11,907 (8)
Obese	6429 (4)	7080 (5)
Body size at 10 years, *n* (%)		
Underweight	5536 (4)	4993 (4)
Normal weight	119,284 (84)	115,446 (83)
Overweight	10,678 (8)	12,343 (9)
Obese	6221 (4)	6627 (5)
Body size at 13 years, *n* (%)		
Underweight	4733 (3)	4720 (3)
Normal weight	113,711 (83)	110,801 (82)
Overweight	11,847 (9)	13,387 (10)
Obese	6253 (5)	6653 (5)

[a]Body size categorization was done according to the CDC definitions [9]

As expected, BMI increased with age for both boys and girls (Table 1). For boys, mean BMI increased from 15.5 (1.3) kg/m^2 at 7 years to 18.2 (2.2) kg/m^2 at 13 years, while mean BMI increased from 15.4 (1.4) kg/m^2 at 7 years to 18.7 (2.5) kg/m^2 at 13 years for girls.

We investigated the association of childhood BMI on the risk of IBD using BMI *z*-scores at ages 7 through 13 years as continuous variables. None of the analyses showed interaction between BMI *z*-score and sex and results were presented for boys and girls combined. The analyses of CD were performed separately for diagnosis before and after 30 years of age due to non-proportional hazards. The risk of CD diagnosed before the age of 30 years was significantly increased with increasing BMI *z*-score (HR ~1.2 (CI ~1.1; 1.3) per 1 unit increase in BMI *z*-score) at each age from 7 to 13 years (Fig. 2). There was no significant association between childhood BMI and risk of CD diagnosed after the age of 30 years. We observed a statistically significant inverse association between childhood BMI and risk of UC. The analyses showed HRs of UC of approximately 0.9 (CI = ~0.9; 1.0) per 1 unit of BMI *z*-scores (Fig. 3) across all ages from 7 to 13 years. The confidence intervals did not include 1.

We further investigated the association of childhood BMI by estimating the risk of CD and UC among underweight, overweight, normal weight, and obese children. There was an increasing risk of CD across the categories, where the lowest risk was observed among the underweight children and the highest risk among the obese children, however, compared to the normal weight group the risk was only significantly different in the obese group and not at all ages (Table 2). There was no interaction between BMI categories and age of diagnosis in the association with CD. There was a slight tendency toward a decreasing risk of UC across the BMI categories, but it was not statistically significant (Table 3).

Moreover, we examined if change in BMI *z*-score during childhood was associated with increased risk of CD and UC. Risk of CD and UC was not significantly influenced by changes in BMI *z*-scores from 7 to 10 years or from 10 to 13 years (Table 4). Hence, the HRs, per 0.5 unit increase in BMI *z*-scores, were close to 1.0 for both CD and UC and the confidence intervals included the reference value HR = 1.0. We also analyzed change in body size from 7 to 13 years using categories of underweight, normal weight, overweight, and obese and found no association between change in body size and later risk of CD and UC (Table 4).

Sensitivity analyses based on alternative IBD definitions (diagnosis made at two separate encounters or exclusion of cases prior to 1997) confirmed the results found in the main analyses. Analyses taking appendicitis into account showed no indications of confounding (Supplementary Material **1**)

DISCUSSION

In the present population-based cohort study with long-term follow-up of 316,799 school children, we found that childhood BMI estimated long before the peak onset of IBD, was associated with risk of IBD in adulthood. We analyzed the association using BMI *z*-scores at ages 7 through 13 years as continuous variables and found that childhood BMI was directly associated with risk of CD but only when diagnosed before the age of 30. On the contrary, we observed a novel inverse association between childhood BMI and the risk of UC. Categorization of BMI into groups of underweight, normal weight, overweight, and obesity revealed an increased risk of CD among obese when compared to normal weight. There was no association between BMI categories and risk of UC. Changes in BMI *z*-score between 7, 10, and 13 years were not associated with later risk of CD and UC.

