Impact of Obesity on Disease Activity and Patient-Reported Outcomes Measurement Information System (PROMIS) in Inflammatory Bowel Diseases

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INTRODUCTION: **We conducted a cohort study on the impact of obesity on disease activity and Patient-Reported Outcomes Measurement Information System (PROMIS) measures in the inflammatory bowel disease (IBD) Partners cohort.**

METHODS: **We performed a cross-sectional and longitudinal study within IBD Partners, an internet-based cohort of >15,000 patients living with Crohn's disease (CD) and ulcerative colitis (UC). We included adult patients with IBD, with recorded body mass index (BMI), with at least 6 months of follow-up, excluding patients with BMI < 18.5 kg/m². We evaluated the independent effect of World Health Organization classes of obesity on risk of clinical relapse or persistent disease activity (using validated disease activity indexes) and PROMIS measures, using multivariate logistic regression and linear regression, respectively.**

RESULTS: **We included 7,296 patients with IBD (4,748 patients with CD, 19.5% obese; 2,548 patients with UC with intact colon, 20.3% obese). Obesity was independently, and in a dose-dependent fashion, associated with an increased risk of persistent disease activity or relapse in both patients with CD (class II or III obesity vs normal BMI: adjusted odds ratio, 1.86; 95% confidence interval, 1.30–2.68) and UC (adjusted odds ratio, 2.97; 95% confidence interval, 1.75–5.17). Obesity was also independently associated with higher anxiety, depression, fatigue, pain, and inferior social function scores in patients with CD and UC at baseline and with worsening depression, fatigue, pain, and social function in patients with CD on longitudinal assessment.**

CONCLUSIONS: **Obesity at baseline is independently associated with worsening disease activity and PROMIS measures in patients with IBD.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/A159

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The incidence and prevalence of inflammatory bowel diseases (IBDs) are rising in parallel with the global obesity epidemic. Approximately 15%–40% of adult patients with IBD are obese (body mass index (BMI) ≥ 30 kg/m²) (1). Obesity has been variably associated with IBD phenotype, with some studies suggesting milder disease and others suggesting lower prevalence of remission in cross-sectional studies (1–4). There are conflicting data on how obesity may impact outcomes in patients with IBD, with some studies showing inferior quality of life and higher health care utilization, whereas others showing no significant difference in the risk of IBD-related surgery, hospitalization, or emergency department use in obese vs overweight vs normal BMI adults (4–8). Obesity has also been shown to negatively impact response to biologic therapy in patients with ulcerative colitis (UC) and other immune-mediated diseases, but this observation has been inconsistent (9,10).

However, most single-center studies have a small sample size, low event rate, and have relied on retrospective physician global assessment or nonvalidated indices, rather than patient-reported outcomes (PROs), to assess the impact of obesity on

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clinical activity; none have systematically evaluated its impact on Patient-Reported Outcomes Measurement Information System (PROMIS) measures in IBD.

Hence, we performed secondary analysis of a prospectively maintained internet-based cohort of >15,000 patients with IBD, IBD Partners, to evaluate the association between obesity and clinical disease activity (risk of relapse in a subset of patients in remission at baseline and risk of persistently active disease in patients with active disease at baseline) and PROMIS measures (at baseline and follow-up).

METHODS

Study population

We performed a cross-sectional and longitudinal study within the Crohn's and Colitis Foundation's IBD Partners cohort. The study cohort has been described in detail previously (11,12). Briefly, patients were recruited to enroll in this online cohort registry via a variety of means, including invitations via email, social media, and recruitment at the Crohn's and Colitis Foundation educational events. More than 15,000 patients with self-reported IBD have enrolled in the cohort since initiation in 2011, and cohort members are followed up at 6-month intervals. Baseline and follow-up surveys include a core survey with information on disease phenotype, activity, medication use, and PROs.

From this cohort, we included (1) patients with IBD (Crohn's disease (CD) or UC) (2), recorded data on BMI at baseline, and (3) at least 6 months of follow-up (i.e., filling a follow-up survey). When data were available at multiple time points, outcomes at 12 months, 18 months, or 6 months were used, in that order; if only 1 time point measure was available, that time point was used for outcome assessment. We excluded patients who were underweight (BMI < 18.5 kg/m^2) (because of potential confounding by disease severity impacting nutritional status) and had end ileostomy or ileoanal pouch (because disease activity indexes are not validated in these specific subpopulations).

Exposure

The primary predictor variable was BMI, based on patient self-reported weight and height, categorized based on World Health Organization obesity classes as normal BMI (BMI 18.5–24.9 kg/m^2, reference), overweight (BMI 25.0–29.9 kg/m^2), class I obesity (BMI 30.0–34.9 kg/m^2), and class II/III obesity (BMI 35.0–39.9 kg/m^2). In addition, BMI was also categorized as a continuous variable, evaluating the association between each 1 kg/m^2 increase in BMI and clinical outcomes.

Outcomes

There were 2 primary outcomes in the study (1): clinical disease activity, measured using short Crohn's Disease Activity Index (sCDAI) in patients with CD and Simple Clinical Colitis Activity Index in patients with UC (2,13,14), PROMIS measures, for anxiety, depression, fatigue, sleep disturbance, satisfaction with social role, and pain interference. Of note, sCDAI is based on abdominal pain, diarrhea frequency, and general well-being, and unlike full CDAI, does not include weight as a variable.

