



HHS Public Access

Author manuscript

Nat Rev Gastroenterol Hepatol. Author manuscript; available in PMC 2017 August 10.

Published in final edited form as:

Nat Rev Gastroenterol Hepatol. 2017 February ; 14(2): 110–121. doi:10.1038/nrgastro.2016.181.

Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes

Siddharth Singh^{1,2}, Parambir S. Dulai¹, Amir Zarrinpar¹, Sonia Ramamoorthy³, and William J. Sandborn¹

¹Division of Gastroenterology, Department of Medicine, University of California San Diego, USA

²Division of Biomedical Informatics, Department of Medicine, University of California San Diego, USA

³Division of Colon and Rectal Surgery, Department of Surgery, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92193, USA

Abstract

Incidence of IBD is rising in parallel with overweight and obesity. Contrary to conventional belief, about 15–40% of patients with IBD are obese, which might contribute to the development of IBD. Findings from cross-sectional and retrospective cohort studies are conflicting on the effect of obesity on natural history and course of IBD. Most studies are limited by small sample size, low event rates, non-validated assessment of disease activity and lack robust longitudinal follow-up and have incomplete adjustment for confounding factors. The effect of obesity on the efficacy of IBD-related therapy remains to be studied, though data from other autoimmune diseases suggests that obesity results in suboptimal response to therapy, potentially by promoting rapid clearance of biologic agents leading to low trough concentrations. These data provide a rationale for using weight loss interventions as adjunctive therapy in patients with IBD who are obese. Obesity also makes colorectal surgery technically challenging and might increase the risk of perioperative complications. In this Review, we highlight the existing literature on the epidemiology of obesity in IBD, discuss its plausible role in disease pathogenesis and effect on disease course and treatment response, and identify high-priority areas of future research.

With an estimated 2.1 billion adults worldwide overweight (BMI ≥ 25 kg/m²), of which 600 million are obese (BMI ≥ 30 kg/m²), the prevalence of overweight and obesity has reached epidemic proportions¹. From 1980 to 2013, the proportion of overweight adults has increased 28% in developed countries and nearly 60% in developing countries, with no country reporting a decrease in prevalence during the same period¹. In the USA, more than

Correspondence to S.S. sis040@ucsd.edu.

Author contributions

S.S. and P.S.D. researched data for the article. S.S., P.S.D., A.Z., S.R. and W.J.S. substantially contributed to the discussion of content for the article. S.S. and P.S.D. wrote the article, and all authors contributed equally to reviewing and editing of the manuscript before submission.

Competing interests statement

W.J.S. has received consulting fees from Abbvie, Janssen Biotech, Prometheus Laboratories and UCB Pharma, research grants from Abbvie, Janssen Pharmaceutical Research & Development and UCB Pharma, and payments for lectures or speakers bureau from Abbvie, Janssen Pharmaceutical Research & Development. S.S., P.S.D., A.Z. and S.R. declare no competing interests.

one-third (35.7%) of adults are obese, with the estimated annual medical costs of a patient with obesity being US\$1,429 higher than individuals of a normal weight².

In parallel with the obesity epidemic, the incidence and prevalence of IBD is rising globally. In a systematic review of 260 population-based studies, the estimated annual incidence of IBD ranged from 10–30 cases per 100,000 persons in the Western world; an estimated 0.5% of adults in the West suffer from IBD³. A time-trend analysis suggests that incidence of IBD has increased over time, particularly in newly industrialized countries^{4,5}. Various environmental exposures have been implicated in these epidemiological trends in IBD, including smoking, improving hygienic standards, infections and antibiotics and dietary factors such as high-fat or low-fibre diets. A potentially understudied factor might be obesity, which has been associated with an increased risk of several autoimmune diseases such as rheumatoid arthritis, psoriasis and psoriatic arthritis^{6,7}. Beyond the potential epidemiological association, the rising prevalence of obesity implies that a substantial proportion of patients with IBD would be obese. Obesity negatively affects disease course and treatment response in other autoimmune diseases, but there is limited synthesis of data on the effect of obesity in IBD.

In this Review, we discuss the epidemiology and pathophysiology of obesity in IBD, the potential effect of obesity on disease course and complications, treatment response and surgical outcomes in patients with IBD, and whether treatment of obesity could modify disease course in patients with IBD.

Epidemiology

Prevalence of obesity in IBD

Cross-sectional studies in patients with IBD show that about 15–40% of adults with IBD are obese, and an additional 20–40% are overweight^{8–14}. In a population-based study of 489 patients with IBD conducted in Scotland, 18% of patients were obese (compared with 23% of the general population), and 38% of patients were overweight; this proportion was comparable between patients with Crohn's disease (18% obese) or ulcerative colitis (17.5% obese)¹⁵. By contrast, only 3% of patients with Crohn's disease and 0.5% of patients with ulcerative colitis were underweight (BMI <18.5 kg/m²). Large US-based, single-centre adult cohort studies have observed similar rates of obesity (TABLE 1).

A similar trend has also been observed in paediatric patients with IBD. In two North American multicentre inception cohorts of paediatric patients with IBD formed between 2000 and 2002, about 9–10% of children with Crohn's disease and 20–34% of children with ulcerative colitis had a sex-specific BMI-for-age above the 85th percentile at diagnosis¹⁶. In another multiple-site registry of 1,598 children with IBD, Long and colleagues⁹ observed 23.6% of children were above the 85th sex-specific BMI-for-age percentile (20.0% patients with Crohn's disease, 30.1% patients with ulcerative colitis), including 9.5% children who were above the 95th percentile; by contrast, only 2.9% of children were below the 5th percentile at diagnosis. A greater proportion of Hispanic children with IBD were obese or overweight than non-Hispanic children with IBD (35.2% versus 23.1%, *P* = 0.02). These

rates of obesity in patients with IBD are not different from rates observed in the general population.

This rise in the prevalence of obesity in patients with IBD seems to parallel the global obesity epidemic. In an early single-centre study conducted in France including 2,065 patients with Crohn's disease seen between 1974 and 2000, the prevalence of obesity was 3%, gradually rising from 1.7% of patients diagnosed with Crohn's disease before 1981 to 4% of patients diagnosed with Crohn's disease after 1990 (P for trend <0.01)¹⁷. By contrast, contemporary cohorts estimate the prevalence of obesity in IBD at 15–40%, as discussed earlier. On analysing 40 trials of 10,282 patients with Crohn's disease conducted between 1991 and 2008, an increase in trial participant weight was observed over time¹⁸. The minimum mean weight of participants increased from 57.1 kg in 1997 to a maximum mean weight of 89.1 kg in 2008.

Premorbid obesity and IBD risk

Besides a high prevalence of obesity in patients with IBD, premorbid obesity has also been associated with a risk of developing Crohn's disease, but not ulcerative colitis, though this relationship has not been consistently observed^{19–21} (TABLE 2). In the Danish National Birth Cohort of over 75,000 women, prepregnancy obesity was associated with a 1.9-fold increase in risk of developing Crohn's disease (hazard ratio (HR) 1.88, 95% CI 1.02–3.47), but not ulcerative colitis (HR 0.77, 95% CI 0.48–1.25)²⁰. Similar effect estimates were observed in the Nurses' Health Study, with BMI at age 18 years being predictive of risk of Crohn's disease (BMI >30 versus normal BMI: HR 2.33, 95% CI 1.15–4.69) but not ulcerative colitis (HR 1.17, 95% CI 0.54–2.52)¹⁹ (FIG. 1). Interestingly, in the Danish National Birth cohort, the association between premorbid BMI and risk of Crohn's disease was U-shaped, as women with a BMI <18.5 were also at increased risk of developing Crohn's disease compared with women of a normal BMI (HR 2.57, 95% CI 1.30–5.06)²⁰. The effect of obesity on risk of developing IBD might be age-dependent, with obesity in teenage or young adulthood associated with higher risk of developing Crohn's disease than obesity at later ages. Using the population-based Swedish Hospital Discharge Register, Hemminki *et al.*²² observed that among patients hospitalized with a primary diagnosis of obesity, the relative incidence of Crohn's disease is highest when obesity is diagnosed before 30 years of age (standardized incidence rate (SIR) 1.92, 95% CI 1.17–2.96), and decreases with increasing age at obesity diagnosis (SIR for Crohn's disease when obesity diagnosed between 40–49 years of age 1.04, 95% CI 0.37–2.28). Additionally, magnitude of weight gain after age 18 years has also been associated with increased risk of Crohn's disease, but not ulcerative colitis. In the Nurses' Health Study, women who gained >13.61 kg (30 lbs) between age 18 years and enrolment in the cohort had a 1.5-fold higher risk of developing Crohn's disease, as compared with women who remained within 2.27 kg (5 lbs) of their weight at age 18, in a dose-dependent manner¹⁹ (FIG. 1).

Of the several compartments of body fat, visceral adiposity is now well recognized to be the metabolically active fraction²³, and might be more predictive of the risk of developing IBD than overall obesity as determined by BMI. Patients with IBD have higher visceral fat volumes than those without IBD²⁴. In a prospective cohort study, Khalili and colleagues¹⁹

observed a trend towards increased risk of Crohn's disease, but not ulcerative colitis, in patients with a high waist-hip ratio (WHR). Among patients with Crohn's disease, participants with a premorbid WHR ≥ 0.83 had a 1.6-fold higher risk of developing Crohn's disease than those with a WHR < 0.73 (HR, 1.58, 95% CI 0.78–3.21, $P = 0.14$) (FIG. 1). Beyond obesity, obesity-related lifestyle factors such as physical activity might also modify risk of IBD. In the Nurses' Health Study, high level of physical activity (recreational or occupational) was associated with decreased risk of developing IBD^{25,26}.

Can IBD contribute to obesity?

