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Measures of Obesity and Risk of Crohn's Disease and Ulcerative Colitis

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Abstract

Introduction—Obesity is associated with intestinal-specific inflammation. Nonetheless, a specific role of obesity in the etiology of inflammatory bowel disease (IBD) is unclear.

Methods—We conducted a prospective cohort study of U.S. women enrolled in 1989 in the Nurses' Health Study II. At baseline, we collected information on height, weight, waist and hip circumference, weight at age 18, and body shape at age 20. We used Cox proportional hazards models to calculate hazard ratios (HR) and 95% confidence intervals (CIs).

Results—Among 111,498 women (median age, 35 years), we documented 153 cases of CD and 229 cases of UC over 18 years of follow-up, encompassing 2,028,769 person-years. Compared to women with normal BMI, the multivariate-adjusted HRs of CD were2.33 (95% CI, 1.15–4.69) for

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Data sharing: Requests for access to data, statistical code, questionnaires, and technical processes may be made by contacting the corresponding author at hkhalilipartners.org.

Authors Contributions
HK - study concept and design; acquisition of data; statistical analysis; interpretation of data; drafting of the manuscript;
ANA- acquisition of data; critical revision of the manuscript.
GK - acquisition of data; critical revision of the manuscript.
LMH - acquisition of data; critical revision of the manuscript for important intellectual content.
JMR - study concept and design; acquisition of data; critical revision of the manuscript.
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obese women at age 18 and 1.58 (95% CI, 1.01–2.47) for obese women at baseline. Increasing weight gain between age 18 and baseline was associated with increased risk of CD (P_{trend}=.04). Adolescent body habitus was also associated with risk of CD with a multivariate-adjusted HR of CD of 1.63 (95% CI, 1.07–2.50) for women with overweight/obese body shape compared to women with a thin/slender body shape. We did not observe a significant association between any of these anthropometric measures and risk of UC.

Conclusion—In a large prospective cohort of US women, measures of adiposity were associated with an increased risk of CD but not UC. Further studies are needed to elucidate the biological mechanisms by which excess adiposity may increase the risk of CD.

Keywords

Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Obesity; Body Mass Index; Waist to Hip Ratio; Nurses' Health Study II

Introduction

Despite the success of genome wide association studies in identifying large number of common variants associated with Crohn's disease (CD) and ulcerative colitis (UC),[1] the exact pathophysiology of the disease remains largely unknown. As the overall risk contribution of these common variants is only modest,[1] identification of novel environmental risk factors with plausible biologic link to disease risk is vital to improve our understanding of disease pathophysiology.

Obesity as measured by body mass index (BMI) has been linked to elevated levels of proinflammatory markers such as tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP).[1,2] More specifically, obese individuals have been shown to have higher levels of inflammation in the gastrointestinal tract as measured by stool calprotectin.[3] Despite the presence of these compelling data, epidemiologic studies have failed to identify a consistent link between obesity and risk of CD and UC. Previous studies have had significant limitations including retrospective design, inability to adjust for important life style factors, and lack of detailed and updated information on BMI and other measures of obesity.

We therefore sought to investigate the association between measures of obesity and risk of CD and UC in the Nurses Health Study (NHS) II. With more than 20 years of biennially updated and validated data on lifestyle, diet, and medical diagnoses, this cohort offered us the unique opportunity to examine the association between measures of obesity assessed at multiple time points over adulthood and subsequent risk of UC and CD in the context of other potential risk factors.

METHODS

Study Population

The NHSII is a prospective cohort that began in 1989 when 116,686 U.S. female registered nurses, ages 25 to 42 years, completed a mailed health questionnaire. Follow-up

questionnaires are mailed every two years to update health information; follow-up has consistently exceeded 90%. A validated assessment of physical activity is administered every two to four years; a validated semi-quantitative food frequency questionnaire is administered every four years. The institutional review board at the Brigham and Women's Hospital approved this study.