Clinical disease activity. In the cross-sectional analysis, the presence of active disease was defined as sCDAI >150 (CD) or Simple Clinical Colitis Activity Index >2 (UC). In the longitudinal analysis, active disease was defined as clinical relapse at follow-up survey (development of active disease, in the subset of patients in remission at baseline) or having persistent disease activity (in the subset of patients with active disease at baseline).

PROMIS measures. The PROMIS initiative of the National Institutes of Health was developed to advance the science and application of PROs among patients with chronic diseases for use in research and clinical practice (15). PROMIS instruments are general (not disease specific) measures that are valid and responsive, allow comparisons within and between conditions, and are grouped into item banks based on symptoms, function, well-being, and general health. PROMIS items are calibrated using a T-score metric with the mean of the US general population equal to 50 and s.d. in the general population equal to 10 (15). Minimal important differences (MIDs), the score that is large enough to have implications for a patient's treatment or care, were deemed to be 2.5 (16). Higher scores indicate more of the domain being measured such that high scores for anxiety, depression, fatigue, sleep disturbance, and pain interference indicate poorer health, whereas high scores for satisfaction with social role indicate better health. In the cross-sectional analysis, difference in the T-score of PROMIS measures was measured between different categories of BMI. In the longitudinal analysis, the association between obesity and change in PROMIS measure over time was measured.

Covariates

Covariates of interest included disease duration, smoking status (stratified as never, past, and current smoking at the time of the baseline questionnaire), ethnicity, education status, self-reported IBD-related hospitalization or surgery, as well as medications for treatment of IBD including 5-aminosalicylates (oral), corticosteroids (oral), immunomodulators, and biologic therapies (infliximab, adalimumab, certolizumab pegol, and natalizumab), and narcotic use. *Post hoc*, we also included change in BMI class at follow-up as a covariate. We also evaluated interaction between BMI and age, sex, smoking, college education, race, previous surgery, previous hospitalization, disease duration, biologic therapy, immunomodulator therapy, corticosteroids, 5-aminosalicylate therapy, and narcotic use in both patients with CD and UC.

Statistical analysis

All analyses were stratified by CD and UC.

Clinical disease activity. In the cross-sectional analysis, we compared the unadjusted prevalence of remission across BMI categories using univariable logistic regression. In the longitudinal analysis, the association between BMI categories and risk of active disease was analyzed using multivariable logistic regression analysis. In this analysis, all key covariates were included in univariable analysis, and all baseline variables with a P value < 0.20 were included in the multivariable model, using a backward model selection approach. In the longitudinal cohort, stratified analysis by patients in remission vs active disease at baseline was performed. Dose-response relationship between BMI and clinical disease activity was analyzed using logistic regression analysis for increase in BMI category.

PROMIS measures. In the cross-sectional analysis, we compared the T-scores for each PROMIS item at baseline across BMI categories, both unadjusted using analysis of variance and after adjustment for key covariates including baseline medication use, disease activity, etc., using linear regression with analysis of variance F test to analyze for significant variability across categories. In the longitudinal analysis, we compared the magnitude of change from the baseline T-score for each item across BMI categories using

multivariable linear regression, after adjusting for key covariates, including the baseline PROMIS score. As noted earlier, MID for PROMIS items was assigned as 2.5.

All hypothesis testing was performed using a 2-sided *P* value with a statistical significance threshold <0.05. All statistical analyses were performed with Stata MP (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). IBD Partners' study protocol was approved by the Institutional Review Board at the University of North Carolina, Chapel Hill, North Carolina; this secondary analysis of previously collected data was deemed exempt by the University of California San Diego Institutional Review Board.

RESULTS

We included 7,296 patients with IBD in our analysis. The number of patients with follow-up at 6, 12, and 18 months was 2,074, 6,056, and 7,018, respectively. On follow-up at 12 months, across baseline BMI categories, 78.3%–91.2% remained in their respective BMI categories at 12 months (eTable 1, see Supplementary Digital Content, http://links.lww.com/AJG/A159). Among patients with change in BMI, most moved up or down 1 category, and <0.5% moved up or down 2 categories (except 2% patients with baseline class II or III obesity who had BMI at follow-up <30 kg/m^2).

Crohn's disease

We included 4,748 patients with CD in our analysis, of whom 19.5% were classified as obese. Baseline demographics and clinical features of patients with CD, stratified by BMI category, are shown in Table 1. Compared with patients with normal BMI, patients with obesity were marginally older, more likely to be female, less likely to have college education, more likely to be current smokers, less likely to have had previous surgery, and were more likely to be on narcotics in this cohort. The prevalence of the use of 5-aminosalicylates, immunomodulators, biologic agents, and corticosteroids was comparable across BMI categories; of note, <10% of the cohort was on corticosteroids at the time of baseline evaluation.

