

Interactions Between Obesity and Inflammatory Bowel Diseases: The Pandemic Promoting ‘Civilisation’ Diseases

Authors: *Andrew Szilagy

Division of Gastroenterology, Department of Medicine, Jewish General Hospital, McGill University Medical School, Montreal, Canada

*Correspondence to aszilagy@jgh.mcgill.ca

Disclosure: The author has declared no conflicts of interest.

Acknowledgements: The author would like to thank Melissa Szilagy for technical assistance in producing the figure and table.

Received: 07.05.21

Accepted: 31.08.21

Keywords: Adipokines, comorbidities, inflammatory bowel diseases (IBD), microbiome.

Citation: EMJ Gastroenterol. 2021;10[1]:78-87.

Abstract

The end of the 20th and the beginning of the 21st centuries witnessed a change in human nutritional status, from malnutrition to an obesity pandemic. During a similar time period, many Western-type, non-communicable diseases increased globally in previously low-incidence areas. One group, inflammatory bowel diseases (IBD), is particularly noteworthy because its treatment does not eliminate the disease. Its current pan-global rise in incidence and prevalence seems to follow regions with more recent increases in prevalence of obesity. Obesity, which has now been redefined as a chronic disease, seems to share some pathogenic features with IBD. These include the promotion of a pro-inflammatory state via fat-derived hormones and oxidative stress induced by insulin resistance. In addition, the intestinal microbiome in obesity and IBD may also contribute to mutual disease development. Finally, the merger of these two diseases impacts the clinical course of IBD. This review explores these relationships.

INTRODUCTION

The end of the 20th and the beginning of the 21st centuries witnessed a remarkable change in human nutritional status. Prior to this period, a large portion of the world's population experienced malnutrition; however, the subsequent four decades witnessed global increases in body weight. While poor nutrition and being underweight are associated with poor health, being overweight and obesity are also associated

with multiple health issues. The National Institute of Health (NIH) recognised obesity as a chronic disease rather than a behavioural disorder in 1998.¹ Specific biochemical, physiological, and microbiomal abnormalities have been described. Furthermore, the pathogenic importance of the intestinal microbiome (bacteria, archaea, fungi, and viruses) has emerged as an important factor in many diseases.^{2,3} It is then plausible that obesity can merge and promote diseases linked with disturbances in the microbiome.

Inflammatory bowel diseases (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), are immunologically mediated conditions in conjunction with disruptions of the microbiome.⁴ More recently, IBD has been reported to be associated with comorbidities found in obesity.⁵ In addition, the geographic expansion of IBD, to some extent, follows the obesity pandemic. This review will outline reported relations between these two diseases.

OBESITY: THE PANDEMIC

Obesity is generally defined by the World Health Organization (WHO) with a formula relating body weight in kg to height in m².⁶ By this definition, overweight is defined as 25–29 kg/m²; Grade I obesity as 30–<35 kg/m² (in Asia it is considered ≥ 27 kg/m²); Grade II obesity as 35–<40 kg/m²; and Grade III obesity (morbid obesity) as ≥ 40 kg/m². Progressive increase in weight adds additional risks, which are also modified by the distribution of body fat. A central location of abdominal fat (android distribution, which is more common in males) confers higher risk for complications than a more diffuse distribution (pear-shaped obesity and gynoid fat distribution, which is more common in females).⁷

Obesity promotes the metabolic syndrome consisting of diabetes, hypertension, sleep apnoea, dyslipidaemia, and chronic fatty liver. In turn, these conditions lead to complications of the cardiovascular system, renal disease, advanced liver dysfunction, as well as hepatocellular carcinoma.⁸ In addition, obesity is associated with a number of gastrointestinal disorders and cancers.⁹

The pandemic of obesity began in Western countries, primarily in the USA, towards the end of the 20th century¹⁰ and is predicted to continue to spread globally well into the first third of the 21st century.¹¹

The causes for obesity are linked to excess caloric intake with reduced energy utilisation. However, dietary factors do not completely explain the difficulties with weight reduction and resistance. An increasing body of information has been compiled on the role of environmental polluting compounds in industrialised societies, 'obesogens', which alter energy homeostasis.¹² Furthermore, approximately 300 polymorphisms have been

discovered by genome-wide association studies to be operational in obesity.¹³ These are thought to interact with environmental variables (e.g., diet, which is the easiest to change, lack of exercise, or other factors).¹³

