

# Environmental Risk Factors for Inflammatory Bowel Disease

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**Abstract:** Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract and is associated with significant morbidity. The etiology of IBD has been extensively studied during the last several decades; however, causative factors in disease pathology are not yet fully understood. IBD is thought to result from the interaction between genetic and environmental factors that influence the normal intestinal commensal flora to trigger an inappropriate mucosal immune response. Although many IBD susceptibility genes have been discovered, similar advances in defining environmental risk factors have lagged. A number of environmental risk factors have been explored, including smoking, appendectomy, oral contraceptives, diet, breastfeeding, infections/vaccinations, antibiotics, and childhood hygiene. However, most of these factors have demonstrated inconsistent findings, thus making additional studies necessary to better understand the etiology of IBD.

Inflammatory bowel disease (IBD), which consists of Crohn's disease (CD) and ulcerative colitis (UC), is a complex genetic disorder that is influenced by environmental risk factors. The importance of genetic susceptibility has been established through genome-wide association scans, which have identified susceptibility genes (such as *NOD2* gene variants)<sup>1,2</sup> linking the pathogenesis of IBD to the dysregulation of the gastrointestinal immune system and the host microbiome.<sup>3,4</sup> Genetic predisposition, however, cannot be solely responsible for disease etiology. The lack of complete penetrance must be accounted for by additional factors in disease etiology.<sup>5</sup> Additionally, genetics cannot account for the rapid rise of IBD incidence in certain geographic regions.<sup>6,7</sup>

IBD has been primarily characterized as a disease of industrialized nations, with increased prevalence in the developed world. Since the 19th century, the incidence of IBD has increased steadily in North America and Europe until stabilizing in the middle and latter parts of the 20th century for UC (2–15/100,000 person-years) and CD (3–15/100,000 person-years), respectively. Although developing regions have traditionally reported lower prevalence of IBD, the incidence of IBD is rising in many of these nations (eg, India and China) as they have become industrialized.<sup>8,9</sup> Furthermore, migrant studies have demonstrated that individuals immigrating from regions with low prevalence to countries with higher prevalence are at an increased risk of developing IBD, particularly

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among first-generation children.<sup>5,6</sup> Thus, environmental exposures are thought to contribute to the development of IBD.

Several theories of environmental causes of IBD have been postulated, and numerous environmental risk factors have been explored. In this paper, we will summarize the current knowledge of the association between the most commonly studied environmental exposures and IBD development.

## Hygiene Hypothesis (Table 1)

Multiple theories have been proposed to explain the unknown environmental exposures that may interact with the immune system and result in an abnormal inflammatory response to intestinal microflora.<sup>10</sup> The most predominant theory is the hygiene hypothesis. This hypothesis proposes that the rising frequency of immunologic disorders can be attributed to a lack of childhood exposure to enteric pathogens.<sup>5,11</sup> Improved sanitation and hygiene, along with decreased exposure to enteric organisms during early childhood, may lead to a greater susceptibility to develop an inappropriate immunologic response upon exposure to new antigens (eg, a gastrointestinal infection) later in life.<sup>12</sup> Many factors have been examined as proxy markers of environmental exposures in early life, including *Helicobacter pylori* infection, family size, sibship, birth order, urban upbringing, and pet exposure.<sup>10,13-15</sup>

### *Helicobacter pylori*

*H. pylori* is an infection often acquired early in childhood. Colonization has been correlated to sibship size, household crowding, and poor sanitary facilities.<sup>16</sup> IBD is more prevalent in developed nations where *H. pylori* infection is less common.<sup>17</sup> A meta-analysis of 23 studies concluded that *H. pylori* infection was negatively associated with both CD and UC.<sup>17</sup> Furthermore, colonization may protect against other immune conditions such as asthma.<sup>17</sup> *H. pylori* infection may protect against the development of IBD by increasing the expression of genes (eg, *FOXP3*) that are involved in T-regulatory cell function.<sup>17</sup> However, reduced colonization of *H. pylori* in IBD patients may be secondary to antibiotic and mesalamine use,<sup>18</sup> which could eradicate *H. pylori* infection in some IBD patients.

### Family Size, Sibship, and Birth Order

Individuals raised with fewer siblings may have fewer opportunities to acquire the enteric infections during childhood that are necessary to program the immune system of the gut to respond appropriately to bowel infections later in life.<sup>12,18</sup> In one population-based study, CD patients were shown to live in smaller households and with fewer siblings<sup>15</sup>; however, similar results were not

found for UC.<sup>15</sup> Other studies have demonstrated that IBD patients were raised with a greater number of older siblings than control patients<sup>18</sup> and that the number of older siblings conferred an incremental increased risk of developing UC.<sup>19</sup> Lower birth rank was associated with an increased risk of both CD and UC.<sup>20</sup>

### Urban Environment

Children raised in urban societies tend to have a more “hygienic” upbringing than those living in rural locations (eg, on a farm). Differences in lifestyles and environmental exposures (eg, diet) in urban versus rural areas may contribute to the higher occurrence of IBD in urban areas.<sup>21</sup> Several observational studies have shown an increase in UC and CD incidence in more densely populated areas.<sup>22-27</sup> Numerous studies, however, have failed to find any association between urban exposure and IBD. A population-based case-control study,<sup>28</sup> as well as a later study conducted by Malekzadeh and associates,<sup>29</sup> failed to find a relationship between urban environment and either CD or UC. Further complicating the understanding of this relationship is a case-control study in the United Kingdom that found an inverse relationship between urban environment and CD but no relationship with UC.<sup>16</sup> These findings are supported by a study in France that used spatial analysis to show that CD was more common in periurban and rural areas.<sup>30</sup>