Clinical disease activity. At baseline, the prevalence of clinical remission was lower in patients with obesity compared with patients with normal BMI, with an exposure-response

Table 1 Baseline characteristics of patients with Crohn's disease by BMI

Characteristic	Normal BMI (18.5–24.9 kg/m^2), (n = 2,284)	Overweight (25.0–29.9 kg/m^2), (n = 1,331)	Class I obesity (30–34.9 kg/m^2), (n = 541)	Class II or III obesity (≥35.0 kg/m^2), (n = 385)	*P* value
Age, mean (SD)	41.5 ± 15.5	45.8 ± 14.6	45.4 ± 13.6	44.7 ± 12.4	**<0.01**
Disease duration, median in years (range)	11 (4–22.5)	12 (5–23)	11 (4–20)	10 (4–18)	**<0.01**
Sex (% female)	74.3%	62.6%	80.4%	85.2%	**<0.01**
Education (% with college degree)	72.3%	70.5%	69.4%	61.5%	**<0.01**
Race					**0.003**
White	95.5%	95.1%	94.2%	92.1%	
African American	1.0%	1.8%	2.1%	3.8%	
Asian	0.7%	0.6%	0.2%	0%	
Other	2.8%	2.5%	3.5%	4.1%	
Previous abdominal surgery (%)	51.0%	49.3%	44.0%	46.0%	**0.02**
Previous hospitalization	74.7%	73.2%	71.5%	72.2%	0.36
Smoking (current, % yes)	7.4%	7.2%	8.7%	11.4%	**0.03**
Baseline medications					
5-aminosalicylates	18.1%	19.8%	20.5%	19.2%	0.44
Steroids	7.5%	6.9%	7.2%	9.1%	0.55
Immunomodulators	20.6%	20.5%	17.4%	22.3%	0.26
Biologics	33.5%	34.2%	33.5%	35.1%	0.92
Narcotics	5.0%	6.1%	9.4%	9.1%	**<0.01**
Baseline PROMIS measures					
Anxiety	51.59 (9.50)	51.57 (9.47)	52.72 (9.78)	54.65 (10.33)	**<0.01**
Depression	49.60 (9.11)	50.04 (9.23)	51.81 (9.27)	53.93 (10.34)	**<0.01**
Fatigue	53.74 (10.84)	54.73 (10.92)	58.11 (10.70)	60.40 (10.35)	**<0.01**
Pain	50.52 (9.43)	51.12 (9.72)	54.08 (9.96)	56.39 (10.35)	**<0.01**
Sleep	52.04 (3.27)	51.86 (3.43)	51.89 (3.57)	52.22 (3.40)	0.20
Social satisfaction	50.34 (9.89)	49.60 (9.70)	46.85 (9.66)	44.54 (9.44)	**<0.01**

BMI, body mass index; PROMIS, Patient-Reported Outcomes Measurement Information System.

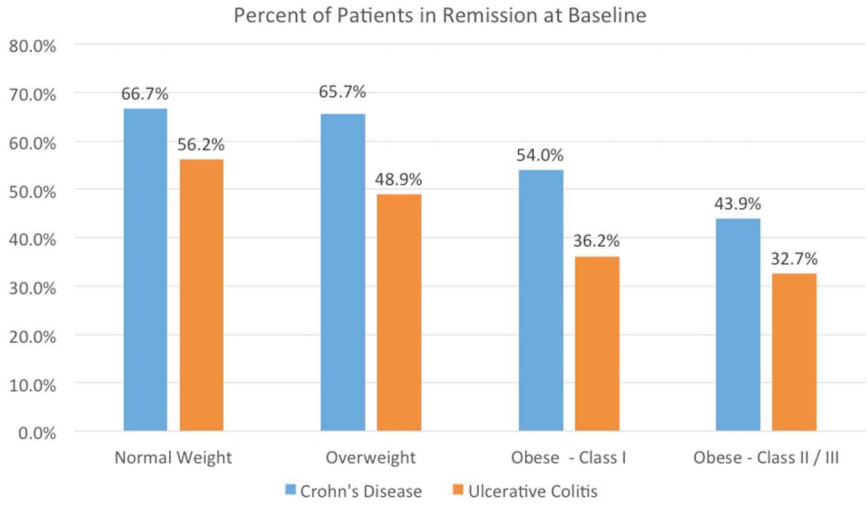

Figure 1 Proportion of patients in clinical remission at baseline, based on body mass index.

relationship ($P < 0.01$) (Figure 1). On longitudinal analysis, patients with obesity were more likely to have active disease on follow-up compared with patients with normal BMI, with an exposure-response relationship (Figure 2). After adjustment for covariates, patients with overweight, class I, and class II/III obesity had 39%, 50%, and 86% higher odds of having active disease at follow-up compared with patients with normal BMI, respectively (Table 2). Each 1 kg/m^2 increase in BMI was associated with a 3% higher odds of having active disease. When analysis was restricted to patients in clinical remission at baseline, a higher risk of relapse was observed in patients with obesity vs patients with normal BMI (obese vs normal BMI: odds ratio, 1.31; 95% confidence interval, 1.00–1.73, $P = 0.049$). Similar results were obtained when analysis was restricted to patients with active disease at baseline. No significant interactions were observed, except race and BMI in CD—African American patients with class I/II/III obesity had a higher risk compared with whites with class I/II/III obesity.

