Inflammatory Bowel Diseases

van der Sloot, Kimberley W. J.; Amini, Marzyeh; Peters, Vera; Dijkstra, Gerard; Alizadeh, Behrooz Z.

Published in:
Inflammatory Bowel Diseases

DOI:
10.1097/MIB.0000000000001217

Publication date:
2017

Inflammatory Bowel Diseases: Review of Known Environmental Protective and Risk Factors Involved

Kimberley W. J. van der Sloot, BSc,†* *Marzyeh Amini, MSc,** *Vera Peters, BSc,*†* *Gerard Dijkstra, MD, PhD,†* *and Behrooz Z. Alizadeh, MSc, MD, PhD**

Abstract: Inflammatory bowel diseases consisting of Crohn's disease and ulcerative colitis are chronic inflammatory diseases of the gastrointestinal tract. In addition to genetic susceptibility and disturbances of the microbiome, environmental exposures forming the exposome play an important role. Starting at birth, the cumulative effect of different environmental exposures combined with a predetermined genetic susceptibility is thought to cause inflammatory bowel disease. All these environmental factors are part of a Western lifestyle, suiting the high incidence rates in Europe and the United States. Whereas receiving breastfeeding, evidence of a *Helicobacter pylori* infection and vitamin D are important protective factors in Crohn's disease as well as ulcerative colitis, increased hygiene, experiencing a bacterial gastroenteritis in the past, urban living surroundings, air pollution, the use of antibiotics, nonsteroidal anti-inflammatory drugs, and oral contraceptives are likely to be the most important risk factors for both diseases. Current cigarette smoking yields a divergent effect by protecting against ulcerative colitis but increasing risk of Crohn's disease, whereas former smoking increases chances of both diseases. This review gives a clear overview of the current state of knowledge concerning the exposome. Future studies should focus on measuring this exposome yielding the possibility of combining all involved factors to one exposome risk score and our knowledge on genetic susceptibility.

(Inflamm Bowel Dis 2017;23:1499–1509)

Key Words: environmental risk factors, environmental protective factors, exposome, environmental exposure

Inflammatory bowel disease (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), is a gastrointestinal disease characterized by chronic inflammation. UC affects only the colon and inflammation is mostly superficial, whereas CD affects the entire gastrointestinal tract and leads to transmural inflammation, strictures, fistulas, and abscess formation.[1] Incidence rates of IBD are highest in industrialized countries affecting up to 2.4 million persons in Europe and 1.3 million persons in the United States.[2] Etiology is complex with a dynamic interaction of genetics, microbiome, and environmental influences (Fig. 1).[3]

The role of genetics is evident. A positive family history of IBD is the most important risk factor for development of IBD, as a concordance rate of 19% and 50% has been shown in monozygotic twins for UC and CD, respectively.[4,5] Genome-wide association meta-analyses have identified 201 independent loci contributing to an increased risk of IBD. Most of these loci were associated with both CD and UC, indicating common pathways for both diseases. However, 37 CD-specific and 27 UC-specific loci have also been identified.[6,7] But known loci account for only a third of risk for either disease. To depict the overall spectrum of disease pathogenesis, the unprecedented accumulating body of evidence on the genetic component of disease should be integrated with all so far known environmental risk factors.[8,9] These environmental factors directly influence the microbiome; the third entity in IBD development. An unbalanced microbial community composition is associated with dysregulation of the gut immune response, and therefore associated with IBD.[1,10] Species richness decreases while some taxa seem to overgrow.[11] Lastly, environmental factors are also directly involved in IBD pathogenesis though numerous different pathways.

Epidemiological research has led to important clues in identifying important environmental risk factors. Whereas the incidence of IBD in developed countries has stabilized, incidences in developing countries in Asia, Eastern Europe, and Northern Africa are rising as they change their lifestyle and living environment.[12] The hypothesis that these environmental factors play an important role in these increases is further supported by the finding that migration from a developing to a developed country leads to an increased risk of IBD in migrants.[13,14]

Continuous exposure to the collective effect of dynamic environmental factors seems to be affecting the incidence of IBD. Christopher Wild was the first to describe "the exposome" as a way to map a life course of environmental exposures, starting in the neonatal period.[15,16] To create an IBD exposome, a clear overview of important environmental factors and their estimated effect size is crucial. Hereby, it is crucial to divide exposures

Received for publication March 6, 2017; Accepted June 7, 2017.

From the Departments of *Epidemiology, and †Gastroenterology and Hepatology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands.

The authors have no conflict of interest to disclose.

Address correspondence to: Kimberley W. J. van der Sloot, BSc, Hanzeplein 1, 9713 GZ Groningen, the Netherlands (e-mail: k.w.j.van.der.sloot@umcg.nl).

DOI 10.1097/MIB.0000000000001217

Published online 2 August 2017.

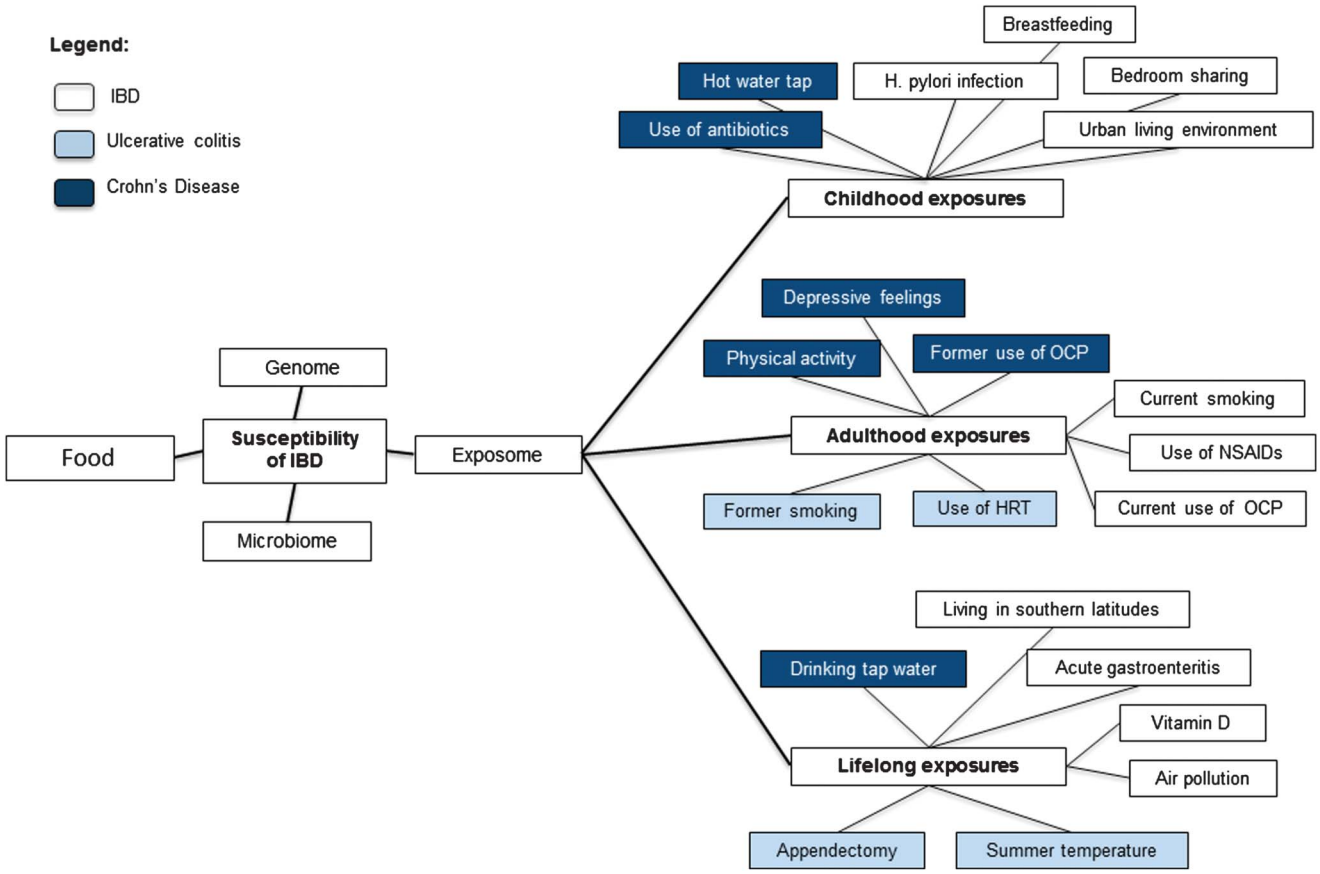

FIGURE 1. Overview of environmental exposures involved in IBD susceptibility.

based on their time of influence. Early childhood exposures contribute to formation of the immune system, whereas adulthood exposures might alter established pathways. Many have reviewed IBD and its causes before, but while some focus on a wider perspective than the exposome alone, others lack important environmental factors or specific effect sizes. Also, to the best of our knowledge, stage of life was not taken into account before.[9,17–21]

In this review, we therefore describe all so-far known risk and protective factors for IBD, based on the time of possible exposure in life and including effect sizes and possible biological background.