### Other Childhood Factors

Other factors that support the hygiene hypothesis include a decreased risk of IBD associated with living on a farm, drinking unpasteurized milk, and housing density, though these findings were more commonly reported in CD compared to UC.<sup>13-15</sup> CD was more than 3-fold more common among those whose childhood homes had a hot-water tap and a separate bathroom.<sup>12</sup> Additionally, CD patients diagnosed in adulthood have been shown to be significantly less likely to have lived with pet cats before 5 years of age<sup>15</sup>; however, exposure to cats in early life was shown to be a risk factor in pediatric-onset CD.<sup>14</sup>

## Specific Risk Factors for Inflammatory Bowel Disease (Table 1)

Numerous environmental risk factors of IBD have been explored, including smoking, oral contraceptive pills (OCPs), appendectomy, diet, breastfeeding, and nonsteroidal anti-inflammatory drugs (NSAIDs); however, none of these factors completely explain the environmental determinants of IBD.

### Smoking

A paradoxical relationship has been consistently demonstrated between smoking and IBD. A meta-analysis

concluded that active smokers were less likely to develop UC compared to individuals who were never smokers or ex-smokers; in contrast, active smokers, followed by ex-smokers, were at an increased risk for acquiring CD.<sup>31</sup> A dose-response relationship between smoke exposure and IBD has been described.<sup>32,34</sup> The exact mechanisms by which smoking influences the development of IBD are unknown. Nicotinic acetylcholine receptors (nAChRs) are present in mucosal epithelial cells of the bowel.<sup>35,36</sup> The expression of nAChRs has also been found on T cells, indicating that nicotine may directly regulate T-cell function.<sup>37</sup> However, clinical trials of nicotine replacement in UC have yielded only a modest benefit at best; thus, nicotine alone may not be the driving factor.<sup>35</sup> Other proposed mechanisms have included modulating cellular immunity,<sup>38</sup> altering cytokine levels,<sup>39</sup> modifying colonic mucus production,<sup>40</sup> and predisposing patients to microvascular thrombi.<sup>35,41</sup> Although the relationship between smoking and IBD is well documented, a paradox exists in that the highest incidence of smoking is found in countries with the lowest incidence of IBD. For example, the incidence of IBD is higher in Canada<sup>42</sup> compared to South Korea<sup>43</sup>; however, the prevalence of smoking in Canada (22%)<sup>44,45</sup> is lower than in South Korea (65%).<sup>45</sup>

A similar relationship has also been proposed with passive smoke exposure.<sup>32,34</sup> However, a meta-analysis did not demonstrate an association for childhood passive smoke exposure or prenatal smoke exposure.<sup>32</sup> A possible explanation for these findings could be the presence of a dose-response relationship between smoking and IBD,<sup>32</sup> in which passive smoking may represent a lower level of exposure, leading to nonsignificant associations.<sup>32</sup>

### Oral Contraceptive Pills

In 1995, a meta-analysis of 2 cohort studies and 7 case-control studies suggested that OCPs may marginally increase the risk of developing CD, but not UC.<sup>46</sup> This paper was limited by small sample sizes, and only 1 of the 9 included studies had a significant association. Additionally, the meta-analysis did not investigate a dose-response effect, as the majority of studies were performed before the introduction of lower OCP estrogen preparations.<sup>47</sup> A meta-analysis conducted in 2008 demonstrated a positive association for both UC and CD.<sup>47</sup> The risk of CD increased with prolonged exposure to OCPs, and its effect was reversed after the medication was discontinued.<sup>47</sup> Furthermore, upon investigating the potential for a dose-response effect, a reduction in the estrogen dose did not reduce the risk of CD; however, due to the limitations of the small sample size, similar investigations were not performed for UC.<sup>47</sup>

OCPs may increase the risk of developing IBD through the effects of estrogen. Estrogen acts as an

**Table 1.** Environmental Risk Factors for Inflammatory Bowel Disease

Risk factor	Ulcerative colitis	Crohn's disease
<b>Smoking</b>		
Current smoker	–	+
Ex-smoker	+	+
Never a smoker	+	–
Passive smoking: prenatal	Null?	Null?
Passive smoking: childhood	Null	Null
<b>Appendectomy</b>	–	?+
<b>Oral contraceptive pills</b>	+	+
<b>Diet</b>		
Sugars	?+	?+
Fats	?+	?+
Fruits and vegetables	?–	?–
Fiber	Null	?–
<b>Breastfeeding</b>	–	–
<b>Infections/vaccinations</b>		
<i>Mycobacterium avium paratuberculosis</i>	Null	?+
Measles infection	?Null	?Null
Measles vaccination	?Null	?Null
Adherent invasive <i>Escherichia coli</i>	?Null	?+
Psychrotrophic bacteria	?Null	?+
Perinatal infections	?+	?+
<b>Antibiotics</b>	?+	?+
<b>Nonsteroidal anti-inflammatory drugs</b>	?+	?+
<b>Proxy measures of hygiene hypothesis</b>		
<i>Helicobacter pylori</i>	?–	?–
Family size	?–	?–
Sibship	?–	?–
Birth order	?+	?+
Urban environment	?+	?+
Pets	?–	?–
Helminths	?–	?–
<b>Prior gastroenteritis</b>	?+	?+

