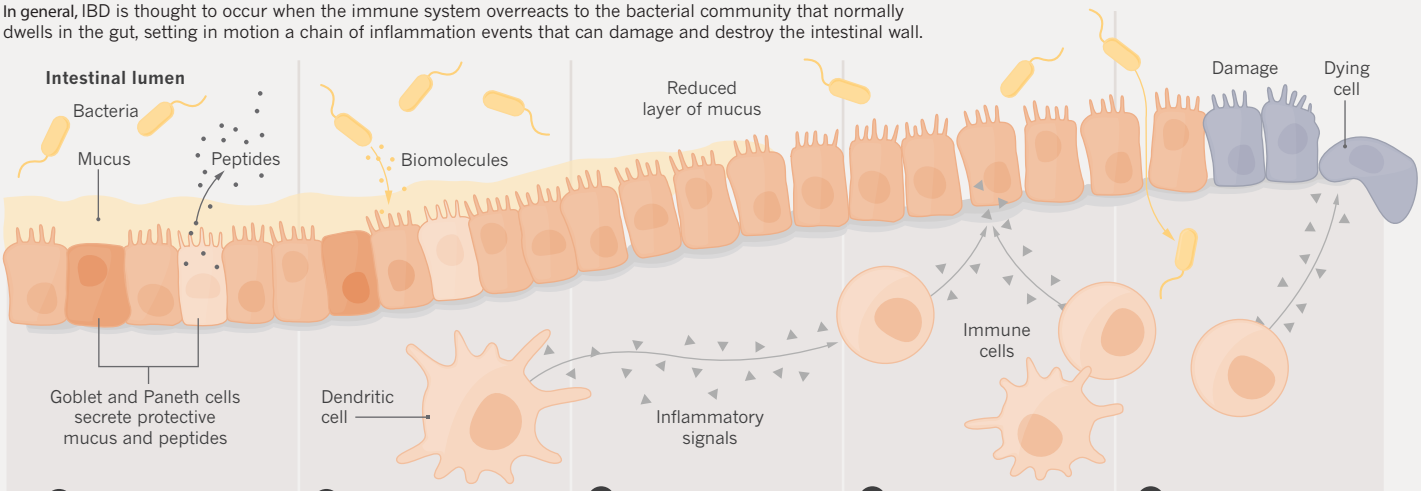
A SLOW-MOTION EPIDEMIC

The symptoms of Crohn's disease and ulcerative colitis, the two main forms of inflammatory bowel disease (IBD), can be severe and lifelong. And the condition is becoming increasingly common worldwide. By ***Michael Eisenstein****; illustration by* ***Lucy Reading-Ikkanda***

THE BATTLE WITHIN

In general, IBD is thought to occur when the immune system overreacts to the bacterial community that normally dwells in the gut, setting in motion a chain of inflammation events that can damage and destroy the intestinal wall.



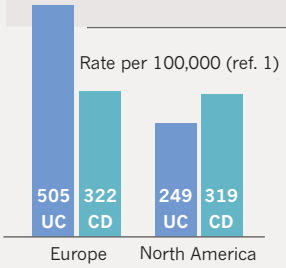
1 Healthy gut epithelial cells form a tightly sealed barrier against materials in the intestinal lumen. Goblet cells form mucus and Paneth cells secrete antimicrobial peptides that fight pathogens and regulate commensal gut bacteria.

2 Biomolecules secreted by gut bacteria trigger an inflammatory response in epithelial cells and in threat detecting immune cells known as dendritic cells.

3 This bacteria-triggered inflammatory process disrupts the tight seal of the epithelial barrier. At the same time, dendritic cells induce inflammation in the tissue layer beneath epithelial cells.

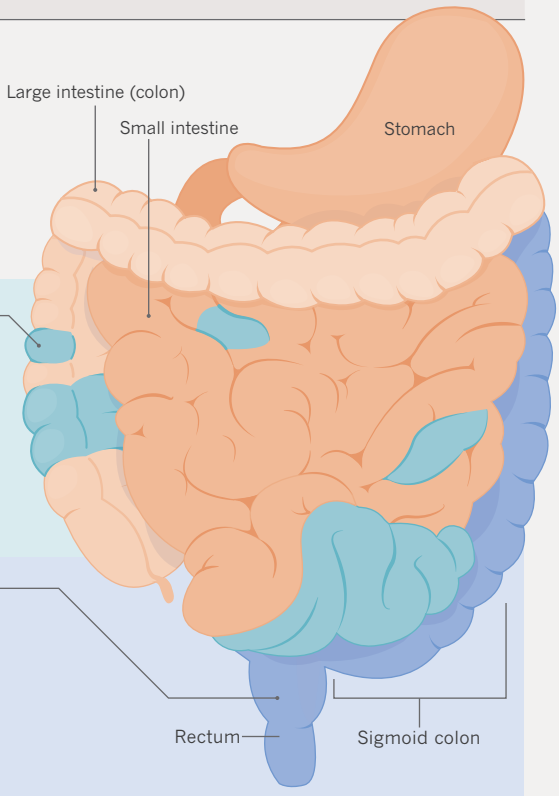
4 Inflammatory signals recruit more dendritic cells and immune cells such as T and B cells. These cells fuel further inflammation and damage the epithelial layer.