PROMIS measures. Mean baseline PROMIS scores for anxiety, depression, fatigue, sleep disturbance, satisfaction with social role, and pain interference by BMI categories are shown in Table 1. Across all items, except sleep disturbance, overall scores were inferior in patients with obesity compared with patients with normal BMI ($P < 0.001$), although we did not specifically evaluate differences in PROMIS measures across predefined individual categories of obesity. After adjustment for covariates including baseline disease activity, these differences were higher than the MIDs for all items (except sleep disturbance) in patients with class II/III obesity vs normal BMI (MIDs ranging from 2.14 to 5.02) (see eTables 2–7, Supplementary Digital Content 1, http://links.lww.com/AJG/A159). On longitudinal analysis, after adjustment for covariates including baseline item scores, patients with obesity had a significantly greater magnitude of decline in PROMIS item scores for depression (change in the T-score, class II/III obesity vs normal BMI: 1.15), fatigue (1.52), pain interference (1.33), and satisfaction with social role (−1.62); however, these did not meet thresholds for MID.

Ulcerative colitis

We included 2,548 patients with UC in our analysis, of whom 20.3% were classified as obese. Baseline demographics and clinical features of patients with UC, stratified by BMI category, are shown in Table 3. Compared with patients with normal BMI, patients with obesity were marginally older, less likely to have college education, and were more likely to be on narcotics; there was no difference in the prevalence of use of 5-aminosalicylates, immunomodulators, biologic agents, and corticosteroids across BMI categories.

Clinical disease activity. At baseline, the prevalence of clinical remission was lower in patients with obesity compared with patients with normal BMI, with an exposure-response relationship ($P < 0.01$) (Figure 1). On longitudinal analysis, patients with obesity were more likely to have active disease on follow-up compared with patients with normal BMI, with an exposure-response relationship (Figure 3). After adjustment for covariates, patients with class I and class II/III obesity had 65% and 197% higher odds of having active disease at follow-up compared with patients with normal BMI, respectively (Table 4). Each 1 kg/m^2 increase in BMI was associated with a 5% higher odds of having active disease. When analysis was restricted to patients in clinical remission at baseline, 40.3% and 27.3% patients with class II/III and class I obesity experienced relapse, respectively, compared with 21.7% patients with normal BMI ($P < 0.01$). After adjustment for covariates, patients with class II/III obesity had 2.4 times higher odds of relapse compared with patients with normal BMI (adjusted odds ratio, 2.41; 95% confidence interval, 1.40–4.17). Similar results were obtained when analysis was restricted to patients with active disease at baseline. No significant interactions between BMI and covariates were observed.

PROMIS measures. Mean baseline PROMIS scores for anxiety, depression, fatigue, sleep disturbance, satisfaction with social role, and pain interference by BMI categories are shown in Table 3. As noted for CD, across all items, except sleep disturbance, overall scores were inferior in obese patients with UC compared with patients with normal BMI ($P < 0.001$), although we did not specifically evaluate differences in PROMIS measures across predefined individual categories of obesity. After adjustment for covariates including baseline disease activity, these differences were higher than the MIDs for all items (except fatigue, MID 1.74) in patients with class II/III obesity vs normal BMI (MIDs ranging from −3.20 to 4.01) (see eTables 8–13, Supplementary Digital Content 1, http://links.lww.com/AJG/A159). On longitudinal analysis, after adjustment for covariates including the