Once obesity is established, a pro-inflammatory reaction is induced. This state is achieved by interactions between fat cell-derived and other hormones and the promotion of insulin resistance. Among several hormones, subcutaneous-derived leptin, which also controls appetite, is increased in obesity and promotes the release of inflammatory cytokines. Adiponectin, from visceral fat cells, counteracts leptin but control is diminished as this hormone secretion is reduced.¹⁴ These hormones induce insulin resistance. Additional hormones, such as resistin derived from the reticulo-endothelial system, also contribute.¹⁵ In the pro-inflammatory response, TNF α inhibits tyrosine kinase at insulin receptors, conferring resistance and leading to enhanced oxidative stress.¹⁶

Additional nutrient-derived energy is provided to the host by the intestinal microflora.¹⁷ Alterations in distribution, diversity, and richness from normal, or dysbiosis, is a term describing bacterial changes that can lead to or are a result of host disease.^{2,18} The microbiome is responsive to external effects related to human culture, diet, antibiotics, and the changing local environment, much of which is related to industrialisation.¹⁹

As outlined above, pathogenic factors that underpin obesity also have profound effects on numerous diseases that have been labelled as 'Western' civilisation diseases.²⁰ Among these, of note is the global spread of IBD into areas previously devoid of or reporting only very low incidence rates. **Figure 1** outlines possible pathogenic mechanisms that might mutually interact to produce diseases.

INFLAMMATORY BOWEL DISEASES AND EXPANDING INCIDENCE

UC and CD are two related, yet different, immune-mediated diseases of the colon and intestines. Both diseases have been associated with progressive Western industrialisation.²¹ There is no cure for IBDs and, although they are associated with relatively low mortality, IBDs are generally lifelong conditions with relapsing clinical flares.

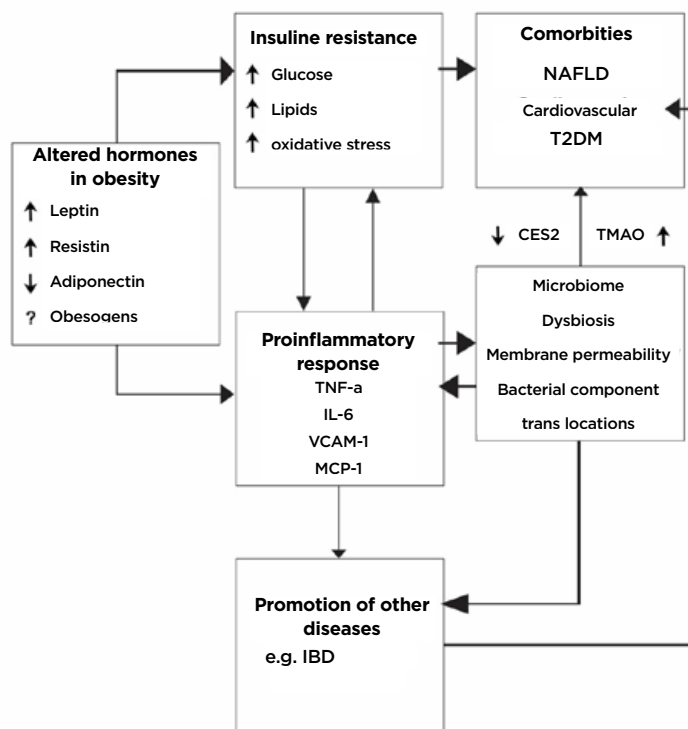


Figure 1: Pathogenic relationships of obesity with comorbidities and the potential for complicity in other illnesses such as inflammatory bowel diseases.

Obesogens are compounds polluting the environment and altering metabolic homeostasis (e.g., polycyclic aromatic hydrocarbons, polybrominated diphenyl ethers, and others).¹² Pro-inflammatory cytokines, TNF α , IL-6, VCAM-1, MCP-1, CES2⁴³ promote NAFLD, TMAO⁵⁵ through diet, and bacterial metabolism promotes atherosclerosis and increases risk for cardiovascular disease.

CES2: carboxylesterase-2; IBD: inflammatory bowel diseases; MCP-1: monocyte chemoattractant protein-1; NAFLD: non-alcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; TMAO: trimethylamine N-oxide; VACM-1: vascular cell adhesion molecule-1.