Assessment of measures of obesity

Information on weight and height and weight at the age of 18 was obtained from the baseline 1989 questionnaire. Participants then updated their current weight on each biennial questionnaire. BMI at age 18, baseline, and every 2 years since baseline was calculated using the corresponding weight and height at baseline. Updated BMI was defined as most recent BMI reported prior to each 2-year interval (time between two consecutive questionnaires). Weight change since the age of 18 was calculated by subtracting the baseline weight from the weight at age 18. Information on body habitus at multiple time points early in life (age 5, 10, and 20) was also reported in the baseline questionnaire using a nine-level pictogram depicting body shapes ranging from 1=most lean to 9=most overweight.

Waist and hip measurements were reported in the 1993 questionnaire. For waist circumference, participants were provided a tape measure and instructed to measure their waist circumference at the level of the navel, and for hip circumference they were instructed to measure the largest circumference around the hips (including the buttocks). 44,291 participants measured their hip and waist sizes. Waist to hip ratio was calculated by dividing waist circumference over hip circumference.

The accuracy of self-reported anthropometric measures was evaluated among 140 NHS participants by having trained technicians visit those participants twice.[4] After adjustment for age and within-person variability, the Pearson correlation coefficient between self-report and the average of the 2 technician measurements was 0.97 for weight, 0.89 for waist circumference, and 0.84 for hip circumference. In addition, recalled weight at age 18 and self-reported height were compared with records obtained from physical examination conducted at college or nursing school entrance in a study of 118 participants in the NHSII.[5] The correlation between recalled and measured past weight was 0.87 and between reported current height and measured past height was 0.94.

Assessment of Other Covariates

On each biennial questionnaire, women were also asked about pertinent lifestyle factors, including smoking status, and use of non-steroidal anti-inflammatory drugs (NSAIDs), hormone therapy, and oral contraceptive use. Information on physical activity was also collected every 2–4 years. Participants' self-report of physical activity and use of NSAIDs and oral contraceptives have been previously validated.[5,6] In 1991 in NHSII, women were also asked their latitude of residence at age 30, which we have previously shown to be associated with risk of UC and CD.[7] Information about history of appendectomy was collected in 1995 in NHSII. Intakes of dietary fiber and vitamin D were assessed using validated, self-administered, semi quantitative food frequency questionnaires (FFQs)

administered in 1991, 1995, 1999, 2003, and 2007 in NHSII. A previous validation study from NHS showed a correlation of 0.61 between dietary fiber intake measured by FFQ and weighted records.[8]

Outcome Ascertainment

We have previously detailed our methods for confirming self-reported cases of CD and UC.[7,9] In brief, since 1989, participants have reported diagnoses of UC or CD through an open-ended response on biennial surveys. In addition, we have specifically queried participants about diagnoses of both UC and CD since 1993. When a diagnosis was reported on any biennial questionnaire, a supplementary questionnaire and related medical records were requested and reviewed by two gastroenterologists blinded to exposure information.

We excluded participants who subsequently denied the diagnosis on the supplementary questionnaire or permission to review their records. Data were extracted on diagnostic tests, histopathology, anatomic location of disease, and disease behavior. Using standardized criteria,[10–13] UC diagnosis was based on a typical clinical presentation ≥ 4 weeks and endoscopic or surgical pathological specimen consistent with UC (e.g. evidence of chronicity). CD diagnosis was based on a typical clinical history for ≥ 4 weeks and endoscopy or radiologic evaluation demonstrating small bowel findings, or surgical findings consistent with CD combined with pathology suggesting transmural inflammation or granuloma. Disagreements were resolved through consensus. Among those women whom we received adequate medical records, the case confirmation rate for IBD was 78%.[9] Women for whom we did not confirm CD or UC were included in the analyses as non-cases. After excluding all cases of CD and UC at the baseline questionnaire and among women with missing physical activity information, we included 153 incident cases of CD and 229 incident cases of UC. These incidence rates are largely consistent with those reported in other U.S. populations.[14–16]