In this review, we aim to give an overview of current knowledge on the role of environment and lifestyle in IBD. Therefore, a literature search was performed to identify primary studies and systematic reviews examining potentially involved factors. Next, a qualitative review of each of these factors was carried out, and studies with the highest quality of evidence, evaluating study limitations, inconsistency, indirectness, imprecision, and the possibility of publication bias based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach were included in this review.[22] All environmental exposures are ordered by the time in life exposure most often starts, providing the opportunity to make a distinction in pathways of effect. For instance, childhood exposures are more likely to affect immunologic development, whereas adulthood exposures are involved through modification of the already existing immunologic system.

Childhood Exposures

Starting at birth, exposures to numerous environmental factors occur, of which some may have a considerable impact on disease development, IBD in particular, later in life. Figure 2 shows childhood environmental exposures based on effect type and size for UC and CD separately. The most important childhood exposures include breastfeeding, use of antibiotics, childhood hygiene, and *Helicobacter pylori* infection, which we discuss below.

Receiving breastfeeding is shown to hold a protective effect for development of IBD, whereas other factors had a more neutral or a subtle risk-increasing effect. Meta-analysis by Klement et al[23] has shown a 1.8-fold (95% confidence interval: 1.2–2.6) and a 2.2-fold (1.3–3.9) risk decrease for UC and CD, respectively. This falls in line with other reports showing a comparable protective effect of breastfeeding in other immune-mediated diseases such as bronchial asthma, atopic dermatitis, allergic rhinitis, and type 1 diabetes mellitus.[24–27] This protective effect may possibly be explained by induction of immune tolerance to specific food antigens and microbiota, transfer of maternal antibodies in breast milk

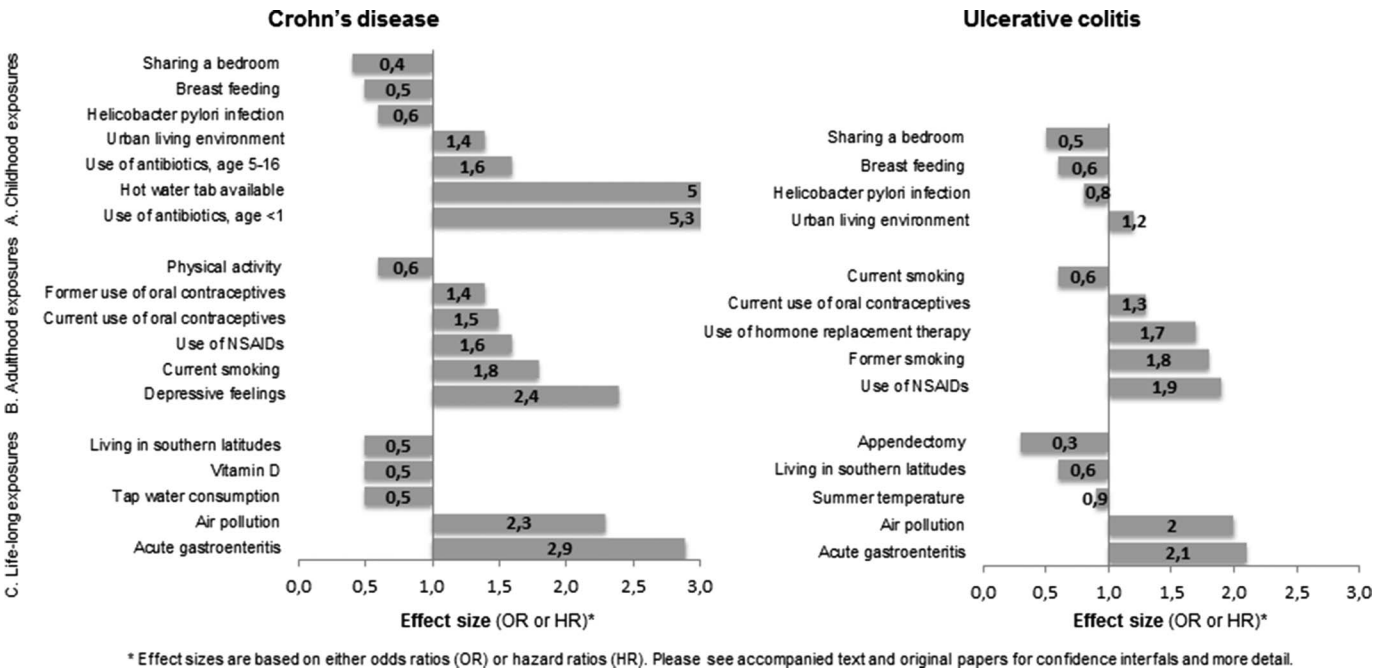

FIGURE 2. Environmental exposures based on effect type (protective or risk increasing) and effect size. *Effect sizes are based on either odds ratios (ORs) or hazard ratios (HRs). Please see accompanied text and original papers for confidence intervals and more detail.

to the infant, and changing of microbiota of the gut flora from pathogenic to nonadherent bacteria, as shown in a mice study.[28–30]

On the same line of evidence, the use of antibiotics during childhood for a variety of reasons may influence the microbiome, and therefore affect the susceptibility to IBD. Nevertheless, the use of antibiotics seems to hold an interesting divergent effect on IBD. Although it showed no effect on development of UC, the risk of developing CD increases in a dose-dependent manner, especially when antibiotics are used in the first year of life by an odds increase of 5.3 (1.6–17.4).[31] This effect tends to decrease (1.6, 1.4–1.8) when antibiotics are used later in childhood (between 6 and 15 yr old), but remains significant.[32] The risk-increasing effect varies across different types of antibiotics, with the strongest risk increase reported for broad-spectrum penicillin (3.1, 1.3–7.4), followed by penicillin V (2.9, 1.2–7.0), and cephalosporin (1.9, 1.4–2.6).[32–34] Though epidemiological studies show support for a role of antibiotics in IBD, biological understanding is insufficient to explain this relationship. One speculation suggests that neonates are born with germ-free bowels, and formation and colonization of their microbiota start immediately through interactions with external factors in the first years of life.[35,36] A disruption, or perhaps better to say derailing, in the formation and composition of the microbiome by using antibiotics within this period may possibly lead to a long-lasting effect and an increased risk of CD.[37] By alternating the microbiome composition, antibiotics may pave the way for pathogenic bacteria to colonize while the normal process of tolerance, crucial for development of the mucosal immune system, could be disrupted.[11,35,38] In this reasoning, CD could rise as the consequence of either an increase of pathogenic bacteria or by an aberrant response of the host immune system to its microflora.[39]

A comparable reasoning involves the role of the hygiene hypothesis in incidence of IBD.[40] Hygiene is generally measured by using proxies such as living area (urban versus rural area), number of siblings, access to hot water, and animal contact. Overall, a high hygiene level increases the risk of IBD. Meta-analysis has shown an increased risk by living in an urban environment of 1.2-fold (1.0–1.3) for UC and a 1.4-fold (1.3–1.6) for CD.[41] Likewise, having a smaller number of siblings leads to a 2.6-fold (1.5–4.6) risk increase of IBD and in contrast, sharing a bedroom decreases risk of UC 2.1-fold (1.1–3.9) and CD 2.3-fold (1.3–4.4).[42] Having a hot water tap at home increased odds of CD 5-fold (1.4–17.3) and having a separate bathroom 3.3-fold (1.3–8.3), whereas no effect was found for UC.[43] Animal contact, an indicator of less hygiene, on the other hand, might decrease risk of UC and CD in migrants.[44] The hygiene hypothesis is not limited to IBD, as similar effects are seen in eczema and asthma.[40] Evidence to explain the association of a higher hygiene level and IBD (and other inflammatory diseases) proposes that increased hygiene leads to less exposure to harmless microorganisms such as helminthes, predominantly found in areas of poor hygiene, leading to less induction of dendritic cell maturation and ability to drive the T-cell regulatory system, as is shown in animal models and studies in patients with CD and UC.[45–49]