immune enhancer, particularly in regard to humoral immunity and the proliferation of macrophages, whereas progesterone acts as an immune-suppressor.<sup>48</sup> 17-beta estradiol may effect tumor necrosis factor secretion and CD16 expression by macrophages.<sup>48</sup> Alternatively, estrogen may play a pathogenic role in IBD through a process of multifocal gastrointestinal infarction due to its thrombotic potential.<sup>47</sup>

### **Appendectomy**

Appendectomy is negatively associated with the development of UC, particularly among children experiencing appendicitis before 10 years of age. Meta-analyses investigating appendectomy and UC demonstrated a significant reduction in the risk of developing UC after an appendectomy.<sup>49,50</sup> In contrast, the relationship between appendectomy and CD is less clear.<sup>51</sup> Several studies have demonstrated that appendectomy is a risk factor for CD,<sup>52-55</sup> whereas other studies have shown an inverse association<sup>56</sup> or no association.<sup>12,57-61</sup> A meta-analysis demonstrated a significant risk of CD following an appendectomy.<sup>51</sup> However, a considerable proportion of the risk of developing CD was observed within the first year following an appendectomy, a time when incipient CD may lead to undue appendectomies.<sup>51</sup> After 5 years, the risk of CD was no longer significant, suggesting that a biological association between appendectomy and the development of CD is less likely.<sup>51</sup>

The mechanism by which appendicitis protects against the development of UC is not known; however, several hypotheses have been proposed.<sup>50,62-64</sup> The appendix may act as a reservoir of enteric bacteria and may be involved in antigen sampling that regulates the immunologic response to host microflora.<sup>50,64</sup> Furthermore, IBD is characterized by a shift in the balance toward a T-helper 1 cell-mediated inflammatory response in CD and a T-helper 2 response in UC.<sup>65</sup> A study by Andersson and colleagues suggests that appendicitis is mediated by T-helper 1 cells, which may explain the inverse associations between appendicitis and UC.<sup>65</sup>

### **Diet**

Diet has been extensively studied in IBD<sup>66</sup>; however, these studies have yielded inconsistent findings.<sup>67</sup> A Japanese study found more than a 2-fold increased risk of CD following the consumption of sugars/sweeteners, sweets, fats and oils, and total fat.<sup>68</sup> Despite genetic susceptibility differences between Japan and the Western world (eg, low-prevalence *NOD2* variants in Japan), similar associations were found in North America.<sup>69</sup> In a Canadian study,<sup>69</sup> CD was associated with greater consumption of total fats, as well as monounsaturated and saturated fats; however, a negative relationship was found for carbohydrate consumption.<sup>69</sup> Similar associations have been found

between UC and monounsaturated and polyunsaturated fat consumption.<sup>70</sup> Consumption of long-chain omega-3 fatty acids has been demonstrated to play a role in IBD<sup>69</sup>; however, findings remain inconsistent, with both protective<sup>69</sup> and risk<sup>68,71</sup> associations shown. Saturated and unsaturated fats may play a role in the inflammatory response through modulation of Toll-like receptors in macrophages.<sup>72</sup> High intake of dietary fiber, including fruit and vegetable consumption, has been shown to protect from IBD<sup>3,68,69,73-75</sup>; however, findings are inconclusive, as several studies have failed to find a relationship.<sup>4,18,68</sup> The mechanism by which fruits and vegetables confer protection may be related to their ability to modify enzymes involved in clearing reactive oxygen species.<sup>69</sup> However, CD patients with underlying strictures may avoid fiber to minimize symptoms, which would result in a biased association. Overall, most dietary studies have reported inconsistent findings, which highlights the challenges of studying diet (eg, recall bias) and the complex effects of diet on IBD development.

### **Breastfeeding**

Breastfeeding, which protects infants against many other immune-mediated diseases,<sup>76</sup> may also reduce the risk of developing IBD. Although several studies support a protective role between breastfeeding and IBD,<sup>76-79</sup> other studies have failed to find an association,<sup>22,74,80</sup> while still others have shown a positive relationship.<sup>18,81</sup> A meta-analysis of 14 case-control studies found a protective role for breastfeeding in both CD and UC.<sup>76</sup> The mechanism by which breastfeeding may have a beneficial effect is likely multifactorial. Breastfeeding is important for acquiring oral tolerance to microflora and food antigens,<sup>10,76</sup> which may prevent IBD development.<sup>76</sup> Infant formula lacks lactoferrin, which is found in breastmilk<sup>10</sup> and may have antibacterial and antiviral effects,<sup>82</sup> as well as anti-inflammatory properties.<sup>82</sup> Although the meta-analysis found a negative association between breastfeeding and IBD, subsequent studies have produced conflicting evidence in which breastfeeding was found to be a significant risk factor for pediatric CD.<sup>18</sup>