Statistical Analysis

We examined the possibility that there is a non-linear association between obesity and risk of CD and UC using a previously reported non-parametic cubic spline method,[17] which also permits controlling for covariates and stepwise selection among spline variables. This analysis provides p-values from the likelihood ratio tests for non-linearity, a linear relation, and any relation. Using this method, the likelihood ratio tests comparing models with linear terms with those with spline terms were not statistically significant (All $P_{comparisons} > 0.50$), indicating that the relationship between obesity and risk of CD and UC is linear. As these analyses are particularly sensitive to outliers we performed further sensitivity analyses removing observations beyond 3 interquartile ranges and confirmed that the likelihood ratio tests comparing models with linear terms with those with spline terms were not statistically significant (All $P_{comparisons} > 0.40$). Based on these findings, we used clinical categories of overweight and obesity for our main analyses. In analyses of waist to hip ratio, because of our limited sample size, we used quartile categories to ensure an even distribution of participants in each category.

Person-time for each participant was calculated from the date of return of their baseline questionnaires to the date of the diagnosis of UC or CD, date of last returned questionnaire, or June 1, 2009, whichever came first. At baseline, we excluded participants with missing anthropometric measurements, history of IBD or cancer (with the exception of non-melanoma skin). We used Cox proportional hazards modeling with time-varying covariates to adjust for other known or suspected risk factors including age, smoking, oral contraceptives use, geographic latitude of residence at age 30, physical activity (Met-hr/week), regular use of NSAID's, menopausal hormone therapy, dietary fat, fiber, and vitamin D intake and appendectomy prior to each 2-year interval to calculate adjusted hazard ratios (HR) and 95% confidence interval (CIs). The multivariate-adjusted HR of CD and UC according to all covariates included in the models are reported in Supplementary Table 1. All *P*-values were 2-sided and < 0.05 was considered statistically significant.

RESULTS

Through 2009, we documented 153 incident cases of CD and 229 incident cases of UC among 111,498 women who contributed 2,028,769 person-years of follow up. The median time from enrollment to diagnosis were 9.7 years for CD and 9.0 years for UC cases At baseline, compared to women with BMI of 20–24.9 kg/m^2, obese women (BMI ≥ 30 kg/m^2) tended to be older, were more likely to have had an appendectomy, use NSAIDs, have a obese body shape at age 20, and have a higher WHR and BMI at age 18 (Table 1). As expected, obese women in average had a lower level of physical activity. There were no significant differences according to geographic latitude of residence at age 30 or use of menopausal hormones or oral contraceptives.

Using BMI at age 18, compared to women with BMI of 20–24.9 kg/m^2, the age-adjusted HR of developing CD subsequently in adulthood was 1.01 (95% CI, 0.54–1.91) for overweight women (BMI of 25–29.9 kg/m^2) and 2.48 (95% CI, 1.24–4.98) for obese women (BMI ≥ 30 kg/m^2) (Table 2). This risk estimate was not significantly altered after adjusting for known and potential risk factors for CD including physical activity, smoking, appendectomy, and use of oral contraceptives, NSAIDs, and menopausal hormone therapy (multivariate-adjusted HR = 2.33, 95% CI 1.15–4.69 for obese women). In analyses in which we examined either BMI at baseline in 1989 or the most recent updated BMI before each two-year follow-up interval, we observed similar findings. Using baseline BMI, compared to women with BMI of 20–24.9 kg/m^2, the multivariate adjusted HR of CD was 0.88 (95% CI, 0.56–1.39) for overweight and 1.58 (95% CI, 1.01–2.47) for obese women. Similarly using updated BMI, compared to women with BMI of 20–24.9 kg/m^2, the multivariate adjusted HR of CD was 1.04 (95% CI, 0.68–1.59) for overweight and1.48 (95% CI, 0.98–2.23) for obese women.

In sensitivity analyses, we additionally adjusted our models for dietary intake of fat, fiber, and vitamin D which have been previously associated with risk of IBD in our cohorts.[18–20] We limited our analyses to follow up after 1991 at which point dietary data were collected in the NHSII. Compared to women with BMI of 20–24.9 kg/m^2 at baseline and age 18, the multivariate-adjusted HRs of CD were 1.57 (95% CI, 1.00–2.45) for obese women at

baseline and 2.33 (95% CI, 1.15–4.69) for obese women at age 18 after additionally adjusting for total fiber and fat intakes.