Further underscoring the importance of hygiene in disease pathogenesis is the finding that early childhood *H. pylori* infection is inversely associated with the incidence of IBD. The overall infection rate is lower in patients with IBD when compared with

controls (27.1% versus 40.9%), with a 1.7-fold (1.4–2.0) and 1.3-fold (1.1–1.6) protective effect for CD and UC, respectively.[50] Of note, a similar effect is described for asthma.[51,52] While the underlying mechanism remains to be explored, *H. pylori* leads to an increase of mucosal Foxp3 expression, the transcription factor of T-regulatory cells, which might be able to explain this protective effect by downregulation of the inflammatory process.[53,54] Vaccination is another way by which our immune system is exposed to bacterial antigens, and as vaccinations clearly influence the immune system as well, their role in IBD was studied. In contrast to past expectations, recent findings show no support for a causative or protective effect for measles infection, or vaccination against smallpox, diphtheria, tetanus, and poliomyelitis.[55–57]

As with the hygiene hypothesis, living environment seems to play a more decisive role in IBD. While overall, air pollution seems to have no effect on IBD development, early-onset disease seems to be affected. Living in regions with high sulfur dioxide (SO_2) before the age of 25 increases chances of UC 2-fold (1.1–3.7), whereas a high nitrogen dioxide (NO_2) before the age of 23 increases chances of CD 2.3-fold (1.3–4.3).[58] Total pollutant emissions also correlate significantly with an increased risk of hospitalization in established IBD.[59] Similar effects are seen for development of other inflammatory diseases, such as rheumatoid arthritis and relapses of multiple sclerosis.[60,61] Previous studies have shown an increased sensitivity of children to pollution, partly because of more time outside, partly because of a higher gastrointestinal absorption of pollutants with younger age, explaining these findings.[62,63] Once absorbed, pollutants may incite the inflammatory process characteristic for IBD, but exact pathways remain unclear.[64]

Examination of all these childhood exposures has shown the long-term effect single factors might have on developing disease later in life by influencing the basis on which the immune system and microbiota are formed. Overall, a high level of hygiene may increase chances of IBD while breastfeeding protects against disease development.

Adulthood Exposures

By aging, the pattern of environmental exposures changes. Passed through the maturation of the immune system, lifestyle becomes a more apparent player, when more freedom of choice is gained and diversity among individuals increases. A few particular environmental exposures from this period in life have been linked to IBD development. Figure 2 shows adulthood environmental exposures based on effect type and size for UC and CD separately. These effect sizes are based on studies selected after a qualitative review of literature using the GRADE approach. The most important adulthood exposures are smoking and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives.

One of the most apparent effects of western lifestyle is the diet and subsequent clear rise of obesity. The influence of diet has been reviewed elsewhere. An increased body mass index (BMI) might lead to an increased risk of CD, but not UC, although results are inconsistent. In regard to the proinflammatory effect of obesity, 2 large European and American cohort studies have examined this association.[65–67] However, only the American cohort shows a 2.5-fold (1.2–5.0) risk-increasing effect for CD in obese women (BMI $\geq$30 kg/m^2) when compared with women with a normal BMI (20.0–24.9 kg/m^2).[66] Conflicting results of these different studies have led to the hypothesis that not total BMI, but visceral adiposity specifically, might be a better measurement to predict disease risk. This hypothesis is supported by our findings describing a higher visceral adiposity at disease diagnosis and a more complicated disease course.[68–71]

Physical activity might also be related to obesity and shows a reverse effect on disease development with a protective role for risk of CD, but not UC, although reported results are inconsistent.[67,72] Prospective analyses have shown a risk reduction of 36 percent (6.0%–56.0%) when comparing high- and low-activity groups, which is supported by findings from other studies.[73–75] Animal studies have confirmed this effect by demonstrating a protective effect against inflammatory diseases, and also insulin resistance, cancer, neurodegenerative disorders, infections, aging, and heart disease by inducing an autophagy pathway; a lysosomal cell destruction pathway which allows cells to adapt to changing nutritional and energy demands, and therefore contributes to beneficial effects of exercise.[76–80]

Another lifestyle-associated factor is stress. When asked, 70% of patients have the perception that a flare of their disease is associated with stressful life events, and stress is perceived to be the leading causative agent in their disease.[81,82] This hypothesis was examined by different researchers, and findings are inconsistent.[83,84] Experiencing depressive feelings, however, was associated with a 2.4-fold (1.4–4.0) increased risk of CD, but not UC (1.1, 0.7–1.9) in a large prospective cohort study by Ananthakrishnan et al.[85] Knowing the adverse effect of stress on sleep, the latter might also be a good determinant in terms of IBD risk.[86] Patients with IBD have an increased risk of sleep disturbances, leading to a 2-fold increase of disease flare.[87,88] Up to 83 percent of underlying mucosal inflammation can be predicted by an abnormal Pittsburg Sleep Quality Index (PSQI).[89] A possible explanation for this effect is activation of the immune cascade by sleep deprivation because a normal sleeping pattern is crucial for maintaining health and a proper regulation of immune function.[90,91] Therefore, the assessment of sleep disturbances in these patients could play an important role in optimal treatment.[92]

The same line of reasoning may be used for examining the role of smoking in IBD. Cigarette smoke might be the most widely studied lifestyle-associated (environmental) factor in IBD with a protective effect of current smoking on UC, but risk-increasing effect on CD. Meta-analysis has shown that current smoking yields a 1.7-fold (1.3–2.2) risk reduction for UC, while being a former smoker increases risk of UC 1.8-fold (1.4–2.3), suggesting that smoking might only postpone the arise of UC.[93] Smoking also leads to a more benign disease course in UC with fewer flares, less need for steroids, and lower colectomy rates.[94–96] The effect of current smoking on CD is more controversial because not all studies display the same trend. However,

combining results of 9 different studies showed a 1.76-fold (1.4–2.2) risk increase of CD.[93] Former smoking also showed a risk increase, although less strong, of 1.3-fold (1.0–1.8).[93] These risk-increasing effects enlarged with increasing pack-years.[97] Passive smoke exposure during childhood and prenatal smoke exposure due to maternal smoking during pregnancy showed no association with the development of IBD.[98] Reasons behind the different effects of smoking on both diseases still remain vague because nicotine and smoking both have numerous effects.[99] Among other things, smoking affects the immune system through the cellular and humeral pathways by altering synthesis of proinflammatory cytokines.[100–102] Other effects include changes of gut permeability, reduction of smooth muscle tone and contractility due to nitric oxide, and changes in microcirculation of the gut.[103–105]

Gut permeability is also influenced by the use of NSAID use. Using NSAIDs at least 15 days per month increases risk of UC 1.9-fold (1.2–3.0) and risk of CD 1.6-fold (1.0–2.6). These risks increase with a higher frequency of use, greater weekly dosages, and a longer duration of use.[106] These findings can be explained by the pharmacokinetics of NSAIDs, as they inhibit cyclooxygenase (COX) leading to a decrease of protective prostaglandins in the gut mucosa, and after undergoing hepatic circulation, this ensures, among other things, an increase in mucosal permeability, and therefore intestinal barrier function disturbance.[107,108]

Besides these analgesics, the use of hormone containing medication is likely to play a role in IBD development. The risk-increasing effect of using the oral contraceptive pill (OCP) on IBD seems clear, whereas the effect of postmenopausal hormone replacement therapy is more controversial. Current use of OCP leads to a 1.3-fold (1.1–1.5) risk increase of UC.[109] Risk of developing CD with current OCP use increases 1.5-fold (1.3–1.7), and this effect might remain visible in former users (1.4, 1.1–1.9), when compared with never-users.[109,110] Postmenopausal hormone replacement therapy also leads to a 1.7-fold (1.1–2.7) increase of risk on UC, after correcting for earlier OCP use and increasing with duration of use, whereas no effect is seen in CD.[111] A different study found reverse findings; an association with CD instead of UC, but used a very small number of cases.[112] Estrogen promotes the humeral immune system, cellular proliferation and mediates the effect of Th2-related cytokines, and because UC is a Th2-mediated disease, this could explain the increased risk. The same effect has also been described in other Th2-mediated diseases such as rheumatoid arthritis and systemic lupus erythematous.[113,114] However, this hypothesis does not hold ground for CD because this is a Th1-mediated disease, and further research should focus on the role of oral contraceptives in this specific pathogenesis.[115] Modification of the colonic barrier function, as described for NSAID use, potentially plays a role.[116,117]

A final medication that has been associated with development of IBD is isotretinoin, commonly used for treatment of severe nodulocystic acne, but its association with risk of IBD development is most likely due to an association with acne itself.[118–120] Reported risk-increasing effects of isotretinoin are weak (1.1, 0.9–1.4) and described for topic acne medication use as well, supporting the hypothesis of acne as a causative agent.[121] Acne should be seen as a systemic inflammatory condition, and was earlier described as part of systemic inflammatory syndromes, although its role remains uncertain.[122]

Differing from the role childhood exposures play in IBD development, adulthood exposures seem to be involved by changing the already developed immune system, and their cumulative effect is likely to be an important step in progression to disease development.