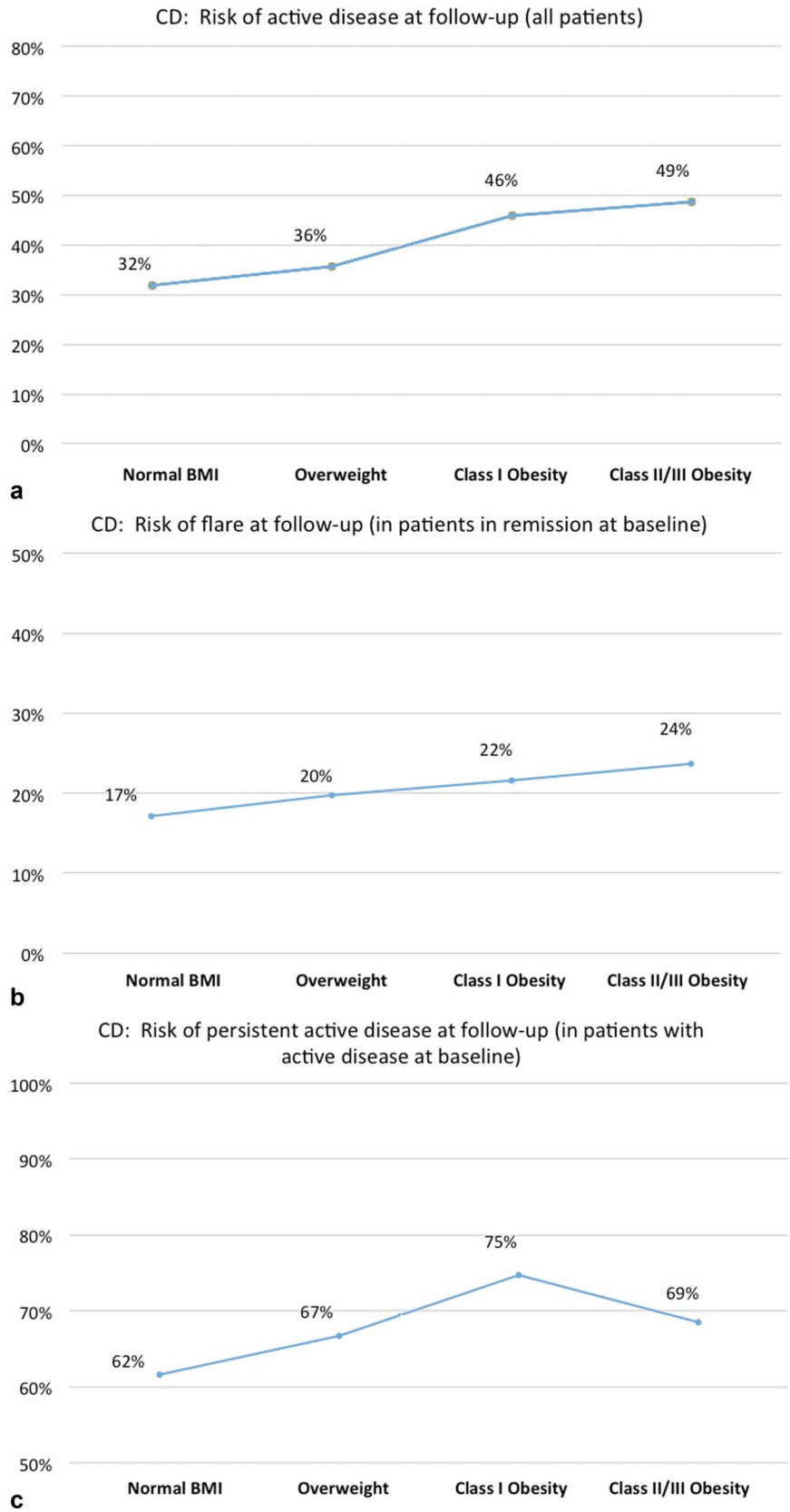

Figure 2 Impact of obesity on clinical disease activity in patients with CD on longitudinal follow-up: (**a**) proportion of patients with active disease, regardless of baseline disease activity, (**b**) proportion of patients with relapse in subset of patients in remission at baseline, and (**c**) proportion of patients with persistent disease activity in subset of patients with active disease at baseline. BMI, body mass index; CD, Crohn's disease.

Table 2 Factors associated with active disease at follow-up in patients with Crohn's disease, regardless of baseline disease activity, on multivariable logistic regression analysis

Predictor variables	OR (95% CI)	*P* value
BMI		
Normal	1.0	
Overweight (25–29.9)	**1.39 (1.08–1.78)**	**0.01**
Class I obesity	**1.50 (1.07–2.09)**	**0.02**
Class II or III obesity	**1.86 (1.30–2.68)**	**<0.01**
Female sex (vs male)	**1.71 (1.34–2.21)**	**<0.01**
College education	**0.72 (0.57–0.90)**	**<0.01**
African American vs white	1.29 (0.61–2.68)	0.50
Other ethnicities vs white	1.59 (0.92–2.70)	0.09
History of previous surgeries	**1.73 (1.35–2.22)**	**<0.01**
History of previous hospitalization	1.11 (0.84–1.48)	0.47
Current smoking status	**2.21 (1.54–3.20)**	**<0.01**
Immunologic therapy at baseline	0.94 (0.73–1.23)	0.67
Narcotic use at baseline	**2.56 (1.73–3.83)**	**<0.01**
Aminosalicylate therapy at baseline	**0.75 (0.57–0.99)**	**0.04**
Steroid use at baseline	1.35 (0.88–2.05)	0.16
Biologic use at baseline	0.87 (0.69–1.09)	0.23
Age (per 1-year increase)	1.00 (0.99–1.01)	0.70
Disease duration (per 1-year increase)	1.00 (0.99–1.01)	0.83
Change in BMI category		
1 category increase	0.90 (0.59–1.35)	0.60
1 category decrease	0.76 (0.48–1.18)	0.23

The bold values highlight variables with significant *P* values (<0.05).
BMI, body mass index; CI, confidence interval; OR, odds ratio.

baseline item score, patients with obesity had a significantly greater magnitude of decline in PROMIS item scores for pain interference (change in the T-score, class II/III obesity vs normal BMI: 2.97), although they experienced a marginal improvement in sleep disturbance (−0.74).

DISCUSSION

In this secondary analysis of prospectively collected data on >7,000 patients with IBD from an internet-based cohort, ~20% of whom were obese, we made several key observations. First, both patients with CD and UC with obesity at baseline had a significantly lower prevalence of clinical remission and inferior scores on multiple PROMIS domains including anxiety, depression, fatigue, satisfaction with social role, and pain interference compared with patients with normal BMI, with an exposure-response relationship. Second, on longitudinal analysis over the course of 12 months, obese patients with CD and UC had a higher risk of having active disease, including a higher risk of relapse (among patients in remission at baseline) and persistently active disease (among patients with active disease at baseline) compared with patients with normal BMI. The magnitude of this effect seems stronger in patients with UC compared with patients with CD. Third, obese patients, particularly those with CD, experienced worsening across multiple PROMIS domains on longitudinal analysis compared with patients with normal BMI. However, these differences did not meet thresholds of MID, and clinical significance of these findings is unclear. Overall, these findings suggest that obesity significantly impacts disease-specific patient-reported clinical activity and disease-agnostic PROs, both at baseline and on longitudinal follow-up over the course of 12 months. In conjunction with evolving findings on the impact of obesity on increased health care utilization, and higher risk of hospitalization, surgery, and biologic treatment failure, especially in patients with UC, these findings firmly identify obesity as a negative prognostic factor in patients with IBD (5,9,10). This has important potential clinical implications. Physicians should be cognizant of this association between obesity and adverse IBD outcomes and should closely monitor these patients and consider early optimization of therapy.