In contrast, we did not observe an association between BMI at age 18, baseline BMI, and updated BMI and risk of UC (Table 3). Compared to women with BMI of 20–24.9 kg/m^2 at age 18, the multivariate-adjusted HR of UC for obese women was 1.17 (95% CI, 0.54–2.52). Similarly, compared to women with BMI of 20–24.9 kg/m^2, the multivariate-adjusted HRs of UC for obese women were 0.99 (95% CI, 0.64–1.53) for baseline BMI and 0.85 (95% CI, 0.58–1.23) for updated BMI.

We also explored the association between change in weight from age 18 to age at baseline enrollment and risk of UC and CD (Table 4). Higher weight gain was associated with increased risk of CD (P_{trend} = 0.04). Specifically, compared to women who maintained their weight (within 5 lbs), women who gained more than 30 lbs had a multivariate-adjusted HR of 1.52 (95% CI, 0.87–2.65). In contrast, we did not observe an association between weight change (from age 18 to baseline) and risk of UC (P_{trend} = 0.17). Compared to women who maintained their weight (within 5 lb) from age 18 to baseline in the cohort, the multivariate-adjusted HR of UC for women who gained more than 30 lbs was 0.92 (95% CI, 0.60–1.40).

We evaluated the association between abdominal obesity and risk of CD and UC (Table 5 and Supplementary Table 2). Compared to women in the lowest quartile of WHR, the multivariate-adjusted HR of CD were1.15 (95% CI, 0.53–2.49) for women in the second quartile, 1.54 (95% CI, 0.79–3.01) for women in the third quartile, and 1.58 (0.78–3.21) for women in the highest quartile, although this trend did not reach statistical significance (P_{trend} = 0.14). this trend did not reach statistical significance (P_{trend} = 0.14). In contrast, there was no association of WHR with risk of UC. Compared to women in the lowest quartile of WHR, the multivariate-adjusted HR of UC for participants in the highest quintile was 1.44 (95% CI, 0.80–2.59, P_{trend}= 0.37).

Finally, we explored the association between adolescent body habitus and risk of CD and UC. Compared to women with a thin/slender body habitus at age 20, the multivariate-adjusted HR of CD for women with overweight/obese habitus was 1.63 (95% CI, 1.07–2.50). Conversely, we did not observe an association between body habitus at age 20 and risk of UC. Compared to women with a thin/slender body habitus at age 20, the multivariate-adjusted HR of UC for women with overweight/obese habitus was 0.90 (95% CI, 0.58–1.39).

DISCUSSION

In a large prospective cohort of US women, we found that obesity, as measured by BMI, is associated with increased risk of CD. Higher weight gain since age 18 and body habitus characteristic of overweight and obesity were also associated with increased risk of CD. Central obesity, as measured by WHR was also associated with non-statistically significant increased risk of CD. In contrast, we did not observe an association between any of these measures of adiposity and risk of UC.

Several lines of evidence suggest that an association between adiposity and CD maybe biologically plausible. First, adipocyte-derived mediators such as leptin, TNF-α, and IL-6 are known to be prominent pro-inflammatory mediators.[21] Second, creeping fat or fat wrapping has long been recognized as marker of CD activity and is strongly correlated with muscular hypertrophy, fibrosis, and stricturing.[22] Third, obesity is associated with increased levels of intestinal inflammation as measured by stool calprotectin.[3] Fourth, obesity has been linked to alterations in the gut microbiome,[23–27] which in turn likely plays a key role in pathogenesis of CD. Lastly, excess adiposity is associated with markers of increased intestinal permeability that may play a key role in development of CD.[28] In addition, the specific finding of creeping fat in CD and the key role of adipose tissue in innate immunity may also explain the unique association between measures of obesity and risk of CD but not UC.[29]