Adapted from Szilagyi A.²²

UC, limited to the colon, was recognised earlier, while CD, potentially involving the entire gastrointestinal tract, was described in detail in the first half of the 20th century. The causes of IBD are complex. While there are differences between UC and CD the current paradigm is the interaction of the role of host genetic factors, which lead to inappropriate immune responses in conjunction with a disturbed balance in host microbial flora. A variety of environmental factors are considered related to IBD development.²³

These IBDs were also initially described in Western societies. Incidence rose somewhat in the second half of the 20th century. Subsequently, from the early 1950s to the end of the 20th century, IBD expanded in Western

cultures and began to stabilise, except in paediatric populations.²⁴

The incidence of UC and CD began to increase in regions of the world previously free of IBD by the end of the 20th century and has risen progressively since. There are some epidemiological differences in IBD in different parts of the world (such as Asia, South America, and Africa).^{25,26} Based on the accumulated tracking of IBD from various regions, Kaplan and Windsor²¹ hypothesised a four-stage evolutionary development of IBD: an early stage of emergence; accelerated incidence followed by a balance between incidence and prevalence; compounding incidence; and, finally, when a balance between incidence and prevalence is reached, prevalence equilibrium.²¹

RELATIONS BETWEEN OBESITY AND INFLAMMATORY BOWEL DISEASES

Epidemiology

Although both obesity and IBD emerged from Western industrialised societies, geographic expansion of IBD and obesity diverge. IBDs, like several other Western civilisation diseases,¹⁹ were observed to follow diminishing latitudes toward the equator.^{27,28} This was initially ascribed to increasing exposure to sunshine and, hence, vitamin D skin synthesis. In turn, new research showed that vitamin D has pleiotropic anti-inflammatory and anti-neoplastic functions.²⁹ As many of these diseases were associated with low serum vitamin D, the lack of sunshine exposure was hypothesised to be the cause for higher incidence rates at higher latitudes. Although obesity was also observed to be associated with low vitamin D,³⁰ its trajectory included a geopolitical West to East direction.¹¹

Perhaps co-incidentally, the incidence of some of Western civilisation diseases including IBD also inversely correlated with increasing population proportions who were unable to digest lactose.³¹ Lactose digestion in adulthood is a dominant genetic trait that occurred in human evolution some 7-10x10³ years ago.³² The genetic trait divides humanity mainly into two phenotypes of lactase-persistent and lactase-non-persistent people (LNP).

On a global scale, obesity is modestly and inversely correlated with LNP status and more weakly but positively with latitude. This relationship of obesity with IBD may interfere with previously observed north-south (south-north) relations with IBD,³³ a topic that was of interest in the late 20th century.

The second epidemiological variation is the relationship of economic growth with increasing rates of IBD. Initially, both obesity and IBD were associated with wealthy countries. Obesity was found more in rural communities but, with time, obesity became associated with poorer economic areas in crowded urban locations.¹⁰ Similarly IBD is associated with more urban crowding but generally higher socioeconomic standards.^{23,26}

This association with national economic growth and industrialisation, as defined by

the Gross National Product (GDP), has also been reported.^{26,34} Globally, GDP correlates positively with latitude and negatively with LNP distributions, similar to IBD. However, correlation of obesity diverges from IBD and GDP.³⁴ Regional relationships, as in China, retain the close associations of IBD with GDP but are more evident in a south- to north-west direction from coastal areas.²⁶ Overall, in Asia all these relationships are negligible.

These findings could suggest that obesity is more dependent on adoption of a Western-type diet, which may precede independently from national economic growth.^{10,35} It also suggests that IBD is associated with other features of acquisition of national wealth besides diet.

Mutual Pathogenic Influences

As described above, obesity promotes a pro-inflammatory milieu through insulin resistance and adipokine-mediated imbalance. Hypothetically, this state could favour any disease where pro-inflammatory cytokines contribute to pathogenesis.

In addition to physiological parameters, as pointed out, intestinal microbial changes likely contribute to obesity, IBD, and other diseases. The microbiome is intimately affected by diet. High fats such as saturated, monosaturated, polyunsaturated, and linoleic acids play roles in modulating the immune system. Western-type diets lead to obesogenic and pro-inflammatory patterns of the microbiome.³⁴ Although there is no clear evidence that a low-fat diet leads to more weight loss than a high-fat diet,³⁶ similar high-fat diets play a probable role in inducing and possibly causing relapses in IBD.^{37,38} High carbohydrates, especially refined sugars, also contribute to a pro-inflammatory state, through the contribution to insulin resistance. However, fibres from vegetables and, to an extent, fruits are considered beneficial in IBD.²³ In obesity, fibres are helpful but fructose may be harmful. Proteins, particularly in dairy foods, may be protective against cardiovascular events, helping to maintain better weight control and reducing the risk of IBD before overt disease development.³⁹ Some similar effects of diet are shown in [Table 1](#).

Consumption of pro-inflammatory nutrients could lead to alterations in gut barrier tight junctions, with bacterial access to the host immune system.