The high prevalence of obesity in patients with IBD might also suggest an independent effect of IBD on the risk of obesity development. Although current epidemiological data is unable to accurately assess the directionality of this association, preclinical data suggests that dysbiosis and altered metabolic gut signalling induced by IBD and acting through hormones (including incretins such as gastric inhibitory polypeptide and glucagon-like peptide), satiety-related peptides (such as ghrelin and peptide YY) and bile acids might contribute to development of obesity and dysmetabolism in patients with IBD^{27,28}. In addition, smoking cessation and use of corticosteroids could contribute to weight gain in patients with IBD; in the general population, the average magnitude of weight gain with smoking cessation and corticosteroid use is 3–5 kg; ~11% of patients who quit smoking and ~24% of patients on corticosteroids for >1 year gain >10 kg body weight^{29–31}.

Limitations of current literature

Most of the available epidemiological data on prevalence of obesity in IBD is cross-sectional, which limits the ability to infer causality or even directionality of the association (that is, whether obesity contributes to IBD pathogenesis, or vice versa). A limited number of prospective cohort studies (Nurses' Health Study, Danish National Birth Cohort and European Prospective Investigation into Cancer and Nutrition study) have measured BMI in adulthood (generally in the 3rd to 5th decades of life) and subsequent development of IBD in an older population. These studies might not be representative of the general IBD population. Moreover, the Nurses' Health Study and the Danish National Birth Cohort have only studied women, and it is not possible to study whether obesity would have a similar effect on risk of developing IBD in men. Finally, given the increasing understanding of the metabolically active nature of visceral fat, overall obesity measured using BMI probably does not adequately capture the association with IBD; current studies have included limited assessment of visceral fat and its effect of development of IBD, usually through a surrogate measure like WHR.

The ideal study to evaluate the association between obesity and risk of developing IBD would involve creating a prospective cohort of paediatric or young adult patients with assessment of overall obesity and visceral adiposity at multiple time points, through both anthropometry as well as more sophisticated methods (such as the ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue on cross-sectional imaging), and subsequent close follow-up for the development and accurate phenotyping of IBD. However, as IBD would be expected to be observed in only 1 in 200 participants, such a study would involve following a large number of participants over many years, and would be cost prohibitive. As

an intermediary step, prospective identification of patients with IBD in diverse historical cohorts established decades ago, similar to efforts from the Nurses' Health Study and the European Prospective Investigation into Cancer and Nutrition study, might help understand the association between obesity and risk of developing IBD.

Obesity in the pathogenesis of IBD

Increasingly, obesity is recognized as a perpetual state of chronic low-grade inflammation³². Whether via the systemic and paracrine increase in levels of cytokines, chemokines and adipokines, the expression of innate immune receptors on preadipocytes and adipocytes or the conversion of preadipocytes to macrophages, adipose tissue is integrally involved in the regulation of inflammation.

Role of adipose tissue

Subcutaneous and visceral adipose tissue compartments display distinct metabolic and immunological profiles. Mesenteric VAT has a predominance of pro-inflammatory M1 macrophages that secrete several inflammatory cytokines, including TNF and IL-1. In addition, adipocytes also produce other pro-inflammatory cytokines such as IL-6, chemokines such as C-C motif chemokine 2 (also known as chemoattractant protein-1) and adipokines such as leptin and resistin. These adipokines affect satiety and lipid metabolism, and regulate the effects of insulin and glucose metabolism through a network of interactions with cytokines³³. In obesity, this altered network of adipokine and cytokine interactions contributes to impaired adipocyte metabolism; animal models and humans with obesity have increased levels of circulating cytokines, which can induce innate immune responses and influence the expression of several inflammatory mediators³⁴. As low-grade inflammation is involved in the pathophysiology of obesity, circulating cytokines have been named as potential therapeutic targets for the treatment of obesity.

Patients with IBD show a unique locally restrictive form of VAT — creeping fat — whereby mesenteric fat hyperplasia is limited to areas of inflamed bowel^{35,36}. Predominately seen in Crohn's disease, creeping fat is thought to be more immunologically active than other VAT, and the extent of creeping fat correlates closely with the extent of histological inflammation and degree of lymphocyte or macrophage infiltration²³. In a case-control study, Zulian and colleagues³⁶ observed that the gene expression profile of omental VAT, which is distant from unhealthy mesenteric depots, from patients with Crohn's disease was similar to that of VAT adipocytes from IBD-free individuals with obesity, with high expression of pro-inflammatory genes, and was distinct from VAT adipocytes in healthy, normal-weight individuals. Furthermore, expression of leptin and adipo nectin has been demonstrated to be increased in the hypertrophied mesenteric fat of patients with Crohn's disease, and specific risk alleles (such as *ATG16LI*) associated with alterations in adiponectins have also been associated with an increased risk of developing Crohn's disease. Levels of other adipokines, such as resistin, also correlate with Crohn's disease severity and disease activity, further supporting the interaction of adipokines and cytokines to promote mucosal inflammation³⁷.

Role of dysbiosis

Central to the pathogenesis of IBD is mucosal barrier dysfunction, bacterial translocation and loss of intestinal immune homeostasis³⁸. Translocation of bacteria has been linked to adipocyte and preadipocyte activation, with ensuing alterations in pro-inflammatory cytokine expression and immune homeostasis^{28,35,38–60} (FIG. 2). Increased gut bacterial translocation is pertinent given its independent links to both obesity and Crohn's disease; both conditions have a reduction in bacterial diversity with accompanying dysbiosis⁶¹. A colonic-mucosa–bacteria–adipose-tissue feedback loop is then slowly established and reinforced by alterations in motility and immunoendocrine axes^{62,63}. High-fat diet (both directly and by contributing to obesity) has been associated with an increased risk of Crohn's disease in preclinical models, with effects mediated through dysbiosis and altered gut permeability^{64–66}. Epidemiological studies have also reported an association between a diet rich in omega fatty acids and saturated, monounsaturated and polyunsaturated fats and risk of developing Crohn's disease and/or ulcerative colitis⁶⁷.

Studies in Crohn's disease have identified genetic polymorphisms in enteroendocrine transcription factors (*PHOX2B*) as well as autoantibodies to specific cell components^{68,69}. This finding, coupled with alterations in the levels of enteroendocrine hormones such as PYY, GLP-1 and GLP-2 (REF. 70), suggests a possible role for enteroendocrine cells in the propagation of inflammation in IBD. Treatment with GLP-2, an epithelial growth factor with anti-inflammatory properties, reduces the severity of injury in animal colitis models⁷¹, and its use as a treatment option for Crohn's disease is currently under investigation⁷². Circulating PYY levels correlate with Crohn's-disease-related nausea and anorexia⁷³, and evidence has demonstrated that enteroendocrine cells might be key producers and mediators of pro-inflammatory cytokines, such as IL-17 (REF. 74). With evidence demonstrating an adipose-tissue–colon feedback loop between substance P, adipocytes and IL-17, alterations in neuroendocrine cells and hormones could play into and further strengthen this feedback mechanism to further promote inflammation. Hence, through a combination of paracrine, enteroendocrine and microbial factors, obesity — in particular visceral adiposity — could contribute to development and perpetuation of inflammation in IBD, particularly Crohn's disease.

Effect of obesity on IBD course

Obesity has been associated with high disease activity and worse clinical outcomes in several autoimmune diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis^{75,76}. Studies in patients with Crohn's disease suggest that overall obesity (as measured by BMI) is not consistently associated with an increased prevalence of IBD-related complications. In a cross-sectional study of 846 patients with Crohn's disease, Pringle and colleagues¹⁰ observed a lower prevalence of penetrating disease complications in patients who were obese (odds ratio (OR) 0.56, 95% CI 0.31–0.99), but comparable risk of stricturing and perianal complications, compared with adults of a normal BMI. In another cross-sectional study of 297 patients with Crohn's disease (30.3% obese), there was no difference in the prevalence of penetrating (20% versus 22%) or stricturing complications (17% versus 22%) between individuals who were obese or those of a normal weight⁸.

Obesity, in particular class II (BMI ≥ 35 kg/m²) or class III obesity (BMI ≥ 40 kg/m²) might be associated with increased prevalence of colonic involvement with Crohn's disease, but this finding has not been consistently observed^{8,10,11,13,14}. Similarly, in patients with ulcerative colitis, obesity has not been associated with disease severity. In a cohort of 202 patients with ulcerative colitis (13.4% of whom were obese), Stabroth-Akil and colleagues¹⁴ observed a lower prevalence of pancolitis in patients who were obese than in patients of a normal BMI (33% versus 61%, respectively).

Longitudinal studies show variable effects of obesity on IBD disease course and the development of complications (TABLE 1). Inferior IBD-related quality of life and a higher frequency of elevated levels of serum C-reactive protein (an inflammatory marker) have been observed in patients with obesity (particularly class II or III obesity) compared with patients of normal weight; however, there was no statistically significant difference in the risk of IBD-related surgery, hospitalization or emergency department use between patients who were obese, overweight or a normal BMI¹². A shorter time to first surgery in those who were overweight or obese versus undernourished individuals (2 years versus 21 years, respectively) has also been found, although there were no differences in the number of surgeries related to Crohn's disease or escalation of medical therapy in patients with BMI ≥ 25 kg/m² versus BMI <25 kg/m² (REF. 77). By contrast, Flores and colleagues⁸ observed a lower risk of IBD-related surgery (41% versus 52% versus 61% for patients who were obese, overweight, or normal or underweight, respectively), hospitalization (42% versus 44% versus 66%) and initiation of anti-TNF therapy (25% versus 26% versus 43%), both in patients with Crohn's disease and ulcerative colitis. Outcomes during an index hospitalization are generally worse among patients with IBD who are obese compared with non-obese patients with IBD. In a cross-sectional study using the Nationwide Inpatient Sample, we observed that among 6,742 hospitalized patients with ulcerative colitis, adults who are obese have higher rates of surgery (23.1% versus 14.2%), severe hospitalization (need for surgery or hospital stay >7 days: 35.3% versus 26.2%) and longer hospital stay (mean 6.0 versus 5.4 days) than patients who are not obese⁷⁸.