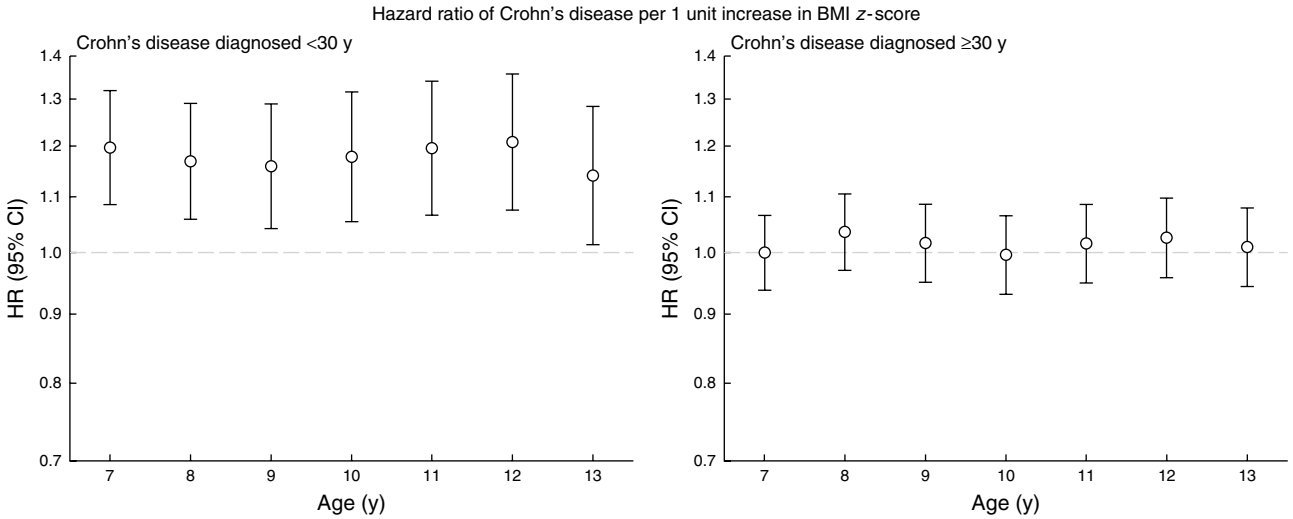

Fig. 2 Hazard ratio and confidence intervals of Crohn's disease diagnosed before and after 30 years of age per 1 unit BMI *z*-score increase at each of the ages 7 through 13 years

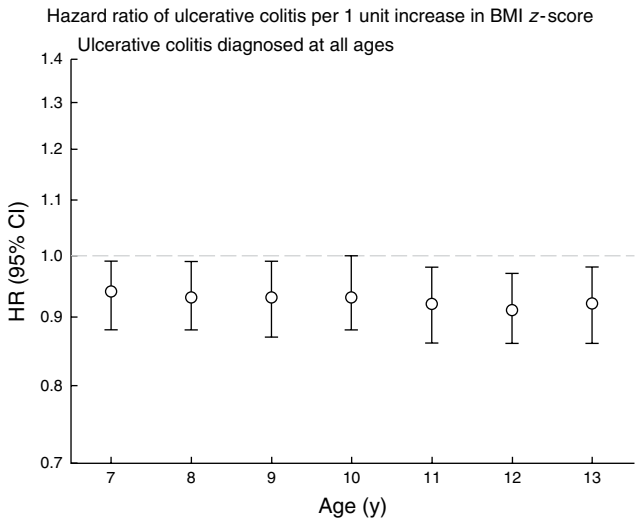

Fig. 3 Hazard ratio and confidence intervals of ulcerative colitis per 1 unit BMI *z*-score increase at each of the ages 7 through 13 years

It is difficult to compare the present findings to the previous literature since previous studies have investigated associations between adult body size and risk of IBD rather than childhood body size [2–5]. However, despite the differences, most of the previous studies agree with the present study that the risk of CD is increased among obese. A prospective study based on the "Nurses' Health Study II" included recalled information of BMI at 18 years of age and found that women with BMI above 30 kg/m^2 had an increased risk of later CD compared to normal weight women (20–25 kg/m^2) [2]. Another prospective study including younger women (median age 30.2 years) from the "Danish National Birth Cohort" found that women with BMI >30 kg/m^2 had increased risk of CD compared to normal weight women (BMI: 18.5–25 kg/m^2) and so did women with BMI <18.5 kg/m^2 [4]. A case–control study based on IBD patients and controls in the age range 50–70 years found an increased risk of obesity (BMI >30 kg/m^2) among CD cases compared to controls [3]. They did not investigate if low BMI was associated with risk of IBD. In the EPIC study with a median age of 52.8 years, they failed to find any association between BMI and IBD [5].

For UC, we found a novel inverse association between childhood BMI and UC. None of the previous studies on the association between BMI and IBD observed any associations with UC. The HRs for UC in our study were approximately 0.9 per BMI *z*-score unit increase, which might be the reason that previous studies with fewer cases were not able to detect an association. The mechanisms behind the association remain unknown. We speculate that the observed association could reflect consequences of altered immunology or gut microbiota induced by childhood underweight. Another speculation is that our observation could reflect subclinical manifestations of UC that present as lower BMI already in childhood. However, the subject needs further investigation before qualified suggestions can be made.