Our findings are supported by previous studies. A previous case-control study showed that obesity was more common among CD patients from a gastroenterology clinic than community controls without IBD (OR = 3.22, 95% CI 1.59–6.52).[30] In addition, numerous other studies have shown that obesity is associated with more complicated disease as reflected by earlier time to surgery and anoperineal complications among patients with established disease.[31,32]In contrast, a recent study[33] using data from the European Prospective Investigation in Cancer (EPIC) cohort found no association between obesity as measured by BMI and risk of UC or CD. However, BMI was only assessed at baseline and the participants in this study were significantly older than our study population (median age at recruitment 50–53 years).A significant limitation of using BMI in such an older population is that it poorly reflects age-associated changes in fat distribution. Specifically, aging is associated with a redistribution of fat into visceral (omental and mesenteric), subcutaneous abdominal, intramuscular, and intrahepatic compartments, which are risk factors for insulin resistance and metabolic diseases associated with chronic inflammation.[34] Therefore, BMI may not fully reflect the level of pro-inflammatory fat depots found in older adults.

Our study has several notable strengths. First, our prospective study design avoids the potential selection biases of retrospective, case-control studies that collect data on lifestyle after diagnosis of CD or UC. Second, we confirmed all cases of CD and UC through medical record review, a significant advantage over studies that rely on self-report or discharge codes, which may not accurately reflect true diagnoses. Third, the availability of detailed and validated information on physical activity, prior oral contraceptive use, and smoking allowed us to control for a number of potential risk factors that may have influenced our observed associations. Fourth, in our analysis, we collected information on BMI at age 18 and every two years staring at the time of enrollment and used time-varying exposures in our Cox models. Thus, we were able to account for changes in participants' weight over much of their adulthood. In addition, we collected information on other anthropometrics including hip and waist measurement and body habitus allowing us to evaluate the link using other measures of obesity. Last, our validation studies[4,5] demonstrated that reported and recalled weight, height, and waist and hip circumferences from our participants are relatively valid and reproducible.

We acknowledge several limitations. First, our cohort may not be representative of the overall US population. However, as we have previously reported,[7] our age-specific incidence of CD and UC are largely similar to rates from other U.S. populations. In addition, previous studies have shown that the prevalence of risk factors, such as smoking and BMI, in our cohort are consistent with those of the broader population of U.S. women.[35,36] Second, despite our high follow-up rate over 20 years and participants' health literacy as nurses, it is possible that some cases of UC and CD were not reported. However, such misclassification of the outcome would tend to attenuate our risk estimates towards the null. Third, we acknowledge that since only a subset of participants had available information on waist and hip measurements, we had limited power to detect an association between central obesity and risk of UC or CD. In addition, the limited number of cases in the highest categories of BMI may have limited the robustness of our findings. Fourth, our study is observational and we cannot exclude the possibility of residual confounding. However, adjustment for the most important risk factors previously identified for UC and CD did not appreciably alter our results. Nevertheless, we acknowledge that in analyses in which we additionally adjusted for dietary factors, the magnitude of our effect estimates were consistent, albeit with lower precision as our confidence interval included one.

In conclusion, in a large prospective cohort of US women we found that obesity as measured by BMI and body habitus, particularly in early adulthood, as well as change in BMI since age 18, is associated with risk of CD but not UC. Future studies examining the exact mechanism by which obesity may influence the development of CD are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics of Study Participants According to Body Mass Index in 1989*

	Body mass index (kg/m^2)			
	< 20 N = 17,196	**20–24.9 N = 60,685**	**25–29.9 N = 20,817**	**≥ 30 N = 12,800**
Age (years), means (SD)	33.7 (4.6)	34.7 (4.6)	35.4 (4.6)	35.9 (4.5)
Race (non-white), %	4.0	5.0	5.0	4.0
Geographic residence at age 30, %				
Southern latitude	18	16	15	15
Smoking, %				
Never	67	65	65	66
Past	19	22	21	21
Current	14	13	14	13
Body mass index at age 18 (kg/m^2), means (SD)	18.8 (1.7)	20.6 (2.3)	22.5 (3.1)	25.7 (4.8)
Waist to hip ratio, means (SD)	0.76 (0.07)	0.77 (0.07)	0.81 (0.08)	0.84 (0.09)
Body shape at age 20, %				
Thin/slender	98	93	86	60
Overweight/obese	2	7	14	40
Physical activity (Mets-hr/week), means (SD)	29.2(42.5)	26.1(37.5)	21.5(31.6)	17.7(28.7)
Ever use of oral contraceptives, %	83	84	83	80
Regular use of NSAIDs, %				
≥ 2 tablets/wk	15	18	22	28
Premenopausal, %	95	94	93	92
Menopausal hormone therapy§, %				
Never Use	40	50	43	43
Past Use	20	17	14	14
Current Use	40	33	43	43
Appendectomy, %	11	12	14	16