Table 1: Summary of current hypotheses related to dietary promotion and prevention of obesity and both forms of inflammatory bowel diseases.^{23,34,36-39}

Variable	Obesity	Pre-IBD	Crohn's disease	Ulcerative colitis
Fats	All animal fats are pro-inflammatory; Dairy may be less obesogenic	High animal fat promotes IBD; Dairy may be protective for both forms of IBD	High fat could precipitate CD and UC flares; Pro-inflammatory diet promotes CD	High fat could precipitate CD and UC flares; Pro-inflammatory diet could be less offensive
Carbohydrates	Excess carbohydrates, especially refined sugars, are pro-inflammatory; Fibres, vegetables are anti-inflammatory; Fructose in excess can damage the liver and is obesogenic	High carbohydrates, especially refined sugars, may promote IBD; High fibre: vegetables>fruits reduces the risk for CD; Fruit may protect against UC	Low fibre increases CD flares; High fibre protects against CD	Low fibre increases UC flares; High fibre protects against UC
Proteins	Processed and red meats are pro-inflammatory; Fish, on the whole, is anti-inflammatory; Dairy, e.g., casein and whey, may promote satiety	Processed and red meats are linked with increased CD and UC risk; Dairy could protect against IBD	Processed and red meats may precipitate flares; Dairy role is unclear	Processed and red meats may precipitate flares; Dairy role is unclear

CD: Crohn's disease; IBD: inflammatory bowel disease; UC: ulcerative colitis.

A microbiome pattern that is altered is referred to as dysbiosis.^{2,18} Although microbiome findings vary in different studies, recently described bacterial milieu in IBD shares a number of similarities with obesity as described in [Table 2](#).²² In IBD, strictly anaerobic microflora are replaced to an extent by facultative bacteria. The similar sharing of bacterial characteristics could, hypothetically, lead to mutual predisposition between diseases. Indeed, the long-term follow-up of patients, especially with CD, show increasing weight gain over time.⁴⁰

Shared Comorbidities

The apparent shared pathogenic similarities between obesity and IBD also lead to increasing

shared comorbidities. Among these, non-alcoholic fatty liver disease (NAFLD) is the best described. This condition, defined as >5% of liver fat, is largely attributed to insulin resistance, which leads to altered lipid metabolism and transport out of the liver. The role of TNF α interfering with insulin receptors is thought to lead to resistance and hence connect pro-inflammatory-dependent disease on predisposition to NAFLD.¹⁶ This mechanism is thought to be similar in individuals who are both overweight and normal- or underweight.⁴¹ A recent study showed that reduced carboxylesterase 2, which affects diglyceride and monoglyceride metabolism in the intestine and liver, could contribute to NAFLD in patients with obesity and CD alike.⁴²

Table 2: Comparison of bacterial abundance in the microbiome of patients who are obese, with Crohn's disease, or with ulcerative colitis.

Bacterial taxa	Obesity	CD	UC
Similar distributions			
Proteobacteria (P)	Increased	Increased	Increased
<i>F. prausnitzii</i> (G and S)	Decreased	Decreased	Decreased
<i>Clostridium leptum</i> (G and S)	Increased or decreased, study depending	Decreased	Decreased
Bifidobacteria (G)	Decreased	Increased or decreased, study depending	Increased or decreased, study depending
<i>E. coli</i> (G and S)	Increased	Increased	Increased
<i>Ruminococcus gnavus</i> (G and S)	Increased	Increased	Increased
Different distributions			
Firmicutes (P)	Increased	Decreased	Decreased
<i>Bacteroides</i> (P)	Decreased	Decreased	Increased or decreased, study depending
<i>Actinobacter</i> (P)	Decreased	Increased	Increased
<i>Roseburia</i> (G)	Increased	Decreased	Decreased
<i>Akkermansia muciniphila</i> (G and S)	Decreased	Decreased	Stable compared with healthy controls
<i>Desulfovibrio</i> (G)	Decreased	Increased	Increased

CD: Crohn's disease; *E. coli*: *Escherichia coli*; *F. prausnitzii*: *faecalibacterium prausnitzii*; G: genus; P: phyla; S: species; UC: ulcerative colitis.