Lifelong Exposures

At last, several (novel) environmental factors have been identified to play a role in IBD development independent of stage of life. Although its effects might differ in size over the years, it is thought that these factors play a role independently of age. Figure 2 shows lifelong environmental exposures based on effect type and size for UC and CD separately. These effect sizes are based on studies selected after a qualitative review of literature using the GRADE approach. The most important exposures are previous development of an acute bacterial gastroenteritis, geographical variation, and vitamin D.

After living through a bacterial gastroenteritis, the risk of developing of UC and CD increases significantly (2.4, 1.7–3.3), especially within the first year (4.1, 2.2–7.4). The largest effect is seen for CD (2.9, 1.5–5.6) compared with UC (2.1, 1.4–3.4).[123–125] This same effect has also been seen for development of Guillain–Barré syndrome and Reiter's syndrome, suggesting a triggering role for gastroenteritis on inflammation. The type of chronic inflammatory disease that develops afterward may be dependent of genetics and other risk factors.[124,126,127] In IBD, the increased risk may be explained by IL-6 production, nonspecific blockage of regulatory T-cells, and activation of self-reactive T-cells as a result of pathogenic infection, leading to a chronic inflammatory response.[128]

Another way the immune system can be influenced is through exposure to harmless microorganisms as discussed in the childhood exposures section above.

Drinking tap water on a regular basis seems to lower risk of CD, while UC is unaffected. Tap water decreases risk of CD by 2-fold (1.3–3.3), although its association is weak and needs further research. A possible explanation for this finding is that because of the presence of harmless environmental species in tap water, regulatory T-cells are triggered, as also suggested in the hygiene hypothesis.[129,130] A similar association is seen for asthma and allergies, emphasizing the importance of further research into its exact role in IBD pathogenesis.[131] But while exposure to harmless microorganisms is likely to protect against IBD as also expressed by the hygiene hypothesis, pathogenic infection is a risk factor. Meanwhile, infection by *Mycobacterium avium* subspecies paratuberculosis (MAP) and its role in IBD remain controversial. Although MAP infection rates are higher in patients with CD, a causative role remains controversial, and no data are available evaluating the role of MAP in UC. Ever since similarities between MAP-caused Johne's disease in cattle and CD were noticed, the same association has been suggested for CD.[132] Meta-analysis has shown a 7-fold increased chance of MAP infection in patients with CD, but because

of study design timing of infection is unknown.[133] Next, a small follow-up study failed to show MAP infection in early disease development.[134] Because its role in disease course also remains unclear, MAP might only be a bystander in CD.

Whereas developing gastroenteritis seems like a clear risk factor for IBD, undergoing an appendectomy, also immune associated, yields a divergent effect. Although a protective effect for UC is seen, risk of CD increases. Meta-analysis has shown a 3.3-fold (2.7–4.0) risk reduction for development of UC accompanied by a decrease of relapse risk in established disease (57.1% versus 78.6%), while risk of colectomy seems unchanged. This effect is largest when appendectomy is performed before the age of 20, independently of its cause.[135–139] Mouse models have shown appendectomy to suppress the development of inflammation, whereas tonsillectomy does not show the same protective effect.[140] The most probable explanation for this protective effect states that by the removal of the appendix, which belongs to the gut-associated lymphoid tissues, imbalance of T-cell helper and inducer cells is altered.[136,141,142] The risk-increasing effect of an appendectomy in CD is controversial and seems most likely caused by diagnostic bias in patients with incipient CD with symptoms mimicking appendicitis.[143] Risk increase being highest within 1 year after surgery and faded after 5 years supports this theory.[144]

Finally, like the role of living environment as described in childhood exposures, living geography and altitude also seem to play a role. Novel research has shown an increased risk of disease flare after high-altitude flights or traveling more than 2000 m above sea level.[145] The mild hypoxia this leads to causes increases of inflammatory markers such as IL-1 receptor antagonist, IL-6, and CRP and may therefore worsen disease course, but its role in disease development is unclear and cohort-based evidence is needed for further evaluation.[146] Also, the weather is associated with IBD. A warm summer, for example, yields a protective effect for UC, and although unconfirmed, the same is suggested for CD. An increase of 1°C yields a protective effect for UC of 1.1 (1.0–1.2).[147] This same protective pattern is seen in other inflammatory diseases such as multiple sclerosis, allergies, rheumatoid arthritis, and systemic lupus erythematosus.[148–151] It is thought that an increase of summer temperature accompanies an increase of microbial species richness, and knowing the role of balance disruption between gut flora and immune regulation in UC pathogenesis, microbial richness might counterbalance this part of disease etiology.[47,152]

Besides summer temperature, living in southern latitudes is also shown to be protective of IBD. When compared with northern latitudes, a protective effect of 1.6 (1.1–2.4) for UC and 2.1 (1.3–3.3) for CD is seen in U.S. women living in southern

TABLE 1. Level of Evidence of Environment and Lifestyle in UC

Exposure	Sample Size	Effect[a]	Quality[b]	Type of Study	Author	Year of Publication
Breastfeeding	17 studies	Protective	⊕⊕⊕⊕	Meta-analysis	Klement et al[23]	2004
Hygiene hypothesis						
Urban environment	25 studies	Risk	⊕⊕⊕	Meta-analysis	Soon et al[41]	2012
Bedroom sharing	768 cases, cohort size 3,99,251	Protective	⊕	Cross-sectional study	Klement et al[42]	2008
H. pylori infection	23 studies	Protective	⊕⊕⊕	Meta-analysis	Luther et al[50]	2010
Air pollution (SO_2)	591 cases, 2,962 controls	Risk	⊕	Case–control	Kaplan et al[58]	2010
Cigarette smoking						
Current	13 studies	Protective	⊕⊕⊕⊕	Meta-analysis	Mahid et al[93]	2006
Former	13 studies	Risk	⊕⊕⊕⊕	Meta-analysis	Mahid et al[93]	2006
Use of NSAIDs	117 cases, cohort size 1,21,700	Risk	⊕	Cohort study	Ananthakrishnan et al[106]	2012
Current use of OCP	14 studies	Risk	⊕⊕⊕	Meta-analysis	Cornish et al[109]	2008
Use of HRT	392 cases, cohort size 2,32,452	Risk	⊕⊕	Cohort study	Khalili et al[111]	2013
Acute gastroenteritis	95 cases, cohort size 93,013	Risk	⊕	Cohort study	Garcia Rodriguez et al[124]	2006
Appendectomy	13 studies	Protective	⊕⊕⊕	Meta-analysis	Koutroubakis and Vlachonikolis[135]	2000
Warm summer temperature	370 cases, cohort size 80,412	Protective	⊕⊕	Cohort study	Aamodt et al[147]	2013
Living in southern latitudes	313 cases, cohort size 1,75,912	Protective	⊕	Cohort study	Khalili et al[153]	2012

[a]"Protective" indicated a decreased chance of developing IBD, and "Risk" indicates increased chance of developing IBD.
[b]Quality of papers based on the GRADE approach evaluating limitations, inconsistency, indirectness, imprecision, and publication bias, ⊕⊕⊕⊕ indicating high quality, ⊕⊕⊕ moderate quality, ⊕⊕ low quality, ⊕ very low quality.
HRT, hormone replacement therapy.