Contribution of visceral adiposity

Although overall obesity has not been consistently associated with more severe disease activity and progression to disease complications, visceral adiposity has been independently associated with increased risk of IBD-related complications. In a cross-sectional study, Erhayiem and colleagues⁷⁹ observed that patients with complications of Crohn's disease had a higher CT-measured visceral fat area and a higher visceral to subcutaneous fat area ratio (mesenteric fat index) than patients with inflammatory Crohn's disease; on multivariate analysis, mesenteric fat index was independently associated with Crohn's disease complications. In a retrospective cohort study of 114 paediatric patients with IBD (101 with Crohn's disease), high VAT volume was associated with increased risk of penetrating or stricturing Crohn's disease complications (OR 1.7, 95% CI 1.1–2.9), Crohn's-disease-related hospitalization (OR, 1.9, 95% CI 1.2–3.4), shorter time interval to surgery (HR 1.4, 95% CI 1.0–2.0) and moderate–severe disease activity scores (OR 1.8, 95% CI 1.1–3.1), after adjusting for age and BMI²⁴. High visceral fat area has also been associated with increased risk of recurrence of Crohn's disease after surgical resection (endoscopic

recurrence: HR 8.6, 95% CI 1.6–47.1; clinical recurrence: HR 2.6, 95% CI 1.0–6.7)⁸⁰. Likewise, the metabolic consequences of obesity, in particular of visceral adiposity, have also been associated with IBD-related disease severity. In a single-centre retrospective cohort study of 868 patients with Crohn's disease (19.0% of whom were obese), an increased incidence of IBD-related hospitalization was observed in the 4% of the cohort with metabolic syndrome (defined as >3 of the following features: obesity, diabetes mellitus, hypertension, high levels of circulating triglycerides and low levels of circulating HDL cholesterol), compared with those without metabolic syndrome (incidence rate ratio 1.79, 95% CI 1.06–3.00). However, on evaluating different components of metabolic syndrome, presence of diabetes mellitus, high circulating triglyceride levels and low HDL cholesterol levels, but not obesity, were associated with increased incidence of IBD-related hospitalization⁸¹. In another retrospective cohort study of 240 patients with Crohn's disease (12.5% of whom were obese), although obesity was identified as a risk factor for surgery on univariate analysis (OR 2.2, 95% CI 1.0–4.8), it was not an independent predictor of surgery after adjustment for confounding variables. On the other hand, diabetes mellitus (which affected 6.7% of cohort) was a strong independent predictor of surgery, even after adjustment for corticosteroid use (OR 5.4, 95% CI 1.7–17.6)⁸². Patients with diabetes also had lower quality of life and higher clinical disease activity than individuals without diabetes.

Limitations of current literature

Current studies on the association between obesity and natural history of IBD have several limitations, and need to be interpreted carefully. Cross-sectional and cohort studies are retrospective in nature, which limits the ability to make causal inference given the dynamic nature of weight as well as IBD activity. This approach is limited by confounding by disease severity, wherein patients with severe disease activity (and at higher risk of disease-related complications) are likely to lose weight, resulting in potential misclassification of their BMI. On the other hand, patients with mild disease activity are more likely to maintain (or might gain) weight, as is the trend in the general population⁸³; in these patients, obesity or overweight might be a manifestation rather than the aetiology of a mild disease course. Additionally, most studies failed to adjust for other potential confounding factors such as smoking and corticosteroid use. Smoking cessation might improve Crohn's disease course, and could also result in weight gain causing a misclassification of obesity category. Similarly, use of corticosteroids, often prescribed to patients with more severe disease, is frequently associated with weight gain, potentially resulting in misclassification of BMI categories. Moreover, single tertiary-centre retrospective cohort studies have low event rates with limited follow-up, hence the independent effect of overweight and obesity on IBD course and development of complications has not been comprehensively studied. Design considerations for a more robust observational study of the relationship between IBD and obesity are described in BOX 1.

Given the increasing recognition of metabolic differences in visceral (and mesenteric) and subcutaneous adiposity, overall BMI might not adequately capture the association between obesity and IBD. As observed in several studies, measurement of visceral fat (through VAT

area or volume, or at least measurement of central obesity using surrogate measures such as WHR) could help us better understand the true effect of obesity on IBD.

Obesity and IBD-related therapy

Observational comparative effectiveness studies in Crohn's disease suggest that infliximab is associated with lower rates of IBD-related hospitalization and abdominal surgery than adalimumab and certolizumab pegol^{84,85}; these observations are also supported by indirect treatment comparison network meta-analyses⁸⁶. These differences could be due to differences in systemic drug exposure related to body weight; infliximab dose is weight-based and intravenously administered, whereas other agents are administered subcutaneously in a fixed dose. For example, in a single-centre retrospective cohort study, Bhalme *et al.*⁸⁷ observed — in adalimumab-treated but not infliximab-treated patients — a higher likelihood of dose escalation in patients who were obese than in patients who were not obese (BMI >35 kg/m² versus BMI <25 kg/m², 40% versus 20%, respectively). In an exploratory analysis of trials of adalimumab in patients with psoriasis, the response rate decreased progressively with increasing quartile of weight, from 74–79% in the lowest quartile to 62–71% in the highest quartile⁸⁸. By contrast, in a pooled analysis of three randomized controlled trials of infliximab in psoriasis, the response rates were comparable in patients who were normal weight, overweight and obese (78% versus 78% versus 74%, no statistically significant difference between groups)⁸⁸. Importantly, patients who are obese, particularly those who are morbidly obese, are less likely to receive optimal weight-appropriate therapy. Seminerio and colleagues¹² observed that the average dose of infliximab in patients with class III obesity was ~4 mg/kg body weight, compared with 7.9 mg/kg body weight in those with normal BMI and 6.4 mg/kg body weight in patients who were overweight. Similarly, the usual per kilogram body weight dose of immunomodulators was lower in patients with class III obesity than in patients with normal BMI (azathioprine dose 1.1 mg/kg body weight per day versus 1.7 mg/kg body weight per day, respectively, and 6-mercaptopurine dose 0.7 mg/kg body weight per day versus 1.2 mg/kg body weight per day, respectively).

However, obesity might affect treatment response to biologics independent of drug exposure. Population pharmacokinetic studies of all biologic agents approved for use in IBD, including anti-TNF agents (infliximab⁸⁹, adalimumab⁹⁰, certolizumab pegol⁹¹, golimumab⁹²), and anti-integrin agents (vedolizumab)⁹³, have identified high body weight as a risk factor associated with increased drug clearance, resulting in short half-life and low trough drug concentrations. This effect might be related to rapid proteolysis⁹⁴ and to a 'TNF sink' phenomenon in patients with obesity, whereby increased levels of adipose-secreted TNF sequester anti-TNF agents. In a retrospective cohort study of 124 infliximab-treated patients with IBD, patients with obesity were 3–9 times more likely to have an IBD flare and require biologic dose escalation than normal weight patients⁹⁵. Each unit increase in BMI was associated with a 6% higher likelihood of Crohn's disease flare (HR 1.06, 95% CI 1.02–1.11) and 30% higher likelihood of ulcerative colitis flare (HR 1.30, 95% CI 1.07–1.58). In another single-centre prospective cohort of 199 patients with Crohn's disease treated with adalimumab and followed over a median of 1 year, over one-third of patients were dose-escalated to weekly adalimumab within a median 5 months of initiating therapy, and BMI

was the only independent predictor of dose escalation⁹⁶. However, these findings have not been consistent. In a prospective, single-centre experience, no statistically significant association was observed between BMI and infliximab or adalimumab trough levels⁹⁷.

Although data on obesity and treatment response in IBD is limited, similar observations have been made in biologic-agent-treated patients with other autoimmune diseases. In a prospective cohort of 89 patients with rheumatoid arthritis treated with infliximab, patients who were obese had lower rates of clinical response (measured using Disease Activity Score in 28 joints) than patients with a normal BMI, even after adjustment for baseline disease activity and anti-citrullinated protein antibody status (BMI >30 kg/m² versus BMI 20–30 kg/m² versus BMI <20 kg/m², 50% versus 75% versus 84%, respectively)⁹⁸. Similarly, in a prospective cohort of 641 patients with rheumatoid arthritis (10.3% of whom were obese), the cumulative rate of clinical remission at 12 months after treatment initiation was lowest in patients with obesity, compared with individuals who were overweight or normal BMI (15.2% versus 30.4% versus 32.9%, respectively)⁹⁹. Likewise, in 557 patients with psoriatic arthritis (35.4% of whom were obese), likelihood of achieving sustained minimal disease activity was lowest in patients who were obese (OR 0.52, 95% CI 0.40–0.67) and overweight (OR 0.65, 95% CI 0.50–0.85), compared with patients with normal BMI¹⁰⁰.

Besides biologic therapy, obesity might also modify response to immunomodulator therapy in IBD. Among 132 patients with IBD treated with thiopurines dosed according to body weight, patients who were obese were less likely to achieve therapeutic 6-thioguanine nucleotide concentrations, with thiopurines instead preferentially metabolized via the 6-methyl mercaptopurine nucleotide pathway¹⁰¹.

Effect of obesity on IBD-related surgery

Intra-abdominal surgeries in patients with obesity are both technically challenging and are usually associated with higher rates of postoperative complications than surgeries in patients with a normal BMI¹⁰². In a systematic review of 33 studies on the effect of obesity on perioperative outcomes with laparoscopic colorectal resection for any aetiology, Makino and colleagues¹⁰³ observed longer operative times and an increased likelihood of conversion to open procedure in patients who were obese. Compared with patients who were not obese, patients with obesity had more comorbidities, a higher risk of postoperative complications (in particular wound infection) and a longer length of hospital stay. In a cohort of patients undergoing colorectal cancer surgery, increased perioperative mortality, higher rates of surgical complications, increased hospital costs and more frequent need for discharge to short-term rehabilitation facilities were observed in those with obesity compared with those who were not obese.