Obesity is recognized as a perpetual state of chronic low-grade inflammation, through systemic and paracrine increase in levels of cytokines, chemokines, and adipokines, and is also associated with dysbiosis (1). Obesity increases leptin secretion from adipocytes and resistin secretion from macrophages and leukocytes that increase levels of proinflammatory cytokines such as tumor necrosis factor and interleukins 1 and 6 (17). In addition to its direct impact on inflammation, obesity can also modify the pharmacokinetics of biologic agents, resulting in rapid drug clearance (18). Hence, obesity could adversely affect both inflammatory burden in IBD and response to medical therapy.

Although obesity has been consistently shown to negatively impact clinical disease activity and treatment response to biologic agents in immune-mediated inflammatory diseases, this evidence has been inconsistent in patients with IBD to date (9). There have been a limited number of conflicting longitudinal studies on the impact of obesity on disease course in IBD. Seminerio and colleagues observed inferior IBD-related quality of life and higher frequency of elevated levels of serum C-reactive protein in patients with obesity (particularly class II or III obesity) compared with normal weight patients (4). In contrast, Flores et al. (2) observed a lower risk of IBD-related surgery (41% vs 52% vs 61% for patients who were obese, overweight, or normal or underweight, respectively), hospitalization (42% vs 44% vs 66%), and initiation of anti-tumor necrosis factor alpha (anti-TNF) therapy (25% vs 26% vs 43%), both in patients with CD and UC. How obesity impacts clinical disease activity and PROs in patients with IBD has not been well studied. To understand the impact of obesity on the natural history of IBD in a controlled setting, we had previously conducted a *post hoc* analysis of 4 placebo-controlled trials of infliximab in adults with moderate-severe IBD. In 575 placebo-treated patients in these trials, we did not observe any association between BMI and odds of achieving clinical remission or mucosal healing, measured using validated clinical disease activity indexes (8). However, in these trials, follow-up was short, and proportion of patients with class II/III obesity was small, which limited meaningful inferences on the impact of morbid obesity on clinical activity in IBD. Moreover, this study did not evaluate the impact of obesity on PROMIS measures. This void was filled by the current study, in which by using a large internet-based cohort of patients with IBD, with follow-up over 12 months, using validated patient-reported disease-related activity indexes and disease-agnostic PROMIS measures, we observed a clear negative association between obesity and PROs across multiple domains.

Table 3 Baseline characteristics of patients with ulcerative colitis by BMI

Characteristic	Normal BMI (18.5–24.9 kg/m^2), (n = 1,279)	Overweight (25.0–29.9 kg/m^2), (n = 752)	Class I obesity (30–34.9 kg/m^2), (n = 304)	Class II or III obesity (≥35.0 kg/m^2), (n = 213)	*P* value
Age, mean (SD)	41.3 ± 14.7	46.4 ± 14.7	47.4 ± 14.3	47.3 ± 12.9	**<0.01**
Disease duration, median in years (range)	7 (3–14)	9 (3–18)	7 (3–15)	8 (3–17)	**0.01**
Sex (% female)	74.1%	60.5%	69.4%	84.1%	**<0.01**
Education (% with college degree)	79.3%	74.8%	65.4%	64.1%	**<0.01**
Race					0.13
White	92.4%	93.8%	91.7%	93.7%	
African American	1.2%	1.3%	2.4%	2.9%	
Asian	2.6%	1.3%	2.1%	0%	
Other	3.8%	3.8%	3.8%	3.4%	
Previous hospitalization	41.8%	39.9%	38.8%	44.9%	0.45
Smoking (current, % yes)	4.1%	2.9%	5.3%	2.8%	0.24
Baseline medications					
5-aminosalicylates	43.4%	46.7%	44.9%	46.7%	0.47
Steroids	6.6%	6.5%	7.6%	9.8%	0.34
Immunomodulators	16.0%	16.8%	19.8%	14.5%	0.36
Biologics	21.6%	18.5%	19.5%	17.3%	0.25
Narcotics	1.8%	2.5%	4.6%	6.5%	**<0.01**
Baseline PROMIS measures					
Anxiety	51.54 (9.16)	50.58 (9.16)	52.74 (9.88)	54.05 (9.55)	**<0.01**
Depression	49.07 (8.66)	49.24 (8.67)	51.57 (9.98)	53.58 (9.82)	**<0.01**
Fatigue	51.75 (11.02)	52.28 (10.75)	55.48 (10.65)	57.97 (10.78)	**<0.01**
Pain	49.03 (9.11)	50.37 (9.46)	52.30 (10.07)	55.36 (10.07)	**<0.01**
Sleep	52.01 (3.30)	51.90 (3.53)	52.28 (3.58)	52.33 (3.60)	0.24
Social satisfaction	51.23 (9.92)	50.63 (10.14)	48.12 (9.64)	46.03 (10.07)	**<0.01**

The bold values highlight variables with significant *P* values (<0.05). BMI, body mass index; PROMIS, Patient-Reported Outcomes Measurement Information System.