latitudes, possibly because of an increase of UV radiation exposure and higher vitamin D level.[153] An increase of vitamin D level has also been shown to be protective in IBD. When comparing high and low predicted vitamin D groups, a protective effect of 1.9 (1.0–3.3) is seen for CD, but not UC. Each 1 ng/mL increase of plasma 25(OH)D level seems to decrease risk of UC and CD but does not reach statistical significance.[154] This protective association is also seen in other chronic immune-mediated diseases, such as multiple sclerosis and type 1 diabetes.[155] Vitamin D is known to play a role in the regulation of the innate immune system. Through activation of the vitamin D receptor on TH1 lymphocytes and monocytes, the inflammatory response is downregulated.[156] These findings have been confirmed by mice studies; vitamin D receptor deficiency leads to an increase of severity of colitis. A low plasma vitamin D level might lead to a comparable outcome.[157,158]

Next to vitamin D, diet is a lifelong exposure that cannot be ignored. The relation between diet and etiology and treatment of IBD is apparent for patients as well as their physicians, but is difficult to prove scientifically.[159,160] Because of the complexity of diet, it is often classified as an independent etiologic factor in IBD development and will therefore only be discussed shortly in this review.[161] Whereas sugar and fat, forming important components of a Western diet, have been identified as risk factors for IBD development, fruits and vegetables seem to hold a protective effect.[162–167] However, results are inconclusive, and no firm conclusion can be drawn given current understandings.

DISCUSSION

In our working hypothesis, environmental exposures either as a part of a Western lifestyle or living surroundings play an

TABLE 2. Level of Evidence of Environment and Lifestyle in CD

Exposure	Sample Size	Effect[a]	Quality[b]	Type of Study	Author	Year of Publication
Breastfeeding	17 studies	Protective	⊕⊕⊕⊕	Meta-analysis	Klement et al[23]	2004
Use of antibiotics						
First yr of life	27 cases, 360 controls	Risk	⊕	Case–control	Shaw et al[31]	2010
Between 6 and 15 yr old	449 cases, cohort size 10,72,426	Risk	⊕⊕	Cohort study	Kronman et al[32]	2012
Hygiene hypothesis						
Urban environment	30 studies	Risk	⊕⊕⊕	Meta-analysis	Soon et al[41]	2012
Bedroom sharing	768 cases, cohort size 3,99,251	Protective	⊕	Cross-sectional study	Klement et al[42]	2008
H. pylori infection	23 studies	Protective	⊕⊕⊕	Meta-analysis	Luther et al[50]	2010
Air pollution (NO_2)	367 cases, 1,833 controls	Risk	⊕	Case–control	Kaplan et al[58]	2010
Obesity	153 cases, cohort size 1,11,498	Risk	⊕	Cohort study	Khalili et al[66]	2015
Physical activity	284 cases, cohort size 1,94,711	Protective	⊕	Cohort study	Khalili et al[73]	2013
Depressive feelings	170 cases, cohort size 1,52,461	Risk	⊕	Cohort study	Ananthakrishnan et al[85]	2013
Cigarette smoking						
Current	9 studies	Risk	⊕⊕⊕⊕	Meta-analysis	Mahid et al[93]	2006
Former	9 studies	Risk	⊕⊕⊕⊕	Meta-analysis	Mahid et al[93]	2006
Use of NSAIDs	123 cases, cohort size 1,21,700	Risk	⊕	Cohort study	Ananthakrishnan et al[106]	2012
Use of OCP						
Current	14 studies	Risk	⊕⊕⊕	Meta-analysis	Cornish et al[109]	2008
Former	315 cases, cohort size 2,32,452	Risk	⊕	Cohort study	Khalili et al[110]	2013
Acute gastroenteritis	54 cases, cohort size 93,013	Risk	⊕	Cohort study	Garcia Rodriguez et al[124]	2006
Tap water consumption	222 cases, 222 controls	Protective	⊕	Case–control study	Baron et al[129]	2005
Living in southern latitudes	257 cases, cohort size 1,75,912	Protective	⊕	Cohort study	Khalili et al[153]	2012
Vitamin D level	122 cases, cohort size 72,719	Protective	⊕	Cohort study	Ananthakrishnan et al[154]	2012

[a]"Protective" indicated a decreased chance of developing IBD, and "Risk" indicates increased chance of developing IBD.
[b]Quality of papers based on the GRADE approach evaluating limitations, inconsistency, indirectness, imprecision, and publication bias, ⊕⊕⊕⊕ indicating high quality, ⊕⊕⊕ moderate quality, ⊕⊕ low quality, ⊕ very low quality.
HRT, hormone replacement therapy.

important role in IBD pathogenesis. Therefore, in this review, we aimed to give a complete overview of environmental exposures possibly involved, as known to date and summarized in Tables 1 and 2. However, with the interpretation of these results, the quality of evidence should be taken in consideration, and results should be interpreted with caution. For a large number of possibly involved environmental factors, meta-analyses are not available yet. Novel factors thought to be involved are often identified in very well carried-out large cohort or case–control studies, but remain to be reproduced and validated by independent research groups. Also, results are not always adjusted for known confounding factors. In comparison to meta-analyses, therefore, the level of evidence provided by individual studies remains low, and one should be cautious with firm conclusions and recommendations concerning adaptation of lifestyle and living environment to prevent and/or treat IBD. Therefore, further research is necessary to further study the exact complex etiology of IBD.

Whereas breastfeeding, increased hygiene, *H. pylori* infection, urban living environment, and the use of antibiotics are important childhood exposures affecting either UC, CD, or both, smoking, physical activity, depressive feelings and the use of oral contraceptives, hormone replacement therapy, and NSAIDs form the most prominent adulthood exposures. Moreover, we have identified several lifelong exposures, some defined by location of residence such as living in southern latitudes, vitamin D level, summer temperature, air pollution, and tap water consumption, whereas others reflect medical history such as a previous appendectomy or bacterial gastroenteritis. As seen for genetic susceptibility, some environmental factors only affect UC or CD, whereas others affect both (Fig. 1).

Everyone is born with a certain genetic susceptibility for IBD, we believe the following exposure to environmental risk factors in a Western lifestyle and living environment can reach a certain threshold, after which IBD is developed. This can also explain the relatively low concordance rate in twin studies. In this theory, the coherent effect of all environmental exposures from neonatal period to death, named as the exposome by Wild, plays an important role.[15] Future studies should focus on measuring this exposome, either through biomarkers or questionnaires in a longitudinally manner, yielding the possibility of combining all involved environmental risk and protective factors in an exposome risk score. This way, coherence of different factors is used, offering a more complete model of exposures. Also, the exposome risk score could now be combined with the already existing genetic risk score, for a more comprehensive model of disease than ever before.[6,7] Also, the role of the exposome in disease course remains mostly unclear and should be explored next.

In contrast to genetic susceptibility, environmental exposures can be influenced actively. Therefore, the exposome is also of clinical value in multiple ways. First of all, as a preventive tool. Families with known genetic IBD susceptibility could be educated about the role of the exposome and its factors, because adaptation of lifestyle might delay or even prevent IBD development, as our suggested exposure threshold might not be reached. Secondly, knowing which environmental exposures are not only involved in development, but also course of disease by increasing chances of disease flare and development of complications, gives you the opportunity to not only treat patients with established disease by medication, but also by environmental exposure changes, leading to a more personalized treatment plan and possibly less need of medications in the future.[8] Extensive studies are needed to compare the incidence of environmental exposures between patients with IBD and healthy controls, as well as to determine its role in disease course.