Key studies on the effect of obesity on surgical outcomes in patients with IBD are summarized in TABLE 3. In a nationwide US study of 382,637 inpatient hospitalizations for surgery in patients with IBD (using the Nationwide Inpatient Sample), Jain and colleagues¹⁰⁵ observed that patients with obesity had increased rates of postoperative wound complications (OR 1.35, *P* = 0.01), infections (OR 1.16, *P* = 0.02), pulmonary complications (OR 1.21, *P* = 0.02), and shock (OR 1.30, *P* = 0.02). No difference in the risk of

cardiovascular complications (OR 1.09, $P=0.52$), perforations (OR 1.04, $P=0.71$), venous thromboembolism (OR 1.18, $P=0.40$) or death (OR 0.73, $P=0.07$) was observed between obese and non-obese IBD surgeries. Two aspects of surgery that might be particularly challenging in patients with IBD merit special mention. First, obesity makes creating a stoma challenging, as it tends to retract, and is associated with higher rates of stoma-related complications such as parastomal hernia, mucocutaneous separation and stoma prolapse^{106,107}. Second, the mesentery of patients with obesity tends to be foreshortened by the mesenteric fat, making it more challenging to create a J-pouch in patients with ulcerative colitis. Obesity increases risk of short-term postoperative complications in patients undergoing ileal pouch–anal anastomosis, although long-term outcomes might be comparable to those in patients without obesity in experienced centres^{108,109}.

Beyond overall obesity, visceral adiposity might be an independent predictor of surgical outcomes and complications in patients with IBD. Using analytic morphomics (the application of machine learning to biomedical images to derive patient-specific biomarkers), Stidham and colleagues observed that a high visceral to subcutaneous fat ratio, and not high BMI, is associated with increased risk of infectious complications after surgical resection for Crohn's disease¹¹⁰. In another retrospective cohort of 164 patients undergoing primary Crohn's disease-related surgery, a high visceral fat area (130 cm^2) was independently associated with a 2.7-fold increased risk of overall postoperative complications¹¹¹.

Besides surgery, an area that merits discussion in patients with IBD who are obese is medical imaging. Two types of abdominal imaging, CT and MRI, are frequently used in patients with IBD, and can impose special challenges in patients who are morbidly obese¹¹². Equipment-specific issues include table weight limit, gantry width and tube capacity; imaging via MRI brings greater equipment-specific issues, as the standard MRI table weight capacity is 350 lbs (158.8 kg) and the standard machine bore diameter is 60 cm, limiting the ability to place patients in the scanner. Image-quality issues are also present, as a result of photon starvation, reduced contrast-to-noise ratio and truncation artefacts¹¹². Owing to difficult intravenous access and risk of extra-vasation, and the need for weight-based contrast administration, there can be issues with intravenous contrast in patients who are obese. Additionally, claustrophobia and patient discomfort are substantial concerns when using MRI. Hence, despite inherent limitations, CT might be the best and easiest way to image larger patients. Specific solutions during imaging and post-image processing might be implemented to optimize image quality in patients who are obese.

Obesity treatment and IBD outcomes

Although there is considerable evidence that obesity adversely affects response to IBD-related therapy, there is a paucity of data on whether treating obesity can favourably affect outcomes in patients with IBD. No interventional studies of interventional weight loss in IBD exist; however, trials of diet and/or lifestyle-induced weight loss in other autoimmune diseases suggest improvement in outcomes with this form of adjunctive therapy. In a meta-analysis of five studies in patients with psoriasis who were obese or overweight, those randomized to weight loss intervention were 2.9 times more likely to achieve 75% reduction in Psoriasis Area and Severity Index score, compared with those not receiving the weight

loss intervention (OR 2.92, 95% CI 1.39–6.13)¹¹³. Achieving as little as 5% weight loss is associated with favourable outcomes. In a 6-month randomized trial comparing a low-calorie or a free-managed diet (comprising dietary advice but no calorific restriction) in 126 patients with psoriatic arthritis starting anti-TNF therapy, Di Munno and colleagues¹¹⁴ observed a greater reduction in levels of pain and inflammatory markers, and higher likelihood of achieving minimal disease activity, in patients receiving a low-calorie diet (42.9% versus 34.9% of patients achieved minimal disease activity on low-calorie diet versus free-managed diet, respectively). Importantly, regardless of the intervention, magnitude of intentional weight loss was associated with improvement in outcomes: the proportion of patients attaining minimal disease activity in those achieving >10% weight loss, 5–10% weight loss and <5% weight loss was 59.5%, 44.8% and 23.1%, respectively. Patients who achieved at least 5% weight loss were 4.2 times more likely to achieve minimal disease activity compared with those who experienced <5% weight loss (OR 4.20, 95% CI 1.82–9.66).

Whether similar benefits would be observed among patients with IBD who are obese is speculative. Although bariatric surgery is technically feasible in patients with IBD, long-term consequences of major restrictive and malabsorptive procedures in these individuals are poorly understood. Case series have suggested that these procedures are safe in highly selected patients who are morbidly obese and have IBD, and have also anecdotally observed improvement in disease activity after weight loss^{115,116}. However, short of bariatric surgery, other weight loss interventions would also probably be beneficial. Although dietary interventions carry low risk of adverse events, adherence to specific diets is limited, and despite intensive lifestyle interventions remaining the cornerstone of initial obesity management, their long-term effectiveness in a real-world setting is limited by small average weight loss with commercial weight-loss programmes and frequent regain of lost weight over time¹¹⁷. Weight loss achieved through pharmacological or endoscopic bariatric interventions might achieve the same effect on outcomes in IBD as in other autoimmune diseases, but has not been studied. With five weight-loss medications now approved by the FDA for long-term management of obesity, with average excess weight loss (over placebo) ranging from 2.6 kg (with orlistat) to 8.8 kg (phentermine–topiramate), and an estimated 44–75% of patients achieving the threshold of at least 5% weight loss, it is very appealing to consider pilot trials of the efficacy and safety of these medications as adjunct therapies in patients with IBD who are obese¹¹⁸. Two medications in particular merit attention: phentermine–topiramate and naltrexone–bupropion. Both of these medications result in statistically and clinically significant weight loss (mean 8.8 kg and 5.0 kg excess weight loss over placebo, respectively, and 75% and 50% patients achieving at least 5% weight loss, respectively), with low rates of serious adverse events. Preclinical data supports an anti-inflammatory role of both topiramate and phentermine. Using a novel computational approach for drug repositioning, Dudley and colleagues¹¹⁹ systematically compared the gene expression profiles of a compendium of 164 drug compounds in human cell lines to the gene expression signature of IBD derived from public microarray data of patient biopsy samples. On the basis of this analysis, they predicted that topiramate is very likely to be effective against both Crohn's disease and ulcerative colitis. Subsequently, *in vivo* testing of topiramate was performed in a 2,4,6-trinitrobenzenesulfonic acid (TNBS) rat model of IBD, with three independent validations. Administration of topiramate for 7 days after TNBS-

induced colitis resulted in markedly reduced diarrhoea and reduced pathological inflammation. Similarly, several lines of evidence have shown that noradrenaline might regulate intestinal mucosal immune responses mediated by intraepithelial lymphocytes via β 1-adrenoreceptors¹²⁰. The individual components of naltrexone–bupropion have also shown favourable effects in IBD. One 12-week trial of low-dose naltrexone (4.5 mg per day) in 40 patients with Crohn’s disease found higher rates of clinical and endoscopic remission in the intervention group than the placebo group; at this low dose, this observed benefit might be mediated through naltrexone’s anti-inflammatory effect rather than through weight loss¹²¹. Preclinical studies have suggested that bupropion might have an anti-TNF effect, with small case series reporting the effectiveness of this medication in inducing clinical remission^{122,123}.

Conclusions

The prevalence of obesity in patients with IBD is sizeable and parallels rates in the general population, contrary to conventional beliefs that patients with IBD are malnourished. Although from a pathophysiological perspective, obesity, and in particular visceral adiposity, seems to promote intestinal inflammation, epidemiological studies implicating obesity in the development of IBD are limited. Understanding of the effects of obesity on cross-sectional disease severity and development of disease complications is incomplete, with studies conducted to date (with flawed designs and inherent limitations) showing conflicting results. On the basis of pharmacokinetic data, obesity seems to promote rapid clearance of biologic agents, regardless of drug dose. The effect of obesity on response to therapy remains to be studied, though data from other autoimmune diseases suggests that obesity is an independent predictor of poor response to medical therapy. This association provides an opportunity for using treatment directed towards obesity, either through lifestyle, pharmacological or endoscopic interventions, as adjunctive therapy in patients with IBD who are obese.

Acknowledgments

S.S. is supported by the NIH/National Library of Medicine training grant T15LM011271, the American College of Gastroenterology Junior Faculty Development Award and the Crohn’s and Colitis Foundation of American Career Development Award. P.S.D. is supported by the National Institute of Diabetes and Digestive and Kidney Diseases training grant 5T32DK007202. A.Z. has received support from NIH K08 DK102902, the American Association for the Study of Liver Diseases Liver Scholar Award, and the American Gastroenterological Association Microbiome Junior Investigator Research Award. The Authors thank L. J. Prokop, Senior Medical Librarian at Mayo Clinic, Rochester, USA, who assisted with a systematic literature review on this topic.