### **Antibiotics**

Exposure to antibiotics in childhood is hypothesized to interfere with the normal process of developing tolerance to enteric bacteria, which may lead to IBD.<sup>83</sup> Card and coworkers demonstrated a positive association between antibiotic use and the development of CD.<sup>84</sup> This finding is supported by evidence from other studies demonstrating a similar relationship.<sup>74,83</sup>

### **Nonsteroidal Anti-Inflammatory Drugs**

A case-control study by Felder and colleagues investigating the effects of NSAIDs on IBD found a positive

association for both UC and CD.<sup>85</sup> NSAIDs can cause damage to the intestinal mucosa of the stomach, small bowel, and colon.<sup>85,86</sup> NSAIDs can also increase intestinal permeability by inhibiting cyclooxygenase, which reduces prostaglandin production.<sup>85,86</sup> Inhibition of prostaglandins has been implicated in IBD due to immunoregulatory effects,<sup>87</sup> particularly through the inhibition of tumor necrosis factor and the induction of anti-inflammatory cytokines such as interleukin (IL)-10.<sup>87</sup>

## Microorganisms

Many microorganisms have been considered as possible causes of IBD. Several candidate organisms have been proposed in the pathogenesis of IBD, including *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the measles virus, and adherent-invasive strains of *Escherichia coli* (AIEC).

### *Mycobacterium avium paratuberculosis*

MAP has been postulated to cause CD due to the similarities between Johne's disease and CD.<sup>3</sup> Johne's disease manifests as a granulomatous ileitis in ruminants and is caused by MAP.<sup>88</sup> The transmission of MAP from infected animals to humans occurs through a variety of sources, including fecal shedding, contaminated raw meat, and consumption of raw milk.<sup>5</sup> Isolation of MAP in CD is inconsistent,<sup>89-94</sup> which is likely due to differences in methodologies. A study by Graham and colleagues<sup>95</sup> did not identify a relationship between the presence of *Mycobacterium* and CD; however, as MAP is slow-growing and does not thrive in standard culture conditions, use of this method may make detection of MAP difficult.<sup>96</sup> Using both polymerase chain reaction (PCR) and culture to test for MAP, Naser and associates<sup>94</sup> detected MAP in 46% of CD cases, 45% of UC cases, and 20% of controls. A study using a laser capture microscope to isolate subepithelial granulomas detected MAP DNA in 40% of examined CD cases and 0% of controls.<sup>96</sup> Another study using human intestinal mucosal biopsy specimens detected MAP in 92% of patients with CD and 26% of controls.<sup>97</sup> However, using PCR techniques, Bernstein and coworkers<sup>92</sup> did not identify a significant difference in MAP in biopsy samples between CD, UC, and healthy controls. Furthermore, a population-based matched case-control study demonstrated no differences in the rates of serology for MAP between CD, UC, and randomly sampled controls.<sup>93</sup> A meta-analysis of 28 case-control studies investigating the relationship between MAP and CD found a positive association when either enzyme-linked immunosorbent assay (ELISA) or PCR techniques were used to detect infection.<sup>98</sup> This meta-analysis included only ELISA and PCR studies, excluding studies conducted through

culture methods. PCR studies primarily use the target sequence IS900 to detect MAP; however, this sequence can be found in other mycobacteria, resulting in reduced specificity of this technique.<sup>99</sup>

The presence of MAP in a subset of CD patients may indicate that MAP infection results in CD; alternatively, the development of CD may predispose benign colonization of MAP. Furthermore, CD occurs more commonly in urban centers. In contrast, rural regions and farmers have greater exposure to MAP, but increased rates of CD have not been observed in these populations. Treatment of MAP was not associated with long-term remission in a large double-blinded, placebo-controlled trial.<sup>100</sup> Furthermore, immune suppression has not been associated with widespread MAP infections, as observed with the use of biologics and tuberculosis. Consequently, the exact relationship between MAP and CD remains elusive.

### *Measles Virus*

Paramyxoviral infection, particularly from the measles virus, has been explored in the pathogenesis of IBD.<sup>10</sup> The measles virus may persist in the mesenteric microvascular endothelium, leading to a chronic granulomatous vasculitis consistent with CD.<sup>101,102</sup> The measles virus has been identified in the endothelium, lymphocytes, and macrophages of inflammatory foci in CD patients that were not found in controls.<sup>101,102</sup> However, other studies have failed to confirm these findings using PCR techniques.<sup>103-105</sup> Epidemiologic studies have investigated this relationship, with similar inconsistencies. Ekbohm and associates<sup>106,107</sup> reported an association between both prenatal and in-utero exposure to measles and CD later in life. However, subsequent studies have failed to find similar results.<sup>108-111</sup> The live attenuated measles vaccine has also been explored as a risk factor for IBD. Although one study demonstrated a relationship between the measles vaccine and IBD,<sup>112</sup> this association has not been reproduced in subsequent studies.<sup>113-115</sup> Consequently, the available evidence does not support an association between IBD and measles infection or measles-containing vaccination.