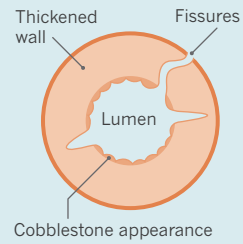
5 Gut microbes in the intestinal lumen pass through the now-leaky epithelial wall, further fuelling the antibacterial immune response. This immune attack and inflammatory damage ultimately lead to epithelial cell death.



SIMILAR, YET DIFFERENT

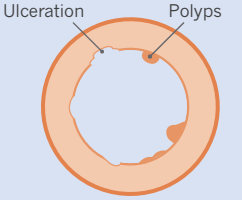
Most cases of IBD are classified as either ulcerative colitis (UC) or Crohn's disease (CD). The relative prevalence of these two conditions varies widely across different geographical regions (see chart). Between 5% and 15% of cases cannot immediately be put into either category and are instead referred to as 'indeterminate colitis'. Despite sharing similar symptoms, there are important pathological distinctions between the two main forms of IBD.





CROHN'S DISEASE

- Commonly occurs in the colon and lower small intestine, but can affect all of the gastrointestinal tract
- Can comprise multiple separate areas of inflammation
- Can damage all layers of the intestinal wall, forming deep perforations (see left)
- Symptoms include rectal bleeding, persistent diarrhoea, urgent need to move bowels, constipation, abdominal cramps and pain



ULCERATIVE COLITIS

- Generally affects only the sigmoid colon and rectum
- Forms a continuous patch of inflammation
- Damages the innermost lining of the intestinal wall (see left)
- Symptoms include bloody diarrhoea, abdominal cramps and pain

NATURE AND NURTURE

A variety of hereditary, environmental and lifestyle factors are thought to influence IBD pathology. However, researchers are still grappling with exactly how these elements individually and collectively affect the natural history of the disease.

Genetics

Up to 14% of people with IBD have a family history of the condition[2]. The strongest genetic risk factor for CD is the gene *NOD2*, which regulates bacterial populations in the gut. The gene is mutated in 25–35% of Europeans with CD[3].

Hygiene

In Western nations, lifestyle factors that expose young children to bacteria — such as living on a farm — may reduce IBD risk by enriching microbial diversity in the gut. Similarly, early antibiotic use, which disrupts these communities, is a risk factor.

Mental health

Stress, anxiety and depression are associated with both IBD risk and recurrence of the disease. Physical inactivity and disrupted sleep are also risk factors. Causality, however, is not yet well established.

Diet

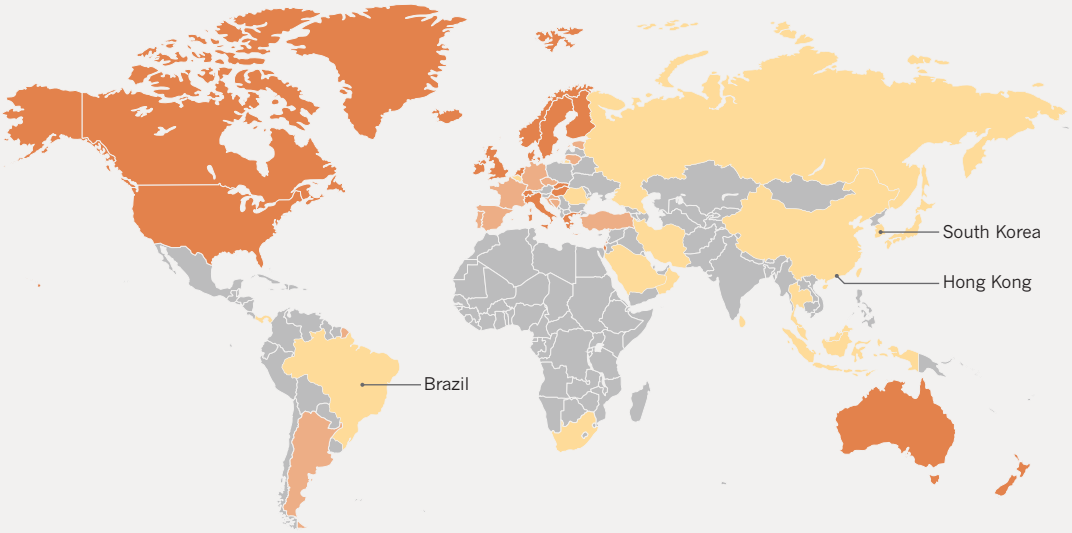
Consumption of saturated fats and low intake of fruit and vegetable fibre may increase IBD risk. Vitamin D seems to help to control inflammation in people with IBD.