Abbreviations: Standard Deviation (SD).

Values are expressed as means (standard deviation) or percentages.

* Characteristics based upon data from baseline questionnaire in 1989 with the exception of race and waist to hip ratio, which were derived from the 1993 questionnaire.

§ Percentages among postmenopausal women.

Table 2

Body Mass Index and Risk of Crohn's Disease (1989–2009)*

	Body mass index (kg/m^2)			
	< 20	**20–24.9**	**25–29.9**	**≥ 30**
Body mass index at age 18				
Person-years of follow-up	798,733	1,022,097	157,742	50,197
No. of cases	62	71	11	9
Age-adjusted HR (95% CI)	1.11 (0.79–1.56)	1.00	1.01 (0.54–1.91)	2.48 (1.24–4.98)
Multivariate-adjusted HR (95% CI)§	1.14 (0.81–1.60)	1.00	0.98 (0.52–1.85)	2.33 (1.15–4.69)
Body mass index at baseline in 1989				
Person-years of follow-up	320,551	1,107,322	373,867	227,028
No. of cases	19	82	25	27
Age-adjusted HR (95% CI)	0.78 (0.47–1.29)	1.00	0.93 (0.59–1.46)	1.68 (1.09–2.60)
Multivariate-adjusted HR (95% CI)§	0.79 (0.48–1.35)	1.00	0.88 (0.56–1.39)	1.58 (1.01–2.47)
Updated body mass index				
Person-years of follow-up	181,993	919,915	507,739	419,121
No. of cases	16	59	35	43
Age-adjusted HR (95% CI)	1.35 (0.77–2.35)	1.00	1.09 (0.72–1.67)	1.60 (1.07–2.39)
Multivariate-adjusted HR (95% CI)§	1.37 (0.78–2.39)	1.00	1.04 (0.68–1.59)	1.48 (0.98–2.23)

*Abbreviations: Hazard Ratio (HR), Confidence Interval (CI)

§Models adjusted for age (months), smoking (never, past, current), physical activity at baseline in quintile (MET-hours/week), oral contraceptive use (never, past, current), menopausal hormone therapy (never, past, current, premenopause), appendectomy (no, yes), geographic latitude of residence at age 30 (southern, middle, northern, missing/unknown), and NSAID's use (< 2 tablets/week, ≥ 2 tablets/week).

Table 3

Body Mass Index and Risk of Ulcerative Colitis (1989–2009)*

	Body mass index (kg/m^2)			
	< 20	**20–24.9**	**25–29.9**	**≥ 30**
Body mass index at age 18				
Person-years of follow-up	798,733	1,022,097	157,742	50,197
No. of cases	88	121	13	7
Age-adjusted HR (95% CI)	0.93 (0.71–1.23)	1.00	0.69 (0.39–1.23)	1.18 (0.55–2.52)
Multivariate-adjusted HR (95% CI)§	0.95 (0.72–1.25)	1.00	0.69 (0.39–1.22)	1.17 (0.54–2.52)
Body mass index at baseline in 1989				
Person-years of follow-up	320,551	1,107,322	373,867	227,028
No. of cases	40	130	34	25
Age-adjusted HR (95% CI)	1.06 (0.75–1.52)	1.00	0.78 (0.54–1.14)	0.96 (0.63–1.48)
Multivariate-adjusted HR (95% CI)§	1.09 (0.76–1.55)	1.00	0.78 (0.54–1.15)	0.99 (0.64–1.53)
Updated body mass index				
Person-years of follow-up	181,993	919,915	507,739	419,121
No. of cases	21	108	59	41
Age-adjusted HR (95% CI)	0.98 (0.61–1.56)	1.00	1.01 (0.73–1.39)	0.85 (0.59–1.23)
Multivariate-adjusted HR (95% CI)§	1.00 (0.63–1.61)	1.00	1.00 (0.73–1.38)	0.85 (0.58–1.23)