A major difference between the present and previous studies is the time from BMI estimation to diagnosis of IBD. Previous studies measured BMI in adulthood and the outcomes were adult IBD leaving a shorter time span to diagnosis than in the present study. Furthermore, one study even looked at BMI at time of IBD diagnosis [3]. Associations observed in adulthood might be influenced by reverse causation, which could be the explanation behind the association between low BMI and CD which was not observed in the present study. On the contrary, it seems that the childhood BMI might be too far away from the time of diagnosis to have any influence on risk of IBD. Our results indicate that after the age of 30 years, other risk factors for CD might dominate or alternatively that tracking of childhood BMI into adulthood diminishes after the age of 30 years obscuring any association with IBD developed in adult life. Mechanisms behind the hypothesized association between BMI and CD include obesity-induced inflammation [14] or obesity-induced intestinal permeability [15] that allows harmful substances to breach the gastrointestinal tract both leading to

Table 2 Hazard ratio (HR) and confidence intervals of Crohn's disease per BMI category at each of the ages 7 through 13 years

Age (years)	Crohn's disease								
	Underweight[a]		Normal weight[a]		Overweight[a]		Obese[a]		
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	*P**
7	1.01	(0.78; 1.30)	1.0	(ref)	1.20	(1.01; 1.44)	1.12	(0.88; 1.42)	0.10
8	0.90	(0.68; 1.19)	1.0	(ref)	1.03	(0.85; 1.24)	1.22	(0.97; 1.54)	0.08
9	0.93	(0.70; 1.24)	1.0	(ref)	0.89	(0.73; 1.09)	1.27	(1.01; 1.60)	0.21
10	0.91	(0.68; 1.22)	1.0	(ref)	0.92	(0.75; 1.13)	1.35	(1.07; 1.70)	0.06
11	0.88	(0.65; 1.20)	1.0	(ref)	1.05	(0.86; 1.27)	1.31	(1.04; 1.66)	0.02
12	0.90	(0.66; 1.22)	1.0	(ref)	1.05	(0.87; 1.28)	1.40	(1.12; 1.77)	0.01
13	0.99	(0.73; 1.34)	1.0	(ref)	1.17	(0.97; 1.40)	1.40	(1.12; 1.76)	0.002

[a]Body size categorization was done according to the CDC definitions [9]
**P* for trend

Table 3 Hazard ratio (HR) and confidence intervals of ulcerative colitis per BMI category at each of the ages 7 through 13 years

Age (years)	Ulcerative colitis								
	Underweight[a]		Normal weight[a]		Overweight[a]		Obese[a]		
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	*P**
7	1.04	(0.86; 1.25)	1.0	(ref)	1.01	(0.87; 1.16)	0.79	(0.64; 0.98)	0.09
8	1.09	(0.90; 1.32)	1.0	(ref)	1.05	(0.92; 1.21)	0.92	(0.75; 1.13)	0.5
9	1.08	(0.88; 1.32)	1.0	(ref)	1.09	(0.95; 1.25)	0.86	(0.70; 1.06)	0.4
10	1.12	(0.92; 1.37)	1.0	(ref)	1.02	(0.88; 1.18)	0.99	(0.81; 1.21)	0.7
11	1.15	(0.94; 1.40)	1.0	(ref)	0.90	(0.77; 1.05)	1.00	(0.82; 1.22)	0.2
12	1.00	(0.81; 1.24)	1.0	(ref)	0.97	(0.84; 1.12)	0.93	(0.76; 1.14)	0.5
13	1.20	(0.98; 1.47)	1.0	(ref)	0.93	(0.80; 1.07)	1.02	(0.83; 1.24)	0.3

[a]Body size categorization was done according to the CDC definitions [9]
**P* for trend

inflammation followed by IBD. Another mechanism could operate through alterations in the microbiota [16].

The major strength of the present study is the large and unselected study population recruited during childhood (before normal onset of IBD) and followed into adulthood (after normal onset of IBD). In this regard, the study differs from earlier studies of BMI in adulthood and risk of IBD. A potential limitation to the study is the lack of adjustment for potential confounders such as family history of IBD, lifestyle factors, and smoking. Typically, smoking is considered a confounder in the association between body size and IBD, but in the present study the timing of body size evaluation precedes the time when most people take up smoking, and therefore smoking must be considered a mediator of the association rather than a confounder and should not be controlled for. All socioeconomic population groups are represented in the CSHRR that contains records of virtually every school child attending public or private schools in the Copenhagen municipality from 1936 onward [6]. Still, there is a socioeconomic gradient in childhood overweight and obesity (with highest prevalence in groups of low socioeconomic status [17]), which we were not able to take into account in the analyses. The incidence of IBD is, on the other hand, highest in persons of high socioeconomic status [18], which in case of confounding would bias the positive association between childhood BMI and CD toward null. However, the inverse association childhood BMI and UC could be an expression of confounding from socioeconomic status if the prevalence of UC is truly higher among persons of high socioeconomic status.