### *Helminths*

IBD manifests in societies with reduced infestation of helminths. For the most part, the prevalence of IBD is inversely associated with the prevalence of helminth colonization. Helminths are thought to play an important immunoregulatory role with the intestinal flora.<sup>10,116</sup> Furthermore, open-label clinical trials of helminth treatment have shown a potential benefit for both UC and CD, which is likely secondary to the ability of the parasite to upregulate immunoregulatory Th2 cytokines (eg, IL-10, IL-4).<sup>117-119</sup>



### Other Microorganisms

Several theories have proposed that IBD develops through dysbiosis between harmful and protective bacteria. Individuals diagnosed with an acute gastroenteritis have been shown to subsequently have an increased risk of developing IBD.<sup>120</sup> Pathogenic bacteria that cause gastroenteritis (such as *Salmonella* and *Campylobacter*) may play a role in the etiology of IBD.<sup>121</sup> AIEC has been shown to be specific for ileal CD and can invade intestinal epithelial cells and replicate within macrophages.<sup>122</sup> CD patients with *NOD2* variants, which predispose them to ileal CD, have been shown to have a reduced cytokine response to AIEC.<sup>123</sup> Defects in autophagy (eg, the *ATG16L* gene) may impair clearance of AIEC, leading to CD.<sup>124</sup> Alternatively, increased utilization of refrigeration (ie, cold chain hypothesis) has allowed psychotropic bacteria such as *Listeria monocytogenes* and *Yersinia enterocolitica* to thrive in modern societies. Exposure to these organisms has been theorized to increase the risk of developing IBD.<sup>10,116</sup> *Candida albicans*, a pro-inflammatory opportunistic pathogen, has been proposed to play a role in IBD; however, findings remain inconsistent.<sup>125-127</sup> This is likely due to the differing techniques used to detect the fungus (eg, ELISA, PCR) and the inherent challenges with these methods.

### Stress

Psychological stress has been suggested to play a role in the etiology and pathogenesis of IBD due to the chronic, relapsing, and remitting nature of this disease.<sup>128,129</sup> Both chronic and acute stress can alter immune function.<sup>128</sup> Results from observational studies have been inconsistent, with findings supporting both positive and null associations.<sup>128,129</sup> However, due to the retrospective nature of these studies, recall bias may have influenced the results.<sup>128</sup> Evidence from animal models indicates that chronic psychological stress may exacerbate IBD by promoting damage to the intestinal mucosa, thereby impeding barrier function.<sup>130,131</sup>

### Summary

Despite years of investigation, the environmental risk factors that have been identified have not explained the pathogenesis of IBD. Several environmental factors, such as smoking, appendicitis, OCPs, diet, breastfeeding, infections/vaccinations, antibiotics, helminths, and childhood hygiene, have been implicated in the increased worldwide incidence of IBD. However, even the most consistently demonstrated environmental risk factor, smoking, contributes only partially to disease pathogenesis (ie, most smokers do not have CD and most CD patients do not

smoke). Thus, further studies are necessary to better understand the environmental determinants of IBD.

### References

- Jess T, Riis L, Jespersgaard C, et al. Disease concordance, zygosity, and NOD2/CARD15 status: follow-up of a population-based cohort of Danish twins with inflammatory bowel disease. *Am J Gastroenterol*. 2005;100:2486-2492.
- Gaya DR, Russell RK, Nimmo ER, Satsangi J. New genes in inflammatory bowel disease: lessons for complex diseases? *Lancet*. 2006;367:1271-1284.
- Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126:1504-1517.
- 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 [see comment]. *Inflamm Bowel Dis*. 2006;12:925-933.
- Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. *Gut*. 2008;57:1185-1191.
- Mikhailov TA, Furner SE. Breastfeeding and genetic factors in the etiology of inflammatory bowel disease in children. *World J Gastroenterol*. 2009;15:270-279.
- Danese S, Sans M, Fiocchi C. Inflammatory bowel disease: the role of environmental factors. *Autoimmun Rev*. 2004;3:394-400.
- Zheng JJ, Zhu XS, Huangfu Z, Gao ZX, Guo ZR, Wang Z. Crohn's disease in mainland China: a systematic analysis of 50 years of research. *Chin J Dig Dis*. 2005;6:175-181.
- Desai HG, Gupte PA. Increasing incidence of Crohn's disease in India: is it related to improved sanitation? *Indian J Gastroenterol*. 2005;24:23-24.
- Koloski N-A, Bret L, Radford-Smith G. Hygiene hypothesis in inflammatory bowel disease: a critical review of the literature. *World J Gastroenterol*. 2008;14:165-173.
- Shanahan F, Bernstein CN. The evolving epidemiology of inflammatory bowel disease. *Curr Opin Gastroenterol*. 2009;25:301-305.
- Gent AE, Hellier MD, Grace RH, Swarbrick ET, Coggon D. Inflammatory bowel disease and domestic hygiene in infancy [see comment]. *Lancet*. 1994;343:766-767.
- Lashner BA, Loftus EV Jr. True or false? The hygiene hypothesis for Crohn's disease. *Am J Gastroenterol*. 2006;101:1003-1004.
- Amre DK, Lambrette P, Law L, et al. Investigating the hygiene hypothesis as a risk factor in pediatric onset Crohn's disease: a case-control study. *Am J Gastroenterol*. 2006;101:1005-1011.
- Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD [see comment]. *Am J Gastroenterol*. 2006;101:993-1002.
- Feeney MA, Murphy F, Clegg AJ, Trebble TM, Sharer NM, Snook JA. A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2002;14:529-534.
- Luther J, Dave M, Higgins PDR, Kao JY. Association between *Helicobacter pylori* infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. *Inflamm Bowel Dis*. 2009 Sep 16. [Epub ahead of print].
- Baron S, Turck D, Leplat C, et al. Environmental risk factors in paediatric inflammatory bowel diseases: a population-based case control study [see comment]. *Gut*. 2005;54:357-363.
- Montgomery SM, Lambe M, Wakefield AJ, Pounder RE, Ekblom A. Siblings and the risk of inflammatory bowel disease. *Scand J Gastroenterol*. 2002;37:1301-1308.
- Hampe J, Heymann K, Krawczak M, Schreiber S. Association of inflammatory bowel disease with indicators for childhood antigen and infection exposure. *Int J Colorectal Dis*. 2003;18:413-417.
- Powell JJ, Harvey RSJ, Ashwood P, Wolstencroft R, Gershwin ME, Thompson RPH. Immune potentiation of ultrafine dietary particles in normal subjects and patients with inflammatory bowel disease. *J Autoimmun*. 2000;14:99-105.
- Ekblom A, Adami HO, Helmick CG, Jonzon A, Zack MM. Perinatal risk factors for inflammatory bowel disease: a case-control study. *Am J Epidemiol*. 1990;132:1111-1119.
- Klement E, Lysy J, Hoshen M, Avitan M, Goldin E, Israeli E. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. *Am J Gastroenterol*. 2008;103:1775-1782.
- Radon K. Contact with farm animals in early life and juvenile inflammatory bowel disease: A case-control study. *Pediatrics*. 2007;120:354-361.
- Wurzelmann JI, Lyles CM, Sandler RS. Childhood infections and the risk of inflammatory bowel disease. *Dig Dis Sci*. 1994;39:555-560.