References

1. Ng M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014; 384:766–781. [PubMed: 24880830]
2. Finkelstein EA, Trogon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. *Health Aff*. 2009; 28:w822–w831.
3. Molodecky NA, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012; 142:46–54. [PubMed: 22001864]
4. Ng SC, et al. Early course of inflammatory bowel disease in a population-based inception cohort study from 8 countries in Asia and Australia. *Gastroenterology*. 2016; 150:86–95.e3. [PubMed: 26385074]

5. Kaplan GG. The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol*. 2015; 12:720–727. [PubMed: 26323879]
6. Qin B, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. *Arthritis Res Ther*. 2015; 17:86. [PubMed: 25890172]
7. Sterry W, Strober BE, Menter A, International Psoriasis Council. Obesity in psoriasis: the metabolic, clinical and therapeutic implications Report of an interdisciplinary conference and review. *Br J Dermatol*. 2007; 157:649–655. [PubMed: 17627791]
8. Flores A, Burstein E, Cipher DJ, Feagins LA. Obesity in inflammatory bowel disease: a marker of less severe disease. *Dig Dis Sci*. 2015; 60:2436–2445. [PubMed: 25799938]
9. Long MD, et al. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011; 17:2162–2168. [PubMed: 21910178]
10. Pringle PL, et al. Body mass index, genetic susceptibility, and risk of complications among individuals with Crohn's disease. *Inflamm Bowel Dis*. 2015; 21:2304–2310. [PubMed: 26181430]
11. Mendall MA, Gunasekera AV, John BJ, Kumar D. Is obesity a risk factor for Crohn's disease? *Dig Dis Sci*. 2011; 56:837–844. [PubMed: 21221790]
12. Seminerio JL, et al. Impact of obesity on the management and clinical course of patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2015; 21:2857–2863. [PubMed: 26241001]
13. Nic Suibhne T, et al. High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. *J Crohns Colitis*. 2013; 7:e241–e248. [PubMed: 23040290]
14. Stabroth-Akil D, Leifeld L, Pfutzer R, Morgenstern J, Kruis W. The effect of body weight on the severity and clinical course of ulcerative colitis. *Int J Colorectal Dis*. 2015; 30:237–242. [PubMed: 25392256]
15. Steed H, Walsh S, Reynolds N. A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. *Obes Facts*. 2009; 2:370–372. [PubMed: 20090388]
16. Kugathasan S, et al. Body mass index in children with newly diagnosed inflammatory bowel disease: observations from two multicenter North American inception cohorts. *J Pediatr*. 2007; 151:523–527. [PubMed: 17961699]
17. Blain A, et al. Crohn's disease clinical course and severity in obese patients. *Clin Nutr*. 2002; 21:51–57. [PubMed: 11884013]
18. Moran GW, Dubeau MF, Kaplan GG, Panaccione R, Ghosh S. The increasing weight of Crohn's disease subjects in clinical trials: a hypothesis-generating time-trend analysis. *Inflamm Bowel Dis*. 2013; 19:2949–2956. [PubMed: 23945182]
19. Khalili H, et al. Measures of obesity and risk of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2015; 21:361–368. [PubMed: 25563694]
20. Harpoe MC, et al. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. *Int J Epidemiol*. 2014; 43:843–855. [PubMed: 24609069]
21. Chan SSM, et al. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). *Am J Gastroenterol*. 2013; 108:575–582. [PubMed: 23318483]
22. Hemminki K, Li X, Sundquist J, Sundquist K. Risk of asthma and autoimmune diseases and related conditions in patients hospitalized for obesity. *Ann Med*. 2012; 44:289–295. [PubMed: 21284531]
23. Kredel LI, Siegmund B. Adipose-tissue and intestinal inflammation — visceral obesity and creeping fat. *Front Immunol*. 2014; 5:462. [PubMed: 25309544]
24. Uko V, et al. Impact of abdominal visceral adipose tissue on disease outcome in pediatric Crohn's disease. *Inflamm Bowel Dis*. 2014; 20:2286–2291. [PubMed: 25222655]
25. Khalili H, et al. Physical activity and risk of inflammatory bowel disease: prospective study from the Nurses' Health Study cohorts. *BMJ*. 2013; 347:f6633. [PubMed: 24231178]
26. Bilski J, Brzozowski B, Mazur-Bialy A, Sliwowski Z, Brzozowski T. The role of physical exercise in inflammatory bowel disease. *Biomed Res Int*. 2014; 2014:429031. [PubMed: 24877092]

27. Zietek T, Rath E. Inflammation meets metabolic disease: gut feeling mediated by GLP-1. *Front Immunol.* 2016; 7:154. [PubMed: 27148273]
28. Karmiris K, et al. Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. *Inflamm Bowel Dis.* 2006; 12:100–105. [PubMed: 16432373]
29. Tian J, Venn A, Otahal P, Gall S. The association between quitting smoking and weight gain: a systemic review and meta-analysis of prospective cohort studies. *Obes Rev.* 2015; 16:883–901. [PubMed: 26114839]
30. Berthon BS, MacDonald-Wicks LK, Wood LG. A systematic review of the effect of oral glucocorticoids on energy intake, appetite, and body weight in humans. *Nutr Res.* 2014; 34:179–190. [PubMed: 24655484]
31. Wung PK, et al. Effects of glucocorticoids on weight change during the treatment of Wegener's granulomatosis. *Arthritis Rheum.* 2008; 59:746–753. [PubMed: 18438908]
32. Winer DA, Luck H, Tsai S, Winer S. The intestinal immune system in obesity and insulin resistance. *Cell Metab.* 2016; 23:413–426. [PubMed: 26853748]
33. Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm.* 2010; 2010:802078. [PubMed: 20671929]
34. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol.* 2010; 72:219–246. [PubMed: 20148674]
35. Kredel L, Batra A, Siegmund B. Role of fat and adipokines in intestinal inflammation. *Curr Opin Gastroenterol.* 2014; 30:559–565. [PubMed: 25188546]
36. Zulian A, et al. Visceral adipocytes: old actors in obesity and new protagonists in Crohn's disease? *Gut.* 2012; 61:86–94. [PubMed: 21930728]
37. Batra A, Zeitz M, Siegmund B. Adipokine signaling in inflammatory bowel disease. *Inflamm Bowel Dis.* 2009; 15:1897–1905. [PubMed: 19408337]
38. Dulai PS, Levesque BG, Feagan BG, D'Haens G, Sandborn WJ. Assessment of mucosal healing in inflammatory bowel disease: review. *Gastrointest Endosc.* 2015; 82:246–255. [PubMed: 26005012]
39. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol.* 2011; 11:85–97. [PubMed: 21252989]
40. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr.* 2004; 92:347–355. [PubMed: 15469638]
41. Schaffler A, Scholmerich J, Salzberger B. Adipose tissue as an immunological organ: Toll-like receptors, C1q/TNFs and CTRPs. *Trends Immunol.* 2007; 28:393–399. [PubMed: 17681884]
42. Stroh T, et al. Nucleotide oligomerization domains 1 and 2: regulation of expression and function in preadipocytes. *J Immunol.* 2008; 181:3620–3627. [PubMed: 18714036]
43. Charriere G, et al. Preadipocyte conversion to macrophage: evidence of plasticity. *J Biol Chem.* 2003; 278:9850–9855. [PubMed: 12519759]
44. Desreumaux P, et al. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology.* 1999; 117:73–81. [PubMed: 10381912]
45. Paul G, et al. Profiling adipocytokine secretion from creeping fat in Crohn's disease. *Inflamm Bowel Dis.* 2006; 12:471–477. [PubMed: 16775490]
46. La Cava A, Matarese G. The weight of leptin in immunity. *Nat Rev Immunol.* 2004; 4:371–379. [PubMed: 15122202]
47. Batra A, et al. Leptin: a critical regulator of CD4⁺ T-cell polarization *in vitro* and *in vivo*. *Endocrinology.* 2010; 151:56–62. [PubMed: 19966187]
48. Siegmund B, Lehr HA, Fantuzzi G. Leptin: a pivotal mediator of intestinal inflammation in mice. *Gastroenterology.* 2002; 122:2011–2025. [PubMed: 12055606]
49. Nishihara T, et al. Effect of adiponectin on murine colitis induced by dextran sulfate sodium. *Gastroenterology.* 2006; 131:853–861. [PubMed: 16952554]
50. Fayad R, et al. Adiponectin deficiency protects mice from chemically induced colonic inflammation. *Gastroenterology.* 2007; 132:601–614. [PubMed: 17258715]
51. Ohashi K, et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *J Biol Chem.* 2010; 285:6153–6160. [PubMed: 20028977]