REFERENCES

1. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature*. 2011;474:307–317.
2. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54.e42. quiz e30.
3. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol.* 2015;12:205–217.
4. Halfvarson J, Bodin L, Tysk C, et al. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. *Gastroenterology*. 2003;124:1767–1773.
5. Orholm M, Munkholm P, Langholz E, et al. Familial occurrence of inflammatory bowel disease. *N Engl J Med.* 1991;324:84–88.
6. Cleynen I, Vermeire S. The genetic architecture of inflammatory bowel disease: past, present and future. *Curr Opin Gastroenterol.* 2015;31:456–463.
7. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012;491:119–124.
8. Ananthakrishnan AN. The exposome in inflammatory bowel disease. *Trop Gastroenterol.* 2014;35:135–140.
9. Ananthakrishnan AN. Environmental triggers for inflammatory bowel disease. *Curr Gastroenterol Rep.* 2013;15:302. 012-0302-4.
10. Manichanh C, Borruel N, Casellas F, et al. The gut microbiota in IBD. *Nat Rev Gastroenterol Hepatol.* 2012;9:599–608.
11. Gevers D, Kugathasan S, Denson LA, et al. The treatment-naive microbiome in new-onset crohn's disease. *Cell Host Microbe.* 2014;15:382–392.
12. Ng SC, Tang W, Leong RW, et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. *Gut*. 2015;64:1063–1071.
13. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011;140:1785–1794.
14. Williams CN. Does the incidence of IBD increase when persons move from a low- to a high-risk area? *Inflamm Bowel Dis.* 2008;14(suppl 2):S41–S42.
15. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev.* 2005;14:1847–1850.
16. Ananthakrishnan AN, Xavier RJ. How does genotype influence disease phenotype in inflammatory bowel disease? *Inflamm Bowel Dis.* 2013;19:2021–2030.
17. Ananthakrishnan AN. Environmental risk factors for inflammatory bowel diseases: a review. *Dig Dis Sci.* 2015;60:290–298.
18. Legaki E, Gazouli M. Influence of environmental factors in the development of inflammatory bowel diseases. *World J Gastrointest Pharmacol Ther.* 2016;7:112–125.
19. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol (N Y).* 2010;6:339–346.
20. Gearry RB. IBD and environment: are there differences between east and west. *Dig Dis.* 2016;34:84–89.
21. Vatn MH, Sandvik AK. Inflammatory bowel disease. *Scand J Gastroenterol.* 2015;50:748–762.

22. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising crohn's disease. *Gut*. 2014;63:1381–1392.
23. Klement E, Cohen RV, Boxman J, et al. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr.* 2004;80:1342–1352.
24. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr.* 2001;139:261–266.
25. Mimouni Bloch A, Mimouni D, Mimouni M, et al. Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. *Acta Paediatr.* 2002;91:275–279.
26. Gdalevich M, Mimouni D, David M, et al. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol.* 2001;45:520–527.
27. Gerstein HC. Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature. *Diabetes Care.* 1994;17:13–19.
28. Faria AM, Weiner HL. Oral tolerance: mechanisms and therapeutic applications. *Adv Immunol.* 1999;73:153–264.
29. Rogier EW, Frantz AL, Bruno ME, et al. Lessons from mother: long-term impact of antibodies in breast milk on the gut microbiota and intestinal immune system of breastfed offspring. *Gut Microbes*. 2014; 5:663–668.
30. Kunz C, Rudloff S, Baier W, et al. Oligosaccharides in human milk: structural, functional, and metabolic aspects. *Annu Rev Nutr.* 2000;20: 699–722.
31. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol.* 2010;105:2687–2692.
32. Kronman MP, Zaoutis TE, Haynes K, et al. Antibiotic exposure and IBD development among children: a population-based cohort study. *Pediatrics*. 2012;130:e794–e803.
33. Hviid A, Svanstrom H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. *Gut*. 2011;60:49–54.
34. Virta L, Auvinen A, Helenius H, et al. Association of repeated exposure to antibiotics with the development of pediatric crohn's disease–a nationwide, register-based finnish case-control study. *Am J Epidemiol.* 2012;175:775–784.
35. Mackie RI, Sghir A, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. *Am J Clin Nutr.* 1999;69:1035S–1045S.
36. Fanaro S, Chierici R, Guerrini P, et al. Intestinal microflora in early infancy: composition and development. *Acta Paediatr Suppl.* 2003;91:48–55.
37. Tannock GW. The search for disease-associated compositional shifts in bowel bacterial communities of humans. *Trends Microbiol.* 2008;16: 488–495.
38. Gronlund MM, Arvilommi H, Kero P, et al. Importance of intestinal colonisation in the maturation of humoral immunity in early infancy: a prospective follow up study of healthy infants aged 0–6 months. *Arch Dis Child Fetal Neonatal Ed.* 2000;83:F186–F192.
39. Rath HC, Schultz M, Freitag R, et al. Different subsets of enteric bacteria induce and perpetuate experimental colitis in rats and mice. *Infect Immun.* 2001;69:2277–2285.
40. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health.* 2002;56:209–217.
41. Soon IS, Molodecky NA, Rabi DM, et al. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. *BMC Gastroenterol.* 2012;12:51. 230X-12-51.
42. Klement E, Lysy J, Hoshen M, et al. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. *Am J Gastroenterol.* 2008;103:1775–1782.
43. Gent AE, Hellier MD, Grace RH, et al. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet*. 1994;343:766–767.
44. Ko Y, Kariyawasam V, Karnib M, et al. Inflammatory bowel disease environmental risk factors: a population-based case-control study of middle eastern migration to Australia. *Clin Gastroenterol Hepatol.* 2015;13: 1453–1463.e1.
45. Summers RW, Elliott DE, Urban JF Jr, et al. Trichuris suis therapy in crohn's disease. *Gut*. 2005;54:87–90.
46. Summers RW, Elliott DE, Urban JF Jr, et al. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology*. 2005;128:825–832.
47. Rook GA, Brunet LR. Microbes, immunoregulation, and the gut. *Gut*. 2005;54:317–320.
48. Weinstock JV, Summers RW, Elliott DE. Role of helminths in regulating mucosal inflammation. *Springer Semin Immunopathol.* 2005;27: 249–271.
49. Elliott DE, Li J, Blum A, et al. Exposure to schistosome eggs protects mice from TNBS-induced colitis. *Am J Physiol Gastrointest Liver Physiol.* 2003;284:G385–G391.
50. Luther J, Dave M, Higgins PD, et al. Association between helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. *Inflamm Bowel Dis.* 2010;16:1077–1084.
51. Chen Y, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis.* 2008;198:553–560.
52. Reibman J, Marmor M, Filner J, et al. Asthma is inversely associated with helicobacter pylori status in an urban population. *PLoS One*. 2008; 3:e4060.
53. Rad R, Brenner L, Bauer S, et al. CD25+/Foxp3+ T cells regulate gastric inflammation and helicobacter pylori colonization in vivo. *Gastroenterology*. 2006;131:525–537.
54. Lundgren A, Suri-Payer E, Enarsson K, et al. Helicobacter pylori-specific CD4+ CD25high regulatory T cells suppress memory T-cell responses to H. pylori in infected individuals. *Infect Immun.* 2003;71: 1755–1762.
55. Pineton de Chambrun G, Dauchet L, Gower-Rousseau C, et al. Vaccination and risk for developing inflammatory bowel disease: a meta-analysis of case-control and cohort studies. *Clin Gastroenterol Hepatol.* 2015;13:1405–1415.e1. quiz e130.
56. Bernstein CN, Rawsthorne P, Blanchard JF. Population-based case-control study of measles, mumps, and rubella and inflammatory bowel disease. *Inflamm Bowel Dis.* 2007;13:759–762.
57. Davis RL, Kramarz P, Bohlke K, et al. Measles-mumps-rubella and other measles-containing vaccines do not increase the risk for inflammatory bowel disease: a case-control study from the vaccine safety datalink project. *Arch Pediatr Adolesc Med.* 2001;155:354–359.
58. Kaplan GG, Hubbard J, Korzenik J, et al. The inflammatory bowel diseases and ambient air pollution: a novel association. *Am J Gastroenterol.* 2010;105:2412–2419.
59. Ananthakrishnan AN, McGinley EL, Binion DG, et al. Ambient air pollution correlates with hospitalizations for inflammatory bowel disease: an ecologic analysis. *Inflamm Bowel Dis.* 2011;17:1138–1145.
60. Oikonen M, Laaksonen M, Laippala P, et al. Ambient air quality and occurrence of multiple sclerosis relapse. *Neuroepidemiology*. 2003;22: 95–99.
61. Hart JE, Laden F, Puett RC, et al. Exposure to traffic pollution and increased risk of rheumatoid arthritis. *Environ Health Perspect.* 2009; 117:1065–1069.
62. Sly PD, Flack F. Susceptibility of children to environmental pollutants. *Ann N Y Acad Sci.* 2008;1140:163–183.
63. Ahamed M, Siddiqui MK. Environmental lead toxicity and nutritional factors. *Clin Nutr.* 2007;26:400–408.
64. Podolsky DK. Inflammatory bowel disease. *N Engl J Med.* 2002;347: 417–429.
65. Poullis A, Foster R, Shetty A, et al. Bowel inflammation as measured by fecal calprotectin: a link between lifestyle factors and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2004;13:279–284.
66. Khalili H, Ananthakrishnan AN, Konijeti GG, et al. Measures of obesity and risk of crohn's disease and ulcerative colitis. *Inflamm Bowel Dis.* 2015;21:361–368.
67. Chan SS, Luben R, Olsen A, 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.
68. Uko V, Vortia E, Achkar JP, et al. Impact of abdominal visceral adipose tissue on disease outcome in pediatric crohn's disease. *Inflamm Bowel Dis.* 2014;20:2286–2291.
69. Bertin B, Desreumaux P, Dubuquoy L. Obesity, visceral fat and crohn's disease. *Curr Opin Clin Nutr Metab Care.* 2010;13:574–580.