Our findings provide potential directions for future research. Although small randomized controlled trials and cohort studies in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis have suggested a beneficial effect of intentional weight loss on treatment response to anti-TNF agents, it is unclear whether such a therapeutic intentional weight loss may improve outcomes in patients with IBD and merits evaluation (19–21). In addition, future clinical trials should consider obesity as a potential effect modifier and consistently report stratified analyses.

There are several strengths to the current study. This is the largest study to date investigating the impact of obesity on PROs in patients with IBD. The IBD Partners cohort includes patients cared for in a variety of settings including academic and community centers. We believe that this real-world cohort, in which 20% of participants were obese (including 8% patients with class II/III obesity), is more representative than evidence from *post hoc* analyses of clinical trials on the natural history of disease. This diverse distribution of BMI in the cohort also helped confirm the presence of an exposure-response relationship. In addition, we used validated self-reported clinical disease activity indexes and PROMIS measures, which make the study more rigorous. Observing consistent findings across both disease-specific indices and disease-independent PRO measures, and the presence of an exposure-response relationship, make these findings more biologically plausible.

Nonetheless, there are some key limitations. First, we relied on patient self-report of weight and height to estimate BMI. Given the simplicity of these measurements and the large sample size of the current study, systematic errors in reporting BMI is less likely; nonetheless, future studies should include objective assessment of both overall obesity and central adiposity in patients with IBD (22). Second, although IBD Partners has notable strengths in recruitment and retention, the data set may not be truly representative of a population of patients with IBD, including a higher percentage of female patients (>70%), white race (>90%), and higher rates of college education than national averages. Third, the IBD Partners cohort does not include physician notes and laboratory, radiology, or endoscopy data. Hence, we were unable to corroborate our findings with simultaneous assessment of the impact of obesity on biochemical and/or endoscopic remission. Fourth, we also do not have validated data on disease phenotype, disease location, or extent in this cohort, limiting detailed