52. Ogunwobi OO, Beales IL. Adiponectin stimulates proliferation and cytokine secretion in colonic epithelial cells. *Regul Pept.* 2006; 134:105–113. [PubMed: 16529829]
53. Schaffler A, Scholmerich J. The role of adiponectin in inflammatory gastrointestinal diseases. *Gut.* 2009; 58:317–322. [PubMed: 19211847]
54. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. *J Immunol.* 2005; 174:5789–5795. [PubMed: 15843582]
55. Konrad A, et al. Resistin is an inflammatory marker of inflammatory bowel disease in humans. *Eur J Gastroenterol Hepatol.* 2007; 19:1070–1074. [PubMed: 17998831]
56. Sideri A, et al. Effects of obesity on severity of colitis and cytokine expression in mouse mesenteric fat. Potential role of adiponectin receptor 1. *Am J Physiol Gastrointest Liver Physiol.* 2015; 308:G591–G604. [PubMed: 25591865]
57. Zulian A, et al. Differences in visceral fat and fat bacterial colonization between ulcerative colitis and Crohn's disease. An *in vivo* and *in vitro* study. *PLoS ONE.* 2013; 8:e78495. [PubMed: 24205244]
58. Peyrin-Biroulet L, et al. Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease. *Gut.* 2012; 61:78–85. [PubMed: 21940721]
59. Yamamoto K, et al. Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. *Gut.* 2005; 54:789–796. [PubMed: 15888786]
60. Sheehan AL, Warren BF, Gear MW, Shepherd NA. Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. *Br J Surg.* 1992; 79:955–958. [PubMed: 1422768]
61. Kim A. Dysbiosis: a review highlighting obesity and inflammatory bowel disease. *J Clin Gastroenterol.* 2015; 49(Suppl. 1):S20–S24. [PubMed: 26447959]
62. Worthington JJ. The intestinal immunoendocrine axis: novel cross-talk between enteroendocrine cells and the immune system during infection and inflammatory disease. *Biochem Soc Trans.* 2015; 43:727–733. [PubMed: 26551720]
63. Cani PD, Everard A, Duparc T. Gut microbiota, enteroendocrine functions and metabolism. *Curr Opin Pharmacol.* 2013; 13:935–940. [PubMed: 24075718]
64. Leone VA, Cham CM, Chang EB. Diet, gut microbes, and genetics in immune function: can we leverage our current knowledge to achieve better outcomes in inflammatory bowel diseases? *Curr Opin Immunol.* 2014; 31:16–23. [PubMed: 25214301]
65. Lee D, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology.* 2015; 148:1087–1106. [PubMed: 25597840]
66. Gruber L, et al. High fat diet accelerates pathogenesis of murine Crohn's disease-like ileitis independently of obesity. *PLoS ONE.* 2013; 8:e71661. [PubMed: 23977107]
67. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol.* 2011; 106:563–573. [PubMed: 21468064]
68. Rioux JD, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet.* 2007; 39:596–604. [PubMed: 17435756]
69. Sakiyama T, Fujita H, Tsubouchi H. Autoantibodies against ubiquitination factor E4A (UBE4A) are associated with severity of Crohn's disease. *Inflamm Bowel Dis.* 2008; 14:310–317. [PubMed: 18069675]
70. Harrison E, Lal S, McLaughlin JT. Enteroendocrine cells in gastrointestinal pathophysiology. *Curr Opin Pharmacol.* 2013; 13:941–945. [PubMed: 24206752]
71. Qi KK, Wu J, Wan J, Men XM, Xu ZW. Purified PEGylated porcine glucagon-like peptide-2 reduces the severity of colonic injury in a murine model of experimental colitis. *Peptides.* 2014; 52:11–18. [PubMed: 24274971]
72. Blonski W, Buchner AM, Aberra F, Lichtenstein G. Teduglutide in Crohn's disease. *Expert Opin Biol Ther.* 2013; 13:1207–1214. [PubMed: 23834252]
73. Moran GW, Leslie FC, McLaughlin JT. Crohn's disease affecting the small bowel is associated with reduced appetite and elevated levels of circulating gut peptides. *Clin Nutr.* 2013; 32:404–411. [PubMed: 22999064]

74. Friedrich M, Diegelmann J, Schaubert J, Auernhammer CJ, Brand S. Intestinal neuroendocrine cells and goblet cells are mediators of IL-17A-amplified epithelial IL-17C production in human inflammatory bowel disease. *Mucosal Immunol*. 2015; 8:943–958. [PubMed: 25492478]
75. Iannone F, et al. Impact of obesity on the clinical outcome of rheumatologic patients in biotherapy. *Autoimmun Rev*. 2016; 15:447–450. [PubMed: 26808074]
76. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. *Autoimmun Rev*. 2014; 13:981–1000. [PubMed: 25092612]
77. Hass DJ, Brensinger CM, Lewis JD, Lichtenstein GR. The impact of increased body mass index on the clinical course of Crohn's disease. *Clin Gastroenterol Hepatol*. 2006; 4:482–488. [PubMed: 16616354]
78. Singh S, Khera R, Sandborn WJ. Obesity is associated with worse outcomes in hospitalized patients with inflammatory bowel diseases: a nationwide study. *Am J Gastroenterol*. 2016; 111:S271.
79. Erhayiem B, Dhingsa R, Hawkey CJ, Subramanian V. Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. *Clin Gastroenterol Hepatol*. 2011; 9:684–687.e1. [PubMed: 21642015]
80. Li Y, et al. Visceral fat area is associated with a high risk for early postoperative recurrence in Crohn's disease. *Colorectal Dis*. 2015; 17:225–234. [PubMed: 25307174]
81. Fitzmorris PS, et al. Impact of metabolic syndrome on the hospitalization rate of Crohn's disease patients seen at a tertiary care center: a retrospective cohort study. *Digestion*. 2015; 91:257–262. [PubMed: 25833139]
82. Harper JW, Welch MP, Sinanan MN, Wahbeh GT, Lee SD. Co-morbid diabetes in patients with Crohn's disease predicts a greater need for surgical intervention. *Aliment Pharmacol Ther*. 2012; 35:126–132. [PubMed: 22074268]
83. Dutton GR, et al. 25-year weight gain in a racially balanced sample of U.S. adults: The CARDIA study. *Obesity*. 2016; 24:19620–1968.
84. Singh S, et al. Comparative effectiveness and safety of anti-tumor necrosis factor agents in biologic-naïve patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2016; 14:1120–1129.e6. [PubMed: 27058635]
85. Osterman MT, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. *Clin Gastroenterol Hepatol*. 2014; 12:811–817.e3. [PubMed: 23811254]
86. Singh S, et al. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: a systematic review and network meta-analysis. *Mayo Clin Proc*. 2014; 89:1621–1635. [PubMed: 25441399]
87. Bhalme M, Sharma A, Keld R, Willert R, Campbell S. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? *Eur J Gastroenterol Hepatol*. 2013; 25:543–549. [PubMed: 23337170]
88. Puig L. Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. *J Eur Acad Dermatol Venereol*. 2011; 25:1007–1011. [PubMed: 21492252]
89. Dotan I, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis*. 2014; 20:2247–2259. [PubMed: 25358062]
90. Sharma S, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. *Inflamm Bowel Dis*. 2015; 21:783–792. [PubMed: 25723614]
91. Colombel JF, et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2014; 12:423–431.e1. [PubMed: 24184736]
92. Xu ZH, et al. Population pharmacokinetics of golimumab in patients with ankylosing spondylitis: impact of body weight and immunogenicity. *Int J Clin Pharmacol Ther*. 2010; 48:596–607. [PubMed: 20860913]
93. Rosario M, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther*. 2015; 42:188–202. [PubMed: 25996351]

94. Brill MJ, et al. Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinet.* 2012; 51:277–304. [PubMed: 22448619]
95. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2013; 19:2118–2124. [PubMed: 23863401]
96. Bultman E, et al. Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. *Aliment Pharmacol Ther.* 2012; 35:335–341. [PubMed: 22191671]
97. Bond A, et al. Comparative analysis of the influence of clinical factors including BMI on adalimumab and infliximab trough levels. *Eur J Gastroenterol Hepatol.* 2016; 28:271–276. [PubMed: 26657455]
98. Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. *Arthritis Rheum.* 2011; 63:359–364. [PubMed: 21279992]
99. Gremese E, et al. Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: an approach to a personalized medicine. *Arthritis Care Res.* 2013; 65:94–100.
100. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. *Ann Rheum Dis.* 2015; 74:813–817. [PubMed: 24431392]
101. Poon SS, et al. Body mass index and smoking affect thioguanine nucleotide levels in inflammatory bowel disease. *J Crohns Colitis.* 2015; 9:640–646. [PubMed: 25968584]
102. Boutros M, Maron D. Inflammatory bowel disease in the obese patient. *Clin Colon Rectal Surg.* 2011; 24:244–252. [PubMed: 23204939]
103. Makino T, Shukla PJ, Rubino F, Milsom JW. The impact of obesity on perioperative outcomes after laparoscopic colorectal resection. *Ann Surg.* 2012; 255:228–236. [PubMed: 22190113]
104. Hussan H, et al. Morbid obesity is associated with increased mortality, surgical complications, and incremental health care utilization in the peri-operative period of colorectal cancer surgery. *World J Surg.* 2016; 40:987–994. [PubMed: 26643515]
105. Jain A, Limketkai BN, Hutfless S. The effect of obesity on post-surgical complications during hospitalizations for inflammatory bowel disease: a nationwide analysis. *Gastroenterology.* 2014; 146:S595–S596.
106. Duchesne JC, Wang YZ, Weintraub SL, Boyle M, Hunt JP. Stoma complications: a multivariate analysis. *Am Surg.* 2002; 68:961–966. [PubMed: 12455788]
107. Beck SJ. Stoma issues in the obese patient. *Clin Colon Rectal Surg.* 2011; 24:259–262. [PubMed: 23204941]
108. Klos CL, et al. Obesity increases risk for pouch-related complications following restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA). *J Gastrointest Surg.* 2014; 18:573–579. [PubMed: 24091910]
109. Kiran RP, et al. Complications and functional results after ileoanal pouch formation in obese patients. *J Gastrointest Surg.* 2008; 12:668–674. [PubMed: 18228111]
110. Stidham RW, et al. Body fat composition assessment using analytic morphomics predicts infectious complications after bowel resection in Crohn's disease. *Inflamm Bowel Dis.* 2015; 21:1306–1313. [PubMed: 25822011]
111. Ding Z, et al. Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. *Colorectal Dis.* 2016; 18:163–172. [PubMed: 26391914]
112. Carucci LR. Imaging obese patients: problems and solutions. *Abdom Imaging.* 2013; 38:630–646. [PubMed: 23008055]
113. Upala S, Sanguankeo A. Effect of lifestyle weight loss intervention on disease severity in patients with psoriasis: a systematic review and meta-analysis. *Int J Obes.* 2015; 39:1197–1202.
114. Di Minno MN, et al. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor α blockers. *Ann Rheum Dis.* 2014; 73:1157–1162. [PubMed: 23771989]
115. Colombo F, et al. Bariatric surgery in patients with inflammatory bowel disease: an accessible path? Report of a case series and review of the literature. *J Crohns Colitis.* 2015; 9:185–190. [PubMed: 25518054]