26. Manousos ON, Koutroubakis I, Potamianos S, Roussomoustakaki M, Gourtsoyiannis N, Vlachonikolis IG. A prospective epidemiologic study of Crohn's disease in Heraklion, Crete. Incidence over a 5-year period. *Scand J Gastroenterol.* 1996;31:599-603.
27. Green C, Elliott L, Beaudoin C, Bernstein CN. A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues. *Am J Epidemiol.* 2006;164:615-623; discussion 624-628.
28. Bernstein CN, Blanchard JF, Rawsthorne P, Wajda A. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol.* 1999;149:916-924.
29. Malekzadeh F, Alberti C, Nouraei M, et al. Crohn's disease and early exposure to domestic refrigeration. *PLoS ONE.* 2009;4:e4288.
30. Declercq C, Gower-Rousseau C, Vernier-Massouille G, et al. Mapping of inflammatory bowel disease in northern France: spatial variations and relation to affluence. *Inflamm Bowel Dis.* 2009 Sep 22. [Epub ahead of print].
31. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci.* 1989;34:1841-1854.
32. Jones DT, Osterman MT, Bewtra M, Lewis JD. Passive smoking and inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol.* 2008;103:2382-2393.
33. Persson PG, Ahlbom A, HELLERS G. Inflammatory bowel disease and tobacco smoke—a case-control study. *Gut.* 1990;31:1377-1381.
34. Franceschi S, Panza E, La Vecchia C, Parazzini F, Decarli A, Bianchi Porro G. Nonspecific inflammatory bowel disease and smoking. *Am J Epidemiol.* 1987;125:445-452.
35. Birrenbach T, Bocker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. *Inflamm Bowel Dis.* 2004;10:848-859.
36. Richardson CE, Morgan JM, Jasani B, et al. Effect of smoking and transdermal nicotine on colonic nicotinic acetylcholine receptors in ulcerative colitis. *QJM.* 2003;96:57-65.
37. Razani-Boroujerdi S, Boyd RT, Davila-Garcia MI, et al. T cells express [alpha]7-nicotinic acetylcholine receptor subunits that require a functional TCR and leukocyte-specific protein tyrosine kinase for nicotine-induced Ca<sup>2+</sup> response. *J Immunol.* 2007;179:2889-2898.
38. Miller LG, Goldstein G, Murphy M, Ginns LC. Reversible alterations in immunoregulatory T cells in smoking. Analysis by monoclonal antibodies and flow cytometry. *Chest.* 1982;82:526-529.
39. Sher ME, Bank S, Greenberg R, et al. The influence of cigarette smoking on cytokine levels in patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 1999;5:73-78.
40. Cope GF, Heatley RV, Kelleher JK. Smoking and colonic mucus in ulcerative colitis. *Br Med J (Clin Res Ed).* 1986;293:481.
41. Sawyerr AM, Wakefield AJ, Hudson M, Dhillon AP, Pounder RE. Review article: the pharmacological implications of leucocyte-endothelial cell interactions in Crohn's disease. *Aliment Pharmacol Ther.* 1991;5:1-14.
42. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study [see comment][erratum appears in *Am J Gastroenterol.* 2006;101:1945]. *Am J Gastroenterol.* 2006;101:1559-1568.
43. Ouyang Q, Tandon R, Goh K-L, Ooi CJ, Ogata H, Fiocchi C. The emergence of inflammatory bowel disease in the Asian Pacific region. *Curr Opin Gastroenterol.* 2005;21:408-413.
44. Gilmore J. Report on smoking in Canada, 1985 to 2001. Statistics Canada, Catalogue 82F0077XIE. 2002. Available at: <http://www.statcan.gc.ca/pub/82f0077x/82f0077x2001001-eng.pdf>. Accessed December 27, 2009.
45. World Development Indicators database. World Bank. Available at: <http://data.worldbank.org/data-catalog>. Accessed December 27, 2009.
46. Godet PG, May GR, Sutherland LR. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut.* 1995;37:668-673.
47. Cornish JA, Tan E, Simillis C, Clark SK, Teare J, Tekkis PP. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol.* 2008;103:2394-2400.
48. Cutolo M, Capellino S, Sulli A, et al. Estrogens and autoimmune diseases. *Ann N Y Acad Sci.* 2006;1089:538-547.
49. Koutroubakis IE, Vlachonikolis IG. Appendectomy and the development of ulcerative colitis: results of a meta-analysis of published case-control studies. *Am J Gastroenterol.* 2000;95:171-176.
50. Koutroubakis IE, Vlachonikolis IG, Kouroumalis EA. Role of appendicitis and appendectomy in the pathogenesis of ulcerative colitis: a critical review. *Inflamm Bowel Dis.* 2002;8:277-286.
51. Kaplan GG, Jackson T, Sands BE, Frisch M, Andersson RE, Korzenik J. The risk of developing Crohn's disease after an appendectomy: a meta-analysis. *Am J Gastroenterol.* 2008;103:2925-2931.