70. Buning C, von Kraft C, Hermsdorf M, et al. Visceral adipose tissue in patients with crohn's disease correlates with disease activity, inflammatory markers, and outcome. *Inflamm Bowel Dis.* 2015;21:2590–2597.
71. Van Der Sloot KW, Joshi AD, Bellavance DR, et al. Visceral adiposity, genetic susceptibility, and risk of complications among individuals with crohn's disease. *Inflamm Bowel Dis.* 2017;23:82–88.
72. Wanner M, Martin BW, Autenrieth CS, et al. Associations between domains of physical activity, sitting time, and different measures of overweight and obesity. *Prev Med Rep.* 2016;3:177–184.
73. Khalili H, Ananthakrishnan AN, Konijeti GG, et al. Physical activity and risk of inflammatory bowel disease: prospective study from the nurses' health study cohorts. *BMJ.* 2013;347:f6633.
74. Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. *Gut*. 1990;31:1037–1040.
75. Persson PG, Leijonmarck CE, Bernell O, et al. Risk indicators for inflammatory bowel disease. *Int J Epidemiol.* 1993;22:268–272.
76. He C, Bassik MC, Moresi V, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature*. 2012; 481:511–515.
77. Kuma A, Mizushima N. Physiological role of autophagy as an intracellular recycling system: with an emphasis on nutrient metabolism. *Semin Cell Dev Biol.* 2010;21:683–690.
78. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. *Cell*. 2008;132:27–42.
79. Yang L, Li P, Fu S, et al. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab.* 2010;11:467–478.
80. Ebato C, Uchida T, Arakawa M, et al. Autophagy is important in islet homeostasis and compensatory increase of beta cell mass in response to high-fat diet. *Cell Metab.* 2008;8:325–332.
81. Gomez-Gil E, Vidal A, Panes J, et al. Relationship between patient's subjective stress perception and the course of inflammatory bowel disease. *Gastroenterol Hepatol.* 2003;26:411–416.
82. Theis MK, Boyko EJ. Patient perceptions of causes of inflammatory bowel disease. *Am J Gastroenterol.* 1994;89:1920.
83. Lerebours E, Gower-Rousseau C, Merle V, et al. Stressful life events as a risk factor for inflammatory bowel disease onset: a population-based case-control study. *Am J Gastroenterol.* 2007;102:122–131.
84. Vidal A, Gomez-Gil E, Sans M, et al. Life events and inflammatory bowel disease relapse: a prospective study of patients enrolled in remission. *Am J Gastroenterol.* 2006;101:775–781.
85. Ananthakrishnan AN, Khalili H, Pan A, et al. Association between depressive symptoms and incidence of crohn's disease and ulcerative colitis: results from the nurses' health study. *Clin Gastroenterol Hepatol.* 2013;11:57–62.
86. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: from physiological to pathological conditions. *Sleep Sci.* 2015;8:143–152.
87. Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis.* 2011;17:1882–1889.
88. Ananthakrishnan AN, Long MD, Martin CF, et al. Sleep disturbance and risk of active disease in patients with crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol.* 2013;11:965–971.
89. Ali T, Madhoun MF, Orr WC, et al. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. *Inflamm Bowel Dis.* 2013;19:2440–2443.
90. Irwin MR, Wang M, Campomayor CO, et al. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med.* 2006;166:1756–1762.
91. Alvarez GG, Ayas NT. The impact of daily sleep duration on health: a review of the literature. *Prog Cardiovasc Nurs.* 2004;19:56–59.
92. Kinnucan JA, Rubin DT, Ali T. Sleep and inflammatory bowel disease: exploring the relationship between sleep disturbances and inflammation. *Gastroenterol Hepatol (N Y).* 2013;9:718–727.
93. Mahid SS, Minor KS, Soto RE, et al. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc.* 2006;81:1462–1471.
94. Fraga XF, Vergara M, Medina C, et al. Effects of smoking on the presentation and clinical course of inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 1997;9:683–687.
95. Mokbel M, Carbonnel F, Beaugerie L, et al. Effect of smoking on the long-term course of ulcerative colitis. *Gastroenterol Clin Biol.* 1998;22:858–862.
96. Boyko EJ, Perera DR, Koepsell TD, et al. Effects of cigarette smoking on the clinical course of ulcerative colitis. *Scand J Gastroenterol.* 1988; 23:1147–1152.
97. Higuchi LM, Khalili H, Chan AT, et al. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. *Am J Gastroenterol.* 2012;107:1399–1406.
98. Jones DT, Osterman MT, Bewtra M, et al. Passive smoking and inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol.* 2008;103: 2382–2393.
99. Lakatos PL, Szamosi T, Lakatos L. Smoking in inflammatory bowel diseases: good, bad or ugly? *World J Gastroenterol.* 2007;13: 6134–6139.
100. Motley RJ, Rhodes J, Williams G, et al. Smoking, eicosanoids and ulcerative colitis. *J Pharm Pharmacol.* 1990;42:288–289.
101. van Dijk AP, Meijssen MA, Brouwer AJ, et al. Transdermal nicotine inhibits interleukin 2 synthesis by mononuclear cells derived from healthy volunteers. *Eur J Clin Invest.* 1998;28:664–671.
102. Wang H, Yu M, Ochani M, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature*. 2003;421: 384–388.
103. Suenaert P, Bulteel V, Den Hond E, et al. The effects of smoking and indomethacin on small intestinal permeability. *Aliment Pharmacol Ther.* 2000;14:819–822.
104. Green JT, Richardson C, Marshall RW, et al. Nitric oxide mediates a therapeutic effect of nicotine in ulcerative colitis. *Aliment Pharmacol Ther.* 2000;14:1429–1434.
105. Danese S. Inflammation and the mucosal microcirculation in inflammatory bowel disease: the ebb and flow. *Curr Opin Gastroenterol.* 2007;23: 384–389.
106. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for crohn disease and ulcerative colitis: a cohort study. *Ann Intern Med.* 2012;156:350–359.
107. Musumba C, Pritchard DM, Pirmohamed M. Review article: cellular and molecular mechanisms of NSAID-induced peptic ulcers. *Aliment Pharmacol Ther.* 2009;30:517–531.
108. Jenkins AP, Trew DR, Crump BJ, et al. Do non-steroidal anti-inflammatory drugs increase colonic permeability? *Gut*. 1991;32:66–69.
109. Cornish JA, Tan E, Simillis C, et al. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol.* 2008;103:2394–2400.
110. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut*. 2013; 62:1153–1159.
111. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Hormone therapy increases risk of ulcerative colitis but not crohn's disease. *Gastroenterology.* 2012;143:1199–1206.
112. Garcia Rodriguez LA, Gonzalez-Perez A, Johansson S, et al. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther.* 2005;22:309–315.
113. Cutolo M, Capellino S, Straub RH. Oestrogens in rheumatic diseases: friend or foe? *Rheumatology (Oxford)*. 2008;47(suppl 3):iii2–iii5.
114. Gonzalez DA, Diaz BB. Rodriguez Perez Mdel C, et al. Sex hormones and autoimmunity. *Immunol Lett.* 2010;133:6–13.
115. Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. *J Clin Invest.* 2004;113:1490–1497.
116. Looijer-van Langen M, Hotte N, Dieleman LA, et al. Estrogen receptor-beta signaling modulates epithelial barrier function. *Am J Physiol Gastrointest Liver Physiol.* 2011;300:G621–G626.
117. Braniste V, Jouault A, Gaultier E, et al. Impact of oral bisphenol A at reference doses on intestinal barrier function and sex differences after perinatal exposure in rats. *Proc Natl Acad Sci U S A.* 2010;107:448–453.
118. Chen K, White TJ, Juzba M, et al. Oral isotretinoin: an analysis of its utilization in a managed care organization. *J Manag Care Pharm.* 2002; 8:272–277.
119. Brelsford M, Beute TC. Preventing and managing the side effects of isotretinoin. *Semin Cutan Med Surg.* 2008;27:197–206.
120. Reniers DE, Howard JM. Isotretinoin-induced inflammatory bowel disease in an adolescent. *Ann Pharmacother.* 2001;35:1214–1216.