*Abbreviations: Hazard Ratio (HR), Confidence Interval (CI)

§Models adjusted for age (months), smoking (never, past, current), physical activity at baseline in quintile (MET-hours/week), oral contraceptive use (never, past, current), menopausal hormone therapy (never, past, current, premenopause), appendectomy (no, yes), geographic latitude of residence at age 30 (southern, middle, northern, missing/unknown), and NSAID's use (< 2 tablets/week, ≥ 2 tablets/week).

Table 4

Weight Change and Risk of Ulcerative Colitis and Crohn's Disease (1989–2009)*

	Weight change (lbs)					
	< −5	**≥ −5 and < 5**	**≥ 5 and < 15**	**≥ 15 and < 30**	**≥ 30**	**P_{trend}**
Person-years of follow-up	200,825	311,881	559,090	500,798	449,068	
Crohn's Disease						
No. of cases	13	19	37	41	43	
Age-adjusted HR (95% CI)	1.07 (0.53–2.16)	1.00	1.10 (0.63–1.91)	1.39 (0.80–2.40)	1.68 (0.97–2.90)	0.03
Multivariate-adjusted HR (95% CI)§	0.96 (0.46–2.00)	1.00	1.08 (0.62–1.88)	1.31 (0.76–2.27)	1.52 (0.87–2.65)	0.04
Ulcerative Colitis						
No. of cases	31	41	57	49	51	
Age-adjusted HR (95% CI)	1.17 (0.73–1.86)	1.00	0.79 (0.53–1.18)	0.75 (0.49–1.14)	0.88 (0.58–1.34)	0.15
Multivariate-adjusted HR (95% CI)§	1.24 (0.76–2.02)	1.00	0.78 (0.52–1.17)	0.75 (0.49–1.14)	0.92 (0.60–1.40)	0.17

*Abbreviations: Hazard Ratio (HR), Confidence Interval (CI).

§Models adjusted for age (months), smoking (never, past, current), oral contraceptive use (never, past/current), physical activity at baseline in quintile (MET-hours/week), BMI at age 18 (< 20, 20–24.9, 25–29.9, ≥ 30 kg/m^2), menopausal hormone therapy (premenopause, never, current, past).

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Table 5

Measurement of Waist to Hip Ratio and Risk of Ulcerative Colitis and Crohn's Disease (1993–2009)*

	≤ 0.73	0.74–0.76	0.77–0.82	≥ 0.83	
Person-years of follow-up	189,993	147,055	208,551	165,080	
Crohn's Disease					
No. of cases	14	12	23	18	
Age-adjusted HR (95% CI)	1.00	1.13 (0.52–2.44)	1.51 (0.78–2.94)	1.51 (0.75–3.04)	0.17
Multivariate-adjusted HR (95% CI)§	1.00	1.15 (0.53–2.49)	1.54 (0.79–3.01)	1.58 (0.78–3.21)	0.14
Ulcerative Colitis					
No. of cases	21	21	23	25	
Age-adjusted HR (95% CI)	1.00	1.34 (0.73–2.46)	1.05 (0.58–1.90)	1.39 (0.78–2.50)	0.42
Multivariate-adjusted HR (95% CI)§	1.00	1.37 (0.74–2.52)	1.07 (0.59–1.95)	1.44 (0.80–2.59)	0.37

*Abbreviations: Hazard Ratio (HR), Confidence Interval (CI).

§Models adjusted for age (months), smoking (never, past, current), oral contraceptive use (never, past/current), physical activity at baseline in quintile (MET-hours/week), menopausal hormone therapy (premenopause, never, current, past).