Nearly all study participants were of Danish origin [6] and the generalizability of the study is therefore restricted to Caucasian populations. Furthermore, the results are restricted to urban populations since all study participants per definition lived in Copenhagen.

The present study included 1500 CD cases and 2732 UC cases, which by far exceeds previous studies of maximum 153 CD cases

Table 4 Hazard ratio (HR) and confidence intervals of Crohn's disease and ulcerative colitis per 0.5 unit BMI *z*-score change and categorical change between ages 7 and 10 years and 10 and 13 years

Change in childhood body size	Crohn's disease			Ulcerative Colitis		
	Cases	HR	95%CI	Cases	HR	95%CI
7–10 years						
0.5 unit BMI *z*-score increase	1283	1.00	(0.95; 1.05)	2343	1.01	(0.97; 1.05)
Categorical change in body size[a]						
No change	1092	1.0	(ref)	1998	1.0	(ref)
Gain	107	1.03	(0.85; 1.26)	199	1.07	(0.93; 1.24)
Loss	84	0.95	(0.76; 1.19)	146	0.91	(0.78; 1.09)
10–13 years						
0.5 unit BMI *z*-score increase	1324	1.02	(0.97; 1.08)	2255	0.99	(0.94; 1.03)
Categorical change in body size[a]						
No change	1049	1.0	(ref)	1962	1.0	(ref)
Gain	111	1.17	(0.96; 1.43)	152	0.89	(0.76; 1.05)
Loss	64	0.86	(0.67; 1.11)	141	1.05	(0.88; 1.24)

[a]Change in body size based on CDC categorization at each age [9]

and 394 UC cases [2–5]. In Denmark, IBD patients are diagnosed in in- or outpatient hospital clinics. The NPR contains discharge diagnosis from all Danish hospitals, which is why the risk of selection bias is minimal. In a validation study using a pathology register as the golden standard, the IBD diagnoses in the NPR were found to be valid and almost complete [12]. However, patients diagnosed and treated outside the hospital were not included in the NPR before 1995 and patients experiencing a less severe IBD might be underrepresented in the present study. Hence, our associations may potentially apply to more severe IBD. Another potential limitation is the definition of CD and UC cases based on the first given diagnosis in the NPR. To avoid conditioning on the future, we did not change a diagnosis to CD, if a UC patient was later recorded with a diagnosis of CD (which may happen in up to 10% of cases). This is a methodological choice, which may bias the risk estimates for UC toward null, if the hypothesis of a higher risk in CD was true. However, sensitivity analyses using other IBD definitions confirmed the observed associations.

A potential limitation was the lack of information on adult body size. However, studies have shown that BMI tracks strongly from childhood to young adulthood [19], which is the time period of great relevance for IBD. An advantage of the early body size estimation is that the risk of reverse causation is reduced since the height and weight measurements preceded the time of diagnosis.

Another potential limitation is the definition of childhood underweight, normal weight, overweight, and obesity based on BMI measures. BMI may not be the optimal measure of body composition, but childhood BMI has been shown to correlate with more direct measures of body composition as DEXA [20].

In the present population-based cohort study of 316,799 prospectively followed school children from Copenhagen, Denmark, we found a direct association between childhood BMI and CD when estimated using BMI *z*-scores at ages 7 through 13 years, but only when the disease was diagnosed earlier than 30 years of age. Furthermore, we found an inverse association between childhood BMI and UC diagnosed at any age. Our results support the previous hypotheses of obesity being a risk factor for CD avoiding concerns over reverse causation. In addition, the novel observation that underweight might be a risk factor for UC is made. These results add to other known consequences of both overweight and underweight and suggest new routes for prevention of IBD.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Obesity-related inflammation might play a role in the etiology of inflammatory bowel disease (IBD).
- ✓ Several studies suggest obesity may be associated with a higher risk of CD.

WHAT IS NEW HERE

- ✓ BMI in childhood is positively associated with risk of Crohn's disease up to age 30 years.
- ✓ Childhood underweight is found to be a risk factor for development of ulcerative colitis in adulthood.
- ✓ Results add to known consequences of overweight and underweight and suggest new routes for prevention of IBD.

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Conflict of interest

Guarantor: CBJ had full access to all data in the study and had the final responsibility for the decision to submit for publication.

Specific author contributions: CBJ and TJ conceived and designed the research; CBJ, LHÄ, and TJ conducted the research; CBJ, LHÄ, TJ, JLB, MAM, and TIAS analyzed data; CBJ and TJ wrote the article and had primary responsibility for final content. All authors read and approved the submitted article.

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Potential competing interests: The authors declare that they have no conflict of interest.

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