Szilagyj A²²

World rates of NAFLD are reported to be 9–43%. In the USA, 27% of the population is reported to have NAFLD. The risk of NAFLD is reported to be 3.5 times higher in people who are obese.⁴³ In IBD, a systemic review found that 39.5% of patients with CD and 23.0% of patients with UC had NAFLD compared with 20.0% (range: 6.0–33.0%) of controls.⁴⁴ In a prospective study of 321 patients with CD, followed for 3 years, one-third developed NAFLD, although <1.0% were considered obese. Of these, 2.2% developed more advanced liver disease over time, such as non-alcoholic steatohepatitis, inflammation, ballooning degeneration, or degrees of fibrosis.⁴⁵ Another study of patients

with IBD reported a prevalence of 32.8%, of which 12.2% were advanced; in this case, 30.4% of patients were overweight and 13.8% were obese (BMI: $\geq 30\text{kg/m}^2$).⁴⁶ The impact of the microbiome on altered intestinal barrier and bacterial translocations are also thought to play an important role in NAFLD development.⁴⁷

Another shared comorbidity between obesity and IBD is cardiovascular complications. However, the risk factors in IBD differ somewhat from those observed in obesity. The types of vascular problems are summarised in a recent review and include venous and arterial thromboembolism; heart failure; arrhythmias; valvulopathies, with or without endocarditis; and Takayasu arteritis.⁴⁸ The

occurrence of ischaemic stroke or myocardial infarction is somewhat controversial. An earlier meta-analysis did find increased episodes of myocardial infarction in IBD,⁴⁹ while another reported study reported inverse association of cardiovascular disease (CVD) with IBD.⁵⁰

However, a more recent meta-analysis did find an increased, albeit modest, risk for cardiovascular events in both CD and UC, interestingly more frequently in women aged <50 years. These events were unaffected by smoking and controlling for obesity.⁵¹

In obesity, traditional risk factors related to adipocytes and insulin resistance promote atherosclerosis⁵² and cardiovascular complications. It is of note that in Class I obesity (but less so in Classes II and III), prognosis for cardiac event outcomes is better than in patients who are of normal weight or lean and with CVD. This has been called the 'obesity or lean paradox'.⁵³

The role of microbial contributions to CVD comorbidities in obesity have been evaluated by examining plasma metabolites in a cohort of patients who are obese and compared with controls who are not obese. In this study, 48 metabolic microbial pathways were linked with CVD risks.⁵⁴ In addition, dietary intake of choline and carnitine (found in animal products) are metabolised by bacteria to produce trimethylamine, which is oxidised in the liver to become trimethylamine N-oxide. This compound increases platelet adhesiveness and promotes atherosclerosis.⁵⁵ A similar effect could contribute to CVD in IBD, depending on diet.

The recent increasing association of Type 2 diabetes mellitus (T2DM) with IBD adds another measure of overlap between obesity and IBD. In obesity, insulin resistance leads to T2DM via the promotion of a pro-inflammatory state. It is suggested that the inflammatory milieu of IBD contributes to insulin resistance as well. One study reported a modest 26% increase in T2DM in UC after an 11-year follow-up compared with healthy controls.⁵⁶ A more recent report from Korea, however, found that T2DM was more frequent in CD (hazard ratio: 1.677; 95% confidence interval: 1.408-1.997), but not in UC. The occurrence was also more common in younger patients.⁵⁷ However, a recent Danish

study, based on more than 6 million persons followed for 37 years, found increased risk (by 54-57%) for T2DM in both CD and UC. Notably the risk increased after 2003 compared to the time period from 1977.⁵⁸ This time difference is of note because the obesity pandemic is hypothesised to have begun around the 1980s.¹⁰

CLINICAL IMPACT OF OBESITY ON INFLAMMATORY BOWEL DISEASE

If these two diseases collide in time and geography, what effects of obesity can be seen on the clinical course of IBD? The influence of obesity on IBD location is not well defined. A population-based study of 488 patients found a trend in favour of colonic involvement,⁵⁹ while another study found increased perianal disease and more hospitalisations in CD,⁶⁰ the previous study⁵⁸ did not substantiate this.

Obesity was reported to increase risk of surgery in UC but decreased in CD,⁶¹ and was reported to be more frequently associated in women with UC.⁶² In that study, metabolic syndrome and C-reactive protein were increased but were not related to BMI.⁶³ However, in another report, the presence of metabolic syndrome was found to increase the risk of hospitalisation two-fold.⁶³ This contrasted with another study that found that obesity was associated with a more mild course of CD.⁶⁴ A meta-analysis of 7 studies (5 UC and 2 CD), reported that patients who were obese were less likely to undergo IBD-related surgery, receive hormonal therapy, or require hospitalisation than patients who were not obese.⁶⁵ The presence of obesity and traditional associated comorbidities may increase perioperative complications, although not all reports agree; these are reviewed by Johnson and Loftus Jr.⁶⁶

There is also a debate over whether patients with IBD who are obese respond as effectively to biologic therapy as patients who are not obese. In the case of TNF α inhibitors, reduced clinical outcome was reported in patients with IBD who were obese.⁶⁷ However, another study failed to support therapeutic failure, and a meta-analysis of therapeutic response to biologics in a number of autoimmune diseases found a 60% higher failure rate but not in IBD.⁶⁸ In addition, a report suggested that the $\alpha 4\beta 7$ integrin

inhibitor vedolizumab trough levels were lower in patients with IBD who were obese.⁶⁹

EVIDENCE THAT OBESITY PROMOTES INFLAMMATORY BOWEL DISEASE

Despite the theoretical similarities in pathogenesis between obesity and IBD, the literature is conflicting on a clear evolution between the two diseases. There are emerging hypotheses suggesting an interchange between these two diseases, despite the presence of malnutrition in IBD in the past.