52. Frisch M, Gridley G. Appendectomy in adulthood and the risk of inflammatory bowel diseases. *Scand J Gastroenterol.* 2002;37:1175-1177.
53. Kurina LM, Goldacre MJ, Yeates D, Seagroatt V. Appendectomy, tonsillectomy, and inflammatory bowel disease: a case-control record linkage study. *J Epidemiol Community Health.* 2002;56:551-554.
54. Frisch M, Johansen C, Mellemkjaer L, et al. Appendectomy and subsequent risk of inflammatory bowel diseases. *Surgery.* 2001;130:36-43.
55. Koutroubakis IE, Vlachonikolis IG, Kapsoritakis A, et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: case-controlled study in Crete. *Dis Colon Rectum.* 1999;42:225-230.
56. Radford-Smith GL, Edwards JE, Purdie DM, et al. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease [see comment]. *Gut.* 2002;51:808-813.
57. Duggan AE, Usmani I, Neal KR, Logan RF. Appendicectomy, childhood hygiene, *Helicobacter pylori* status, and risk of inflammatory bowel disease: a case control study [see comment]. *Gut.* 1998;43:494-498.
58. Reif S, Lavy A, Keter D, et al. Appendectomy is more frequent but not a risk factor in Crohn's disease while being protective in ulcerative colitis: a comparison of surgical procedures in inflammatory bowel disease [see comment]. *Am J Gastroenterol.* 2001;96:829-832.
59. Garcia Rodriguez LA, Gonzalez-Perez A, Johansson S, Wallander MA. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther.* 2005;22:309-315.
60. Russel MG, Dorant E, Brummer RJ, et al. Appendectomy and the risk of developing ulcerative colitis or Crohn's disease: results of a large case-control study. South Limburg Inflammatory Bowel Disease Study Group [see comment]. *Gastroenterology.* 1997;113:377-382.
61. Sicilia B, Lopez Miguel C, Arribas F, Lopez Zaborras J, Sierra E, Gomollon F. Environmental risk factors and Crohn's disease: a population-based, case-control study in Spain. *Dig Liver Dis.* 2001;33:762-767.
62. Mizoguchi A, Mizoguchi E, Chiba C, Bhan A. Role of appendix in the development of inflammatory bowel disease in TCR-alpha mutant mice. *J Exp Med.* 1996;184:707-715.
63. Dasso JF, Howell MD. Neonatal appendectomy impairs mucosal immunity in rabbits. *Cell Immunol.* 1997;182:29-37.
64. Mayer L, Eisenhardt D. Lack of induction of suppressor T cells by intestinal epithelial cells from patients with inflammatory bowel disease. *J Clin Invest.* 1990;86:1255-1260.
65. Andersson RE, Olaison G, Tysk C, Ekblom A. Appendectomy is followed by increased risk of Crohn's disease [see comment]. *Gastroenterology.* 2003;124:40-46.
66. Wild GE, Drozdzowski L, Tartaglia C, Clandinin MT, Thomson AB. Nutritional modulation of the inflammatory response in inflammatory bowel disease—from the molecular to the integrative to the clinical. *World J Gastroenterol.* 2007;13:1-7.
67. Riordan AM, Ruxton CH, Hunter JO. A review of associations between Crohn's disease and consumption of sugars. *Eur J Clin Nutr.* 1998;52:229-238.
68. Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. *Inflamm Bowel Dis.* 2005;11:154-163.
69. 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 [erratum appears in *Am J Gastroenterol.* 2007;102:2614]. *Am J Gastroenterol.* 2007;102:2016-2025.
70. Geerling BJ, Dagnelie PC, Badart-Smook A, Russel MG, Stockbrugger RW, Brummer RJ. Diet as a risk factor for the development of ulcerative colitis. *Am J Gastroenterol.* 2000;95:1008-1013.
71. Plat J, Mensink RP. Food components and immune function. *Curr Opin Lipidol.* 2005;16:31-37.
72. Lee JY, Zhao L, Youn HS, et al. Saturated fatty acid activates but polyunsaturated fatty acid inhibits Toll-like receptor 2 dimerized with Toll-like receptor 6 or 1. *J Biol Chem.* 2004;279:16971-16979.
73. Reif S, Klein I, Lubin F, Farbstein M, Hallak A, Gilat T. Pre-illness dietary factors in inflammatory bowel disease. *Gut.* 1997;40:754-760.
74. Gilat T, Hacohen D, Lilos P, Langman MJ. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. *Scand J Gastroenterol.* 1987;22:1009-1024.
75. Russel MG, Engels LG, Muris JW, et al. Modern life in the epidemiology of inflammatory bowel disease: a case-control study with special emphasis on nutritional factors [see comment]. *Eur J Gastroenterol Hepatol.* 1998;10:243-249.
76. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis [see comment]. *Am J Clin Nutr.* 2004;80:1342-1352.