116. Aminian A, et al. Outcomes of bariatric surgery in patients with inflammatory bowel disease. *Obes Surg.* 2016; 26:1186–1190. [PubMed: 26420765]
117. Johnston BC, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA.* 2014; 312:923–933. [PubMed: 25182101]
118. Khera R, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA.* 2016; 315:2424–2434. [PubMed: 27299618]
119. Dudley JT. Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. *Sci Transl Med.* 2011; 3:96ra76.
120. Takayanagi Y, et al. Norepinephrine suppresses IFN-gamma and TNF-alpha production by murine intestinal intraepithelial lymphocytes via the beta(1) adrenoceptor. *J Neuroimmunol.* 2012; 245:66–74. [PubMed: 22398028]
121. Smith JP, et al. Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial. *Dig Dis Sci.* 2011; 56:2088–2097. [PubMed: 21380937]
122. Brustolim D, Ribeiro-dos-Santos R, Kast RE, Altschuler EL, Soares MB. A new chapter opens in anti-inflammatory treatments: the antidepressant bupropion lowers production of tumor necrosis factor-alpha and interferon-gamma in mice. *Int Immunopharmacol.* 2006; 6:903–907. [PubMed: 16644475]
123. Kane S, Altschuler EL, Kast RE. Crohn's disease remission on bupropion. *Gastroenterology.* 2003; 125:1290. [PubMed: 14552325]
124. Krane MK, et al. Does morbid obesity change outcomes after laparoscopic surgery for inflammatory bowel disease? Review of 626 consecutive cases. *J Am Coll Surg.* 2013; 216:986–996. [PubMed: 23523148]
125. Causey MW, et al. The impact of obesity on outcomes following major surgery for Crohn's disease: an American College of Surgeons National Surgical Quality Improvement Program assessment. *Dis Colon Rectum.* 2011; 54:1488–1495. [PubMed: 22067176]

Box 1**Observational studies of obesity and IBD: clarifying the relationship**

A better designed observational study to evaluate the association between obesity and disease course and outcomes in IBD would possess the following features:

- Inclusion of incident or prevalent cases with IBD
- Measurement of BMI at cohort inception (preferably at a time when weight has been stable, when patients are in remission, off corticosteroids, in patients without recent change in smoking status)
- Prospective evaluation of disease-related complication risk, stratified by baseline BMI
- Adjustment for confounding factors (such as disease severity and current or prior disease complications, prior surgery and IBD-related therapy, among other factors)

Key points

- ~20–40% of patients with IBD in Western countries are obese
- Premorbid obesity, in particular visceral adiposity, might increase the risk of developing Crohn's disease
- Obesity might contribute to the pathogenesis of IBD through dysbiosis, mucosal barrier dysfunction with bacterial translocation and activation of adipocytes
- Risk of complications, such as surgery, hospitalization and infection, might be increased in patients with IBD who are obese
- Obesity is associated with rapid clearance of biologic agents, resulting in low trough concentrations, and could result in suboptimal response to biologics
- Treating obesity could be a potential adjunct therapeutic target in patients with IBD who are obese

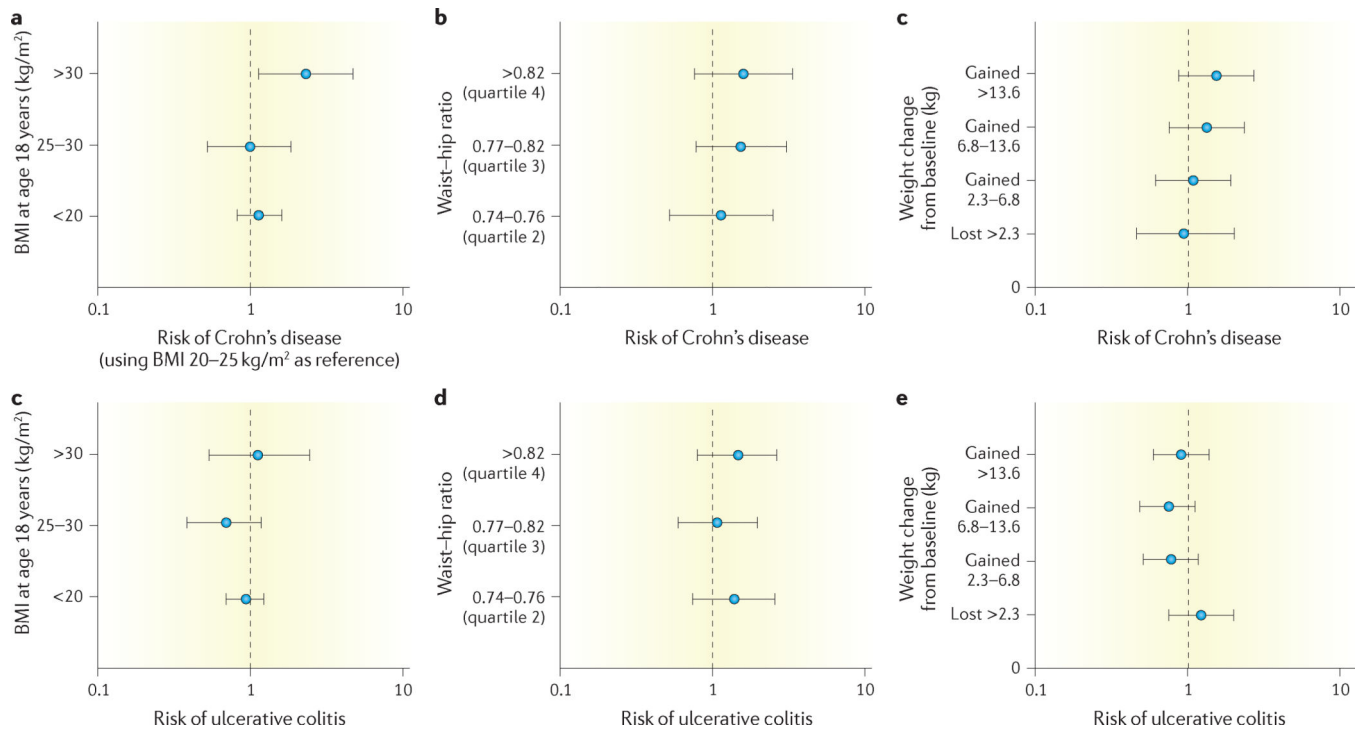


Figure 1. Association between premorbid obesity, waist-hip ratio and weight gain since age 18 years and IBD risk

Data from the Nurses' Health Cohort¹⁸ showing the relationship between premorbid obesity at 18 years of age, waist-hip ratio and weight gain since age 18 years on the risk of developing Crohn's disease and ulcerative colitis.

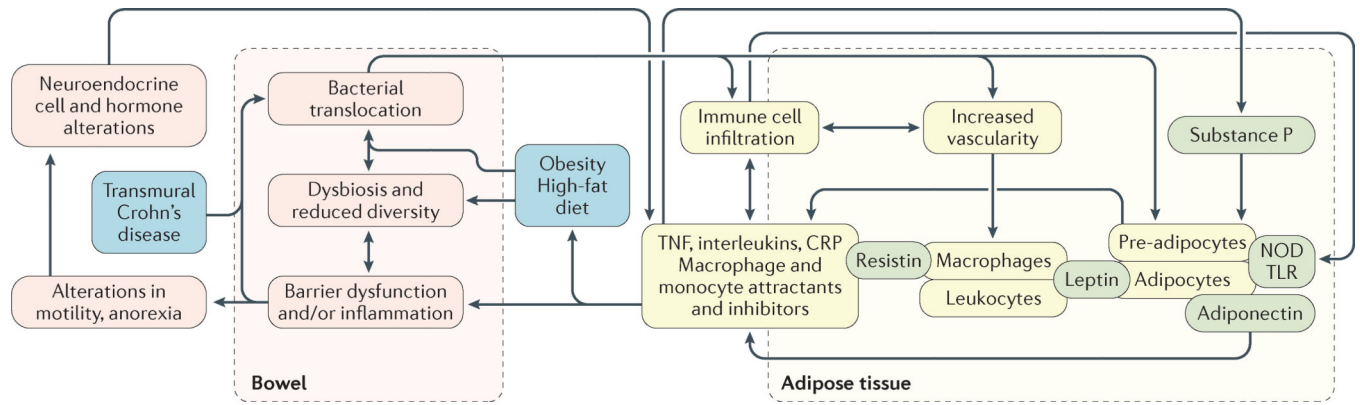


Figure 2. Postulated pathogenesis and feedback loop between visceral adipose tissue and intestinal inflammation in IBD

In patients with IBD, the T-cell compartment shifts from a homeostatic regulatory environment consisting of M2 macrophages, natural killer cells and CD4⁺ T_{reg} cells toward a pro-inflammatory environment characterized by M1 macrophages, CD4⁺ T_{H1} and CD8⁺ cytotoxic subtypes. Leptin, a member of the IL-6 protein family, is produced by adipocytes in proportion to fat mass. Leptin increases synthesis of pro-inflammatory cytokines in monocytes and macrophages, and is involved in T-cell-mediated immune responses. Adiponectin, produced by adipocytes in an inverse proportion to fat mass, functions as an insulin sensitizer and anti-inflammatory adipokine in patients who do not have IBD. However, in IBD, and in particular in Crohn's disease, evidence supports its role as a pro-inflammatory adipokine that results in increased cytokine secretion and epithelial cell proliferation. Macrophages and monocytes are the main source of resistin, the expression of which is induced by pro-inflammatory cytokines (IL-1, IL-6 and TNF), and circulating levels correlate with acute-phase reactants (C-reactive protein, CRP). Resistin can promote expression of TNF and IL-6. Evidence from the past decade has demonstrated the existence of an adipose-tissue–colonic-mucosa feedback loop, in which preadipocytes release IL-17A in response to substance P; the colonic mucosa from these individuals shows an increase in IL-17A receptors. Obesity and a high-fat diet, as well as transmural inflammation in Crohn's disease, results in impaired mucosal barrier function through alterations in tight-junction proteins, thereby promoting bacterial translocation. TLR, Toll-like receptor.