Mendall et al.⁷⁰ initially suggested that obesity may promote CD. In a cohort of 524 patients, obesity at diagnosis was linked more with CD than UC or healthy controls.⁷⁰ More recent studies showed that obesity at the age of 18 years increased the risk for CD but not UC in the Nurse's Health Study II.⁷¹ These reports were similar to previous findings.⁷⁰ In two other Danish studies, one found that increasing BMI in children between the ages of 7 and 13 years increased the risk for CD until age 30 years, but there was an inverse relationship with UC.⁷³ In the second study of young military conscripts, there was a 'U'-shaped risk profile for CD up to the age of 60 years. However, only a low BMI (<18.5 kg/m²) was statistically significantly associated with CD. This study also showed an inverse association with UC.⁷³

As stated above, the reverse observations have also been reported, that patients with CD enrolled in clinical trials gain weight with time over follow-up.³⁹

SUMMARY AND CONCLUSIONS

In this review, the obesity pandemic has been examined together with the coincidental extension of both forms of IBD, UC and CD, into

areas of previous low incidence. Both diseases, with differences in detail, are linked with a pro-inflammatory state. A large part is related to the functions and alterations in the intestinal microbiome. In addition, adipocytes in obesity contribute to the pro-inflammatory pattern. Although genetic predispositions differ, the internal milieu in each disease leads to similar development of comorbidities such as NAFLD, some cardiovascular complications, and T2DM. As such, there are suggestions that some features of obesity and IBD are interchangeable. That is, the pathogenic changes in IBD can lead to weight gain and, under some circumstances, obesity may promote IBD. These interactions favour CD more than UC.

The consequences of these interactions could lead to variations in clinical outcomes in IBD. It is not yet clear whether a 'paradoxical' effect in IBD occurs as it has been described in CVD. On an epidemiological level, it is hypothesised that the geographic distribution of obesity impacts on patterns of IBD, which is best seen in Europe. This impact may partly have led to the disruption of previously observed north-south disease distributions there. Secondly, although obesity and IBD both emerged in Western societies, often in wealthier, industrialised regions, the two diseases diverge in their expansion somewhat. In areas where obesity is evident and not accompanied by increased economic wealth, IBD rates are proportionately lower. However, IBD may be closely following areas affected by increased obesity. Thus, there may be a subtle interaction evident that promotes both conditions. While 'Western' diets may precede economic growth, chemical pollutants may affect these interactions in ways that are not yet clear. Seen in this light, obesity may be a marker for impending regional development of IBD (and some other civilisation diseases).

References

1. Purnell JQ. "Definitions, classification, and epidemiology of obesity," Feingold KR et al. (eds.) Endotext [Internet] (2000), South Dartmouth: MDText.com, Inc.
2. Meng X et al. Gut dysbacteriosis and intestinal disease: mechanism and treatment. *J Appl Microbiol.* 2020;129(4):787-805.
3. Górowska-Kowolik K, Chobot A. The role of gut micorbiome in obesity and diabetes. *World J Pediatr.* 2019;15(4):332-40.
4. DeGruttola AK et al. Current understanding of dysbiosis in disease in human and animal models. *Inflamm Bowel Dis.* 2016; 22(5): 1137-50.
5. Dragasevic S et al. Metabolic syndrome in inflammatory bowel disease: association with genetic markers of obesity and inflammation. *Metab Syndr Relat Disord.* 2020;18(1):31-8.
6. de Onis M et al. Development of a WHO growth reference for school-