Smoking

Scientists investigating the effect of smoking on IBD risk have discovered an apparent contradiction: current smokers are nearly twice as likely to have CD as non-smokers, but they also seem to be at lower risk of UC.

A GROWING GLOBAL DISEASE

IBD is most common in North America, Western and Northern Europe, Australia and New Zealand[4]. Cases are much less common in non-Western nations, but this is changing — incidence rates have climbed rapidly in recent years in parts of Asia and South America.



IBD prevalence, 2015:

- Highest
- Intermediate
- Lowest
- No data

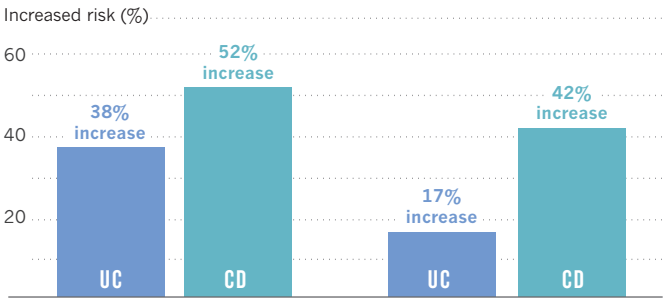
Hong Kong (1990–2001)[5]
- 50% increase in UC incidence
- 150% increase in CD incidence

South Korea (1991–2000)[5]
- 100% increase in UC incidence
- 136% increase in CD incidence

Brazil (1991–2000)[6]
- 75% increase in UC incidence
- 117% increase in CD incidence

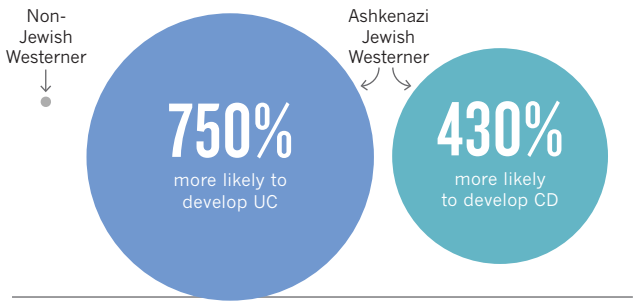
REGIONAL, LOCAL, INDIVIDUAL

Beneath the global data lie smaller-scale trends that reveal the complex mix of factors that determine a person's risk of disease.



Women in northern latitudes are at greater risk compared with those in the south[7]

Urbanites are at greater risk than rural denizens[8]



Ashkenazi Jews living in Western nations are much more likely to have IBD than their non-Jewish neighbours[9]

Sources: 1. Molodecky, N. A. *et al. Gastroenterology* **142,** 46–54 (2012). 2. Ananthakrishnan, A. N. *Nature Rev. Gastroenterol. Hepatol.* **12,** 205–217 (2015). 3. Sartor, R. B. *et al. Nature Clin. Prac. Gastroenterol. Hepatol.* **3,** 390–407 (2006). 4. Kaplan, G. G. *Nature Rev. Gastroenterol. Hepatol.* **12,** 720–727 (2015). 5. Thia, K. T. *et al. Am. J. Gastroenterol.* **103,** 3167–3182 (2008). 6. Victoria, C. R. *et al. Arq. Gastroenterol.* **46,** 20–25 (2009). 7. Khalili, H. *Gut* **61,** 1686–1692 (2012). 8. Soon, I. S. *et al. BMC Gastroenterol.* **12,** 51 (2012). 9. Bernstein, C. N. *et al. Am. J. Gastroenterol.* **101,** 993–1002 (2006).