Table 1
Key studies on obesity epidemiology and its effect on disease course and complications in IBD

Study	Study characteristics	Patient characteristics	Prevalence of obese and overweight	Key findings	Refs
Flores <i>et al.</i> (2015)	<ul style="list-style-type: none"> Two-centre retrospective cohort study Conducted in Dallas, Texas, USA, 2000–2012 Median follow-up 5.2 years 	<p>Crohn's disease:</p> <ul style="list-style-type: none"> $n = 297$, 31% female Mean disease duration 15 years Ileocolonic disease in 47% Penetrating disease in 20% Biologic use in 45% <p>Ulcerative colitis:</p> <ul style="list-style-type: none"> $n = 284$; 24% female Mean disease duration 12 years Extensive disease in 59% Biologic use in 16% 	<p>Crohn's disease:</p> <ul style="list-style-type: none"> 30.3% obese 33.3% overweight (based on mean BMI of each patient during the study period) <p>Ulcerative colitis:</p> <ul style="list-style-type: none"> 35.2% obese 71.5% overweight (based on mean BMI of each patient during the study period) 	<p>Crohn's disease:</p> <ul style="list-style-type: none"> No differences between Crohn's disease phenotype (age at onset, location, behaviour) in patients who were obese vs overweight vs normal or underweight Lower rates of a composite endpoint of Crohn's-disease-related surgery or hospitalization and/or initiation of anti-TNF therapy in patients who were obese (73%) and overweight (77%) than patients who were normal weight or underweight (94%) <p>Ulcerative colitis:</p> <ul style="list-style-type: none"> No differences in disease extent (age at onset, location, behaviour) in patients who were obese vs overweight vs normal or underweight Lower rates of a composite endpoint of ulcerative-colitis-related surgery or hospitalization and/or initiation of anti-TNF therapy in patients who were obese (40%) and overweight (49%) than patients who were normal weight or underweight (67%) 	8
Seminario <i>et al.</i> (2015)	<ul style="list-style-type: none"> Single-centre, retrospective cohort study Conducted in Pittsburgh, Pennsylvania, USA, 2009–2011 Median follow-up not reported 	<p>Crohn's disease:</p> <ul style="list-style-type: none"> $n = 1,494$ with IBD (860 with Crohn's disease, 634 with ulcerative colitis), 51% female Mean disease duration ~16 years 	<p>Crohn's disease:</p> <ul style="list-style-type: none"> 31.5% obese, 4.4% of whom severely obese (BMI 40 kg/m²) 40% overweight (based on average BMI of each patient during the study period) 	<p>Crohn's disease:</p> <ul style="list-style-type: none"> No difference in risk of IBD-related surgery, hospitalization, emergency department use in patients who were obese vs overweight vs normal BMI Obesity, in particular BMI 35 kg/m², associated with poorer IBD-related quality of life and higher frequency of elevated CRP compared with normal BMI patients Actual dose of prescribed medication for weight-based therapies lower than anticipated based on body weight (for example, mean infliximab dose in patients with class III obesity was 3.96 mg/kg and that of azathioprine was 1.1 mg/kg) Increasing BMI associated with increased rates of diabetes mellitus, hypertension and hyperlipidaemia 	12

Study	Study characteristics	Patient characteristics	Prevalence of obese and overweight	Key findings	Refs
Pringle <i>et al.</i> (2015)	<ul style="list-style-type: none"> Single-centre cross-sectional study Conducted in Boston, Massachusetts, USA, 2004–? 	<ul style="list-style-type: none"> $n = 846$ with Crohn's disease, 55% female Mean disease duration 12 years Penetrating disease in 29% Biologic use in 56% 	<ul style="list-style-type: none"> 16% obese 30% overweight (at Crohn's disease diagnosis) 	<ul style="list-style-type: none"> Compared with adults with BMI <25 kg/m², patients who were obese had lower prevalence of penetrating disease (OR 0.56, 95% CI, 0.31–0.99), but comparable rates of perianal and stricturing disease and prior surgery Genetic predisposition did not seem to modify the effect of obesity on Crohn's disease-related complications 	10
Hass <i>et al.</i> (2006)	<ul style="list-style-type: none"> Single-centre, retrospective cohort study Conducted in Philadelphia, Pennsylvania, USA, 1997–2002 	<ul style="list-style-type: none"> $n = 138$ with Crohn's disease, 59% female Mean disease duration 13 years Perianal disease in 10% Biologic use in 45% 	<ul style="list-style-type: none"> 32% overweight or obese (at Crohn's disease diagnosis) 	<ul style="list-style-type: none"> No difference in the number of Crohn's disease-related surgeries or escalation of medical therapy in patients with BMI <25 kg/m² vs BMI >25 kg/m² No difference in the time to first surgery between patients who were overweight vs normal weight, although time to first surgery was shorter in those overweight vs underweight (2 years vs 21 years, respectively, $P = 0.04$) 	77

CRP, C-reactive protein; OR, odds ratio.

Table 2

Key studies on the association between pre-morbid obesity and risk of developing incident IBD

Study	Study characteristics	Patient characteristics	Key findings	Refs
Khalili <i>et al.</i> (2014)	US population-based cohort of 111,498 women (Nurses' Health Study II) followed over 18 years	Incident Crohn's disease and ulcerative colitis in 153 and 229 participants, respectively	<ul style="list-style-type: none"> • 2.3-fold higher risk of developing Crohn's disease in women with obesity compared with women with normal BMI at age 18 (HR 2.33, 95% CI, 1.15–4.69), after adjusting for key confounding variables including physical activity • A greater magnitude of weight gain (from age 18 to age at enrolment) associated with increased risk of developing Crohn's disease (weight gain >13.6 kg vs <2.3 kg: HR 1.52, 95% CI 0.87–2.65) • No association between obesity during young adulthood (or weight change since young adulthood) and risk of developing ulcerative colitis (obese vs normal BMI at age 18: HR 1.17, 95% CI, 0.54–2.52) • Association between overweight or obese body habitus (but not slender or thin body habitus) during young adulthood and development of Crohn's disease but not ulcerative colitis 	18
Harpsoe <i>et al.</i> (2015)	Danish National Birth Cohort study of 75,008 women (median 30 years of age at cohort entry), followed over median 11 years	Incident Crohn's disease and ulcerative colitis in 138 and 394 participants, respectively	<ul style="list-style-type: none"> • Women who were obese (based on prepregnancy body weight) had a 1.9-fold higher risk of developing Crohn's disease (OR 1.88, 95% CI 1.02–3.47) • No association between prepregnancy obesity and risk of developing ulcerative colitis (OR 0.77, 95% CI 0.48–1.25) 	19
Chan <i>et al.</i> (2013)	Nested case-control study within the European Prospective Cohort Study of 300,724 participants, from 23 centres in 10 countries	Incident Crohn's disease and ulcerative colitis in 75 and 177 participants, respectively	No association between obesity and risk of developing Crohn's disease (obese vs normal BMI: OR 0.85, 95% CI 0.29–2.45) or ulcerative colitis (obese vs normal BMI: OR 1.15, 95% CI 0.62–2.12)	20

Table 3

Key studies on the effect of obesity on surgical outcomes in patients with IBD.

Study	Study characteristics	Patient characteristics	Obesity rate	Key findings	Refs
Krane <i>et al.</i> (2013)	<ul style="list-style-type: none"> Single-centre, retrospective cohort study Conducted in Chicago, Illinois, USA, 2002–11 	626 patients (all with BMI >18.5 kg/m ²) undergoing laparoscopic colorectal resection	<ul style="list-style-type: none"> 13.6% obese (mean BMI 35.1 kg/m²) 46.5% overweight or obese 	<ul style="list-style-type: none"> Longer operative time in patients overweight and obese compared with normal weight patients Higher rate of conversion to open surgery in patients overweight (10.7%) and obese (12.9%) vs normal weight (8.3%) patients, predominantly related to visceral obesity Overall rate of intraoperative and post-operative complications comparable between groups, except a higher rate of incisional hernia in patients with obesity vs normal weight patients 	124
Causey <i>et al.</i> (2011)	Multi-centre, retrospective cohort study (National Surgical Quality Improvement Program), USA, 2005–2008	2,319 patients undergoing abdominal surgery for Crohn's disease (25% performed laparoscopically)	16% obese (2% morbidly obese)	<ul style="list-style-type: none"> Longer operative time in patients who were obese (177 min) vs non-obese (164 min) Higher perioperative morbidity in patients who were obese vs non-obese (32% vs 22%, respectively, OR 1.9) Higher rate of postoperative complications in patients who were obese vs non-obese, particularly wound infection (OR 1.7, increasing to 7.1 when BMI >40 kg/m²) 	125
Klos <i>et al.</i> (2014)	<ul style="list-style-type: none"> Single-centre retrospective cohort study Conducted in St Louis, Missouri, USA, 1990–2011 	178 patients with ulcerative colitis undergoing IPAA	42% obese	<ul style="list-style-type: none"> Higher rate of complications in patients who were obese (80%) vs non-obese (64%) Higher rate of pouch-related complications in patients who were obese vs non-obese (61% vs 26%, respectively), including anastomotic/pouch strictures (27% vs 6%, respectively), inflammatory pouch complications (17% vs 4%, respectively) and pouch fistulae (12% vs 3%, respectively) 	108

IPAA, ileal pouch–anal anastomosis.