121. Alhusayen RO, Juurlink DN, Mamdani MM, et al. Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study. *J Invest Dermatol.* 2013;133:907–912.
122. Lindor NM, Arsenault TM, Solomon H, et al. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. *Mayo Clin Proc.* 1997;72:611–615.
123. Ternhag A, Torner A, Svensson A, et al. Short- and long-term effects of bacterial gastrointestinal infections. *Emerg Infect Dis.* 2008;14:143–148.
124. Garcia Rodriguez LA, Ruigomez A, Panes J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology*. 2006;130:1588–1594.
125. Porter CK, Tribble DR, Aliaga PA, et al. Infectious gastroenteritis and risk of developing inflammatory bowel disease. *Gastroenterology*. 2008; 135:781–786.
126. Bereswill S, Kist M. Recent developments in campylobacter pathogenesis. *Curr Opin Infect Dis.* 2003;16:487–491.
127. Irving PM, Gibson PR. Infections and IBD. *Nat Clin Pract Gastroenterol Hepatol.* 2008;5:18–27.
128. Pasare C, Medzhitov R. Toll pathway-dependent blockade of CD4 +CD25+ T cell-mediated suppression by dendritic cells. *Science*. 2003; 299:1033–1036.
129. Baron S, Turck D, Leplat C, et al. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. *Gut*. 2005;54:357–363.
130. Rook GA, Adams V, Hunt J, et al. Mycobacteria and other environmental organisms as immunomodulators for immunoregulatory disorders. *Springer Semin Immunopathol.* 2004;25:237–255.
131. Shenker BJ, Rooney C, Vitale L, et al. Immunotoxic effects of mercuric compounds on human lymphocytes and monocytes. I. Suppression of T-cell activation. *Immunopharmacol Immunotoxicol.* 1992;14: 539–553.
132. Dalziel TK. Thomas kennedy dalziel 1861–1924. Chronic interstitial enteritis. *Dis Colon Rectum.* 1989;32:1076–1078.
133. Feller M, Huwiler K, Stephan R, et al. Mycobacterium avium subspecies paratuberculosis and crohn's disease: a systematic review and meta-analysis. *Lancet Infect Dis.* 2007;7:607–613.
134. Ricanek P, Lothe SM, Szpinda I, et al. Paucity of mycobacteria in mucosal bowel biopsies from adults and children with early inflammatory bowel disease. *J Crohns Colitis.* 2010;4:561–566.
135. Koutroubakis IE, Vlachonikolis IG. Appendectomy and the development of ulcerative colitis: results of a metaanalysis of published case-control studies. *Am J Gastroenterol.* 2000;95:171–176.
136. Kurina LM, Goldacre MJ, Yeates D, et al. Appendicectomy, tonsillectomy, and inflammatory bowel disease: a case-control record linkage study. *J Epidemiol Community Health.* 2002;56:551–554.
137. Andersson RE, Olaison G, Tysk C, et al. Appendectomy and protection against ulcerative colitis. *N Engl J Med.* 2001;344:808–814.
138. Naganuma M, Iizuka B, Torii A, et al. Appendectomy protects against the development of ulcerative colitis and reduces its recurrence: results of a multicenter case-controlled study in Japan. *Am J Gastroenterol.* 2001;96: 1123–1126.
139. Parian A, Limketkai B, Koh J, et al. Appendectomy does not decrease the risk of future colectomy in UC: results from a large cohort and meta-analysis. *Gut*. 2017;66:1390–1397.
140. Mizoguchi A, Mizoguchi E, Chiba C, et al. Role of appendix in the development of inflammatory bowel disease in TCR-alpha mutant mice. *J Exp Med.* 1996;184:707–715.
141. Firouzi F, Bahari A, Aghazadeh R, et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: a case control study in Iran. *Int J Colorectal Dis.* 2006;21:155–159.
142. Kawanishi H. Immunocompetence of normal human appendiceal lymphoid cells: in vitro studies. *Immunology*. 1987;60:19–28.
143. Kaplan GG, Pedersen BV, Andersson RE, et al. The risk of developing crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. *Gut*. 2007;56:1387–1392.
144. Kaplan GG, Jackson T, Sands BE, et al. The risk of developing crohn's disease after an appendectomy: a meta-analysis. *Am J Gastroenterol.* 2008;103:2925–2931.
145. Vavricka SR, Rogler G, Maetzler S, et al. High altitude journeys and flights are associated with an increased risk of flares in inflammatory bowel disease patients. *J Crohns Colitis.* 2014;8:191–199.
146. Hartmann G, Tschop M, Fischer R, et al. High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. *Cytokine*. 2000;12:246–252.
147. Aamodt G, Bengtson MB, Vatn MH. Can temperature explain the latitudinal gradient of ulcerative colitis? cohort of Norway. *BMC Public Health*. 2013;13:530. 2458-13-530.
148. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. *Neurology*. 2008;71:129–135.
149. Wjst M, Dharmage S, Andre E, et al. Latitude, birth date, and allergy. *PLoS Med*. 2005;2:e294.
150. Vieira VM, Hart JE, Webster TF, et al. Association between residences in U.S. northern latitudes and rheumatoid arthritis: a spatial analysis of the nurses' health study. *Environ Health Perspect.* 2010;118:957–961.
151. Walsh SJ, Gilchrist A. Geographical clustering of mortality from systemic lupus erythematosus in the United States: contributions of poverty, hispanic ethnicity and solar radiation. *Lupus*. 2006;15:662–670.
152. Backhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human intestine. *Science*. 2005;307:1915–1920.
153. Khalili H, Huang ES, Ananthakrishnan AN, et al. Geographical variation and incidence of inflammatory bowel disease among US women. *Gut*. 2012;61:1686–1692.
154. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin D status is associated with reduced risk of crohn's disease. *Gastroenterology*. 2012;142:482–489.
155. Grant WB. Epidemiology of disease risks in relation to vitamin D insufficiency. *Prog Biophys Mol Biol.* 2006;92:65–79.
156. Lim WC, Hanauer SB, Li YC. Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol.* 2005;2:308–315.
157. Froicu M, Cantorna MT. Vitamin D and the vitamin D receptor are critical for control of the innate immune response to colonic injury. *BMC Immunol.* 2007;8:5.
158. Froicu M, Weaver V, Wynn TA, et al. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. *Mol Endocrinol.* 2003;17:2386–2392.
159. Rajendran N, Kumar D. Role of diet in the management of inflammatory bowel disease. *World J Gastroenterol.* 2010;16:1442–1448.
160. Kinsey L, Burden S. A survey of people with inflammatory bowel disease to investigate their views of food and nutritional issues. *Eur J Clin Nutr.* 2016;70:852–854.
161. Lee D, Albenberg L, Compher C, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology*. 2015;148:1087–1106.
162. Octoratou M, Merikas E, Malgarinos G, et al. A prospective study of preillness diet in newly diagnosed patients with crohn's disease. *Rev Med Chir Soc Med Nat Iasi.* 2012;116:40–49.
163. Hansen TS, Jess T, Vind I, et al. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. *J Crohns Colitis.* 2011;5:577–584.
164. Halfvarson J, Jess T, Magnuson A, et al. Environmental factors in inflammatory bowel disease: a co-twin control study of a Swedish-Danish twin population. *Inflamm Bowel Dis.* 2006;12:925–933.
165. Ripoli J, Miszputen SJ, Ambrogini O Jr, et al. Nutritional follow-up of patients with ulcerative colitis during periods of intestinal inflammatory activity and remission. *Arq Gastroenterol.* 2010;47:49–55.
166. Maconi G, Ardizzone S, Cucino C, et al. Pre-illness changes in dietary habits and diet as a risk factor for inflammatory bowel disease: a case-control study. *World J Gastroenterol.* 2010;16:4297–4304.
167. Amre DK, D'Souza S, Morgan K, et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for crohn's disease in children. *Am J Gastroenterol.* 2007;102:2016–2025.