- aged children and adolescents. *Bull World Health Organ.* 2007;85(9):660-7.
7. De Lorenzo A et al. New obesity classification criteria as a tool for bariatric surgery indication. *World J Gastroenterol.* 2016;;22(2):681-703.
 8. Kinlen D et al. Complications of obesity. *QJM.* 2017;111(7):437-43.
 9. Lauby-Secretan B et al. Body fatness and cancer—viewpoint of the IARC working group. *N Engl J Med.* 2016;375(8):794-8.
 10. Popkin BM et al. Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev.* 2012;70(1):3-21.
 11. Hossain P et al. Obesity and diabetes in the developing world—a growing challenge. *N Engl J Med.* 2007;356(3):213-5.
 12. Shahnazaryan U et al. Role of obesogens in the pathogenesis of obesity. *Medicina (Kaunas).* 2019;55(9):515.
 13. Goodarzi MO. Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. *Lancet Diabetes Endocrinol.* 2018;6(3):223-36.
 14. Yadav A et al. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta.* 2013;417:80-4.
 15. Jamaluddin MS et al. Resistin: functional roles and therapeutic considerations for cardiovascular disease. *Br J Pharmacol.* 2012;165(3):622-32.
 16. Hotamisligil GS et al. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF- α - and obesity-induced insulin resistance. *Science.* 1996;271(5249):665-8.
 17. Turnbaugh PJ et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature.* 2006;444(7122):1027-31.
 18. Levy M et al. Dysbiosis and the immune system. *Nat Rev Immunol.* 2017;17(4):219-32.
 19. Gorvitovskaia A et al. Interpreting *Prevotella* and *Bacteroides* as biomarkers of diet and lifestyle. *Microbiome.* 2016;4:15.
 20. Kopp W. How Western diet and lifestyle drive the pandemic of obesity and civilization diseases. *Diabetes Metab Syndr Obes.* 2019;12:2221-36.
 21. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol.* 2021;18(1):56-66
 22. Szilagyi A. Relationship(s) between obesity and inflammatory bowel diseases: possible intertwined pathogenic mechanisms. *Clin J Gastroenterol.* 2020;13(2):139-52.
 23. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol.* 2015;(4):205-17.
 24. Molodecky NA et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on a systematic review. *Gastroenterology.* 2012;142(1):46-54.
 25. Ng SC et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet.* 2017;390(10114):2769-78.
 26. Ng SC et al. Population density and risk of inflammatory bowel disease: a prospective population-based study in 13 countries or regions in Asia-Pacific. *Am J Gastroenterol* 2019;114(1):107-15.
 27. Grant WB. Update on evidence that support a role of solar ultraviolet-B irradiance in reducing cancer risk. *Anticancer Agents Med Chem* 2013;13(1):140-6.
 28. Olmedo-Martín RV et al. Sunlight exposure in inflammatory bowel disease outpatients: predictive factors and correlation with serum vitamin D. *Gastroenterol Hepatol.* 2019;42(10):604-13.
 29. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med (Maywood).* 2004;229(11):1136-42.
 30. de Azevedo FR, Caramelli B. Hypovitaminosis D and obesity—coincidence or consequence? *Eur Endocrinol.* 2013;9(2):128-31.
 31. Shrier I et al. Impact of lactose containing foods and the genetics of lactase on diseases: an analytical review of population data. *Nutr Cancer.* 2008;60(3):292-300.
 32. Tishkoff SA et al. Convergent adaptation of human lactase persistence in Africa and Europe. *Nat Genet.* 2007;39(1):31-40.
 33. Szilagyi A et al. Changing patterns of relationships between geographic markers and IBD: possible intrusion of obesity. *Crohns Colitis* 360. 2020;2(2):1-8.
 34. Szilagyi A et al. Global associations of national economic wealth are more robust with inflammatory bowel diseases than with obesity. *Med Hypotheses.* 2021;148:110505.
 35. Cândido FG et al. Impact of dietary fat on gut microbiota and low-grade systemic inflammation: mechanisms and clinical implications on obesity. *Int J Food Sci Nutr.* 2018;69(2):125-43.
 36. Tobias DK et al. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. *Lancet Diabet Endocrinol.* 2015;3(12):968-79.
 37. Lo CH et al. Dietary inflammatory potential and risk of Crohn's disease and ulcerative colitis. *Gastroenterology.* 2020;159(3):873-83.
 38. Fritsch J et al. Low-fat, high-fiber diet reduces markers of inflammation and dysbiosis and improves quality of life in patients with ulcerative colitis. *Clin Gastroenterol Hepatol.* 2021;19(6):1189-99.
 39. Opstelten JL et al. Dairy products, dietary calcium, and risk of inflammatory bowel disease: results from a European prospective cohort investigation. *Inflamm Bowel Dis.* 2016;22(6):1403-11.
 40. Moran GW et al. The increasing weight of Crohn's disease subjects in clinical trials: a hypothesis-generating time-trend analysis. *Inflamm Bowel Dis.* 2013;19(13):2949-56.
 41. Adams LC et al. Non-alcoholic fatty liver disease in underweight patients with inflammatory bowel disease: a case-control study. *PLoS One.* 2018;13(11):e0206450.
 42. Chalhoub G et al. Carboxylesterase 2 proteins are efficient diglyceride and monoglyceride lipases possibly implicated in metabolic disease. *J Lipid Res* 2021;62:100075.
 43. Li L et al. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. *Obes Rev.* 2016;17(6):51009.
 44. Gizard E et al. Systematic review: the epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2014;40(1):3-15.
 45. Bessissow T et al. Incidence and predictors of nonalcoholic fatty liver disease by serum biomarkers in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2016;22(8):1937-44.
 46. Saroli Palumbo C et al. Screening for nonalcoholic fatty liver disease in inflammatory bowel diseases: a cohort study using transient elastography. *Inflamm Bowel Dis.* 2019;25(1):124-33.
 47. Sharpton SR et al. Emerging role of the gut microbiome in nonalcoholic fatty liver disease: from composition to function. *Clin Gastroenterol Hepatol.* 2019;17(2):296-306.
 48. Bunu D-M et al. Cardiovascular manifestations of inflammatory bowel disease: pathogenesis, diagnosis, and preventive strategies. *Gastroenterol Res Pract* 2019;2019:3012509.
 49. Fumery M et al. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis.* 2014;8(6):469-79.
 50. Barnes EL et al. Hospitalizations for acute myocardial infarction are decreased among patients with