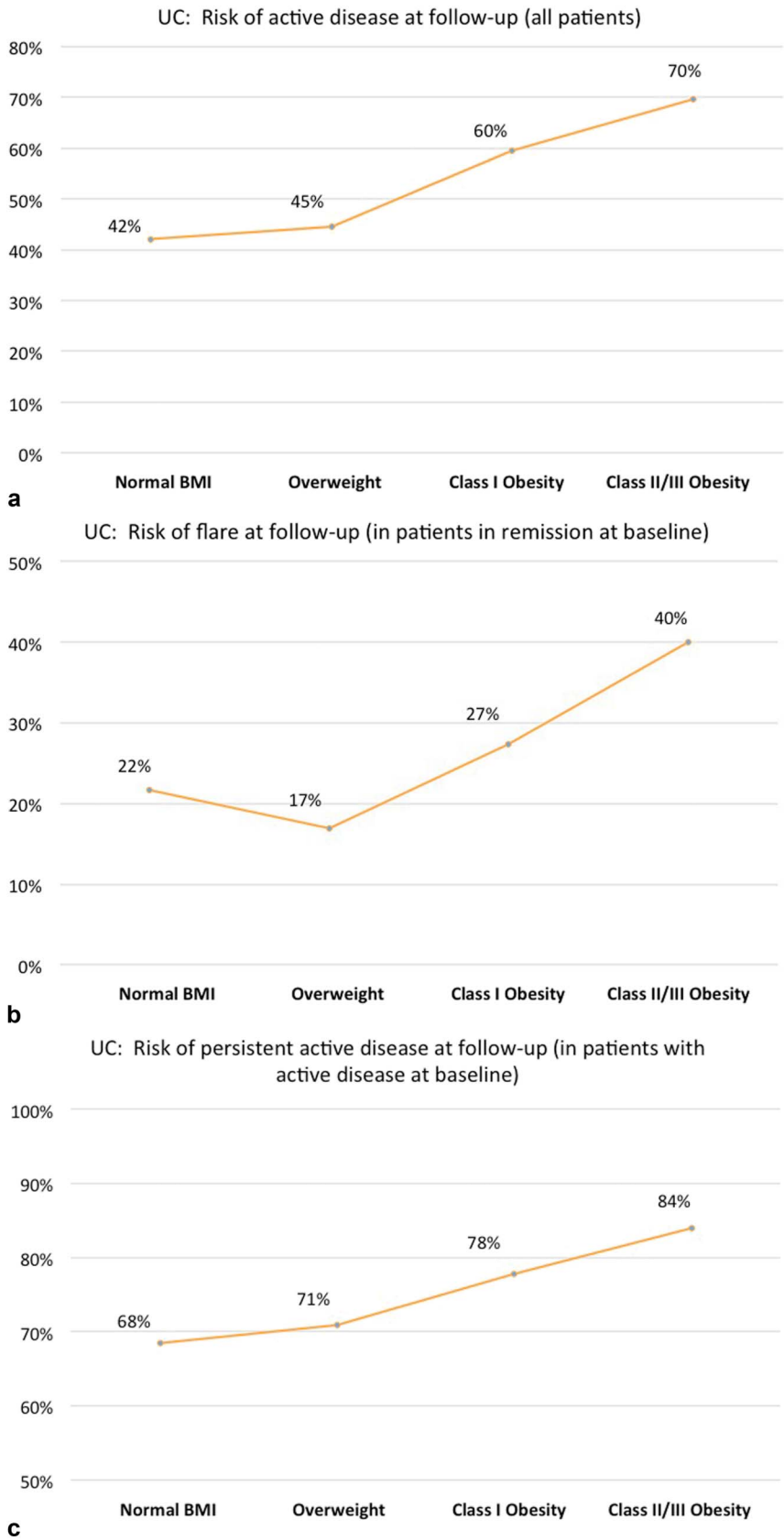

Figure 3 Impact of obesity on clinical disease activity in patients with ulcerative colitis on longitudinal follow-up: (**a**) proportion of patients with active disease, regardless of baseline disease activity, (**b**) proportion of patients with relapse in subset of patients in remission at baseline, and (**c**) proportion of patients with persistent disease activity in subset of patients with active disease at baseline. BMI, body mass index; UC, ulcerative colitis.

Table 4 Factors associated with active disease at follow-up in patients with ulcerative colitis, regardless of baseline disease activity, on multivariable logistic regression analysis

Predictor variables	OR (95% CI)	*P* value
BMI		
Normal	1.0	
Overweight (25-29.9)	1.03 (0.75–1.42)	0.84
Class I obesity	**1.65 (1.05–2.61)**	**0.03**
Class II or III obesity	**2.97 (1.75–5.17)**	**<0.01**
Female sex	1.14 (0.84–1.54)	0.41
College education	0.73 (0.53–1.00)	0.05
African American vs white	0.88 (0.28–2.64)	0.82
Other ethnicities vs white	1.65 (0.92–2.99)	0.09
History of previous hospitalization	**1.55 (1.16–2.07)**	**<0.01**
Current smoking status	1.62 (0.76–3.57)	0.22
Immunologic therapy at baseline	**0.56 (0.37–0.83)**	**<0.01**
Aminosalicylate therapy at baseline	0.81 (0.61–1.08)	0.15
Narcotic use at baseline	1.67 (0.75–3.95)	0.22
Steroid use at baseline	**2.26 (1.30–4.01)**	**<0.01**
Biologic use at baseline	1.12 (0.79–1.60)	0.53
Age (per 1-year increase)	1.00 (0.99–1.01)	0.64
Disease duration (per 1-year increase)	1.00 (0.98–1.01)	0.67
Change in BMI category		
1 category increase	0.63 (0.36–1.09)	0.10
1 category decrease	0.75 (0.43– – 1.29)	0.30

BMI, body mass index; CI, confidence interval; OR, odds ratio.

analyses of how obesity may impact disease activity across these strata. Finally, we were unable to evaluate stability of BMI at baseline assessment; however, as noted, on follow-up, the proportion of patients with significant change in BMI was small. Likewise, previous medication exposure or change in medication exposure on follow-up could not be systematically analyzed.

In conclusion, based on a large internet-based cohort study of >7,000 patients with IBD, we observed a strong and consistent association between obesity and lower rates of clinical remission and inferior PROMIS measures on cross-sectional and longitudinal analyses in both patients with CD and UC. Among patients in remission at baseline, obesity was associated with an increased risk of relapse, with stronger associations in patients with UC. Prospective cohort studies, including objective measures of overall obesity and central adiposity and disease activity, are warranted to confirm this association.

CONFLICTS OF INTEREST

Guarantor of the article: Siddharth Singh, MD, MS.

Specific author contributions: Study concept and design: A.J., M.D.K., M.D.L., and S.S. Acquisition of data: A.J., C.F.M., M.D.L., and S.S. Analysis and interpretation of data: A.J., N.H.N., J.A.P., M.D.L., and S.S. Drafting of the manuscript: A.J. and S.S. Critical revision of the manuscript for important intellectual content: N.H.N., J.A.P., C.F.M., W.J.S., M.D.K., and M.D.L. Approval of the final manuscript: A.J., N.H.N., J.A.P., C.F.M., W.J.S., M.D.K., M.D.L., and S.S.

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Study Highlights

WHAT IS KNOWN

- ✓ Approximately 15%–40% patients with IBD are obese.
- ✓ Obesity has been variably associated with IBD phenotype, with some cross-sectional studies suggesting milder disease and others suggesting lower prevalence of remission.
- ✓ There are conflicting data on how obesity may impact outcomes in patients with IBD.

WHAT IS NEW HERE

- ✓ In a large internet-based cohort of patients with IBD, obesity was independently associated with persistent disease activity (in patients with active disease at baseline) and relapse (in patients in clinical remission at baseline) in patients with UC and CD in a dose-dependent manner.
- ✓ Obesity was also independently associated with higher anxiety, depression, fatigue, pain, and inferior social function scores in patients with CD and UC.

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