- inflammatory bowel disease using a nationwide inpatient database. *Inflamm Bowel Dis.* 2016;22(9):2229-37.
51. Feng W et al. Inflammatory bowel disease and risk of ischemic heart disease: an updated meta-analysis of cohort studies. *J Am Heart Assoc.* 2017;6(8):e005892.
 52. Csige I et al. The Impact of obesity on the cardiovascular system. *J Diabetes Res.* 2018;2018:3407306.
 53. Elagizi A et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis.* 2018;61(2):142-50.
 54. Kurilshikov A, et al. Gut microbial associations to plasma metabolites linked to cardiovascular phenotypes and risk. *Circ Res.* 2019;124(12):1808-20.
 55. Zhu W et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell.* 2016;165(1):111-24.
 56. Dregan A et al. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. *Circulation.* 2014;130(10):837-44.
 57. Kang EA et al. Increased risk of diabetes in inflammatory bowel disease patients: a nationwide population-based study in Korea. *J Clin Med.* 2019;8(3):343.
 58. Jess T et al. Inflammatory bowel diseases increase risk of type 2 diabetes in a nationwide cohort study. *Clin Gastroenterol Hepatol.* 2020;18(4):881-8.e1.
 59. Lynn AM et al. Su1855 - prevalence of obesity and influence on phenotype within a population-based cohort of inflammatory bowel disease patients. *Gastroenterology.* 2018;154(6 Suppl 1):S608.
 60. Blain A et al. Crohn's disease clinical course and severity in obese patients. *Clin Nutr.* 2002;21(1):51-7.
 61. Steed H et al. A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. *Obes Facts.* 2009;2(6):370-2.
 62. Seminerio JL et al. Impact of obesity on the management and clinical course of patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2015;21(12):2857-63.
 63. 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(3):257-62.
 64. Flores A et al. Obesity in inflammatory bowel disease: a marker of less severe disease. *Dig Dis Sci.* 2015;60(8):2436-45.
 65. Hu Q et al. The impact of obesity on the clinical course of inflammatory bowel disease: a meta-analysis. *Med Sci Monit.* 2017;23:2599-606.
 66. Johnson AM, Loftus Jr EV. Impact of obesity on the management of inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2020;16(7):350-9.
 67. Harper JW et al. 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(10):2118-24.
 68. Singh S et al. Obesity and response to anti-tumor necrosis factor- α agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. *PLoS One.* 2018;13(5):e0195123.
 69. Dreesen E et al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2018;16(12):1937-46.e8.
 70. Mendall MA et al. Is obesity a risk factor for Crohn's disease? *Dig Dis Sci.* 2011;56(3):837-44.
 71. Khalili H et al. Measures of obesity and risk of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis.* 2015;21(2):361-8.
 72. Jensen CB et al. Childhood body mass index and risk of inflammatory bowel disease in adulthood: a population-based cohort study. *Am J Gastroenterol.* 2018;113(5):694-701.
 73. Mendall MA et al. The body mass index in young men and risk of inflammatory bowel disease through adult life: a population-based Danish cohort study. *Sci Rep.* 2019;9(1):6360.

FOR REPRINT QUERIES PLEASE CONTACT: INFO@EMJREVIEWS.COM