77. Acheson ED, True Love SC. Early weaning in the aetiology of ulcerative colitis. A study of feeding in infancy in cases and controls. *Br Med J*. 1961;2:929-933.
78. Whorwell PJ, Holdstock G, Whorwell GM, Wright R. Bottle feeding, early gastroenteritis, and inflammatory bowel disease. *Br Med J*. 1979;1:382.
79. Kozletzko S, Sherman P, Corey M, Griffiths A, Smith C. Role of infant feeding practices in development of Crohn's disease in childhood. *BMJ*. 1989;298:1617-1618.
80. Kozletzko S, Griffiths A, Corey M, Smith C, Sherman P. Infant feeding practices and ulcerative colitis in childhood. *BMJ*. 1991;302:1580-1581.
81. Thompson NP, Montgomery SM, Wadsworth ME, Pounder RE, Wakefield AJ. Early determinants of inflammatory bowel disease: use of two national longitudinal birth cohorts. *Eur J Gastroenterol Hepatol*. 2000;12:25-30.
82. Brock JH. The physiology of lactoferrin. *Biochem Cell Biol*. 2002;80:1-6.
83. Hildebrand H, Malmberg P, Asklung J, Ekblom A, Montgomery SM. Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. *Scand J Gastroenterol*. 2008;43:961-966.
84. Card T, Logan RFA, Rodrigues LC, Wheeler JG. Antibiotic use and the development of Crohn's disease [see comment]. *Gut*. 2004;53:246-250.
85. Felder JB, Korelitz BI, Rajapakse R, Schwarz S, Horatagis AP, Gleim G. Effects of nonsteroidal anti-inflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol*. 2000;95:1949-1954.
86. Cipolla G, Crema F, Sacco S, Moro E, de Ponti F, Frigo G. Nonsteroidal anti-inflammatory drugs and inflammatory bowel disease: current perspectives. *Pharmacol Res*. 2002;46:1-6.
87. Berg DJ, Zhang J, Weinstock JV, et al. Rapid development of colitis in NSAID-treated IL-10-deficient mice. *Gastroenterology*. 2002;123:1527-1542.
88. Chacon O, Bermudez LE, Barletta RG. Johne's disease, inflammatory bowel disease, and Mycobacterium paratuberculosis. *Annu Rev Microbiol*. 2004;58:329-363.
89. Hermon-Taylor J. Mycobacterium avium subspecies paratuberculosis is a cause of Crohn's disease. *Gut*. 2001;49:755-757.
90. Greenstein RJ. Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease. *Lancet Infect Dis*. 2003;3:507-514.
91. Kruiningen HJV. Lack of support for a common etiology in Johne's disease of animals and Crohn's disease in humans. *Inflamm Bowel Dis*. 1999;5:183-191.
92. Bernstein CN, Nayar G, Hamel A, Blanchard JF. Study of animal-borne infections in the mucosae of patients with inflammatory bowel disease and population-based controls. *J Clin Microbiol*. 2003;41:4986-4990.
93. Bernstein CN, Blanchard JF, Rawsthorne P, Collins MT. Population-based case control study of seroprevalence of Mycobacterium paratuberculosis in patients with Crohn's disease and ulcerative colitis. *J Clin Microbiol*. 2004;42:1129-1135.
94. Naser SA, Ghobrial G, Romero C, Valentine JF. Culture of Mycobacterium avium subspecies paratuberculosis from the blood of patients with Crohn's disease. *Lancet*. 2004;364:1039-1044.
95. Graham DY, Markesich DC, Yoshimura HH. Mycobacteria and inflammatory bowel disease. Results of culture. *Gastroenterology*. 1987;92:436-442.
96. Ryan P, Bennett MW, Aarons S, et al. PCR detection of Mycobacterium paratuberculosis in Crohn's disease granulomas isolated by laser capture microdissection. *Gut*. 2002;51:665-670.
97. Bull TJ, McMinn EJ, Sidi-Boumedine K, et al. Detection and verification of Mycobacterium avium subsp. paratuberculosis in fresh ileocolonic mucosal biopsy specimens from individuals with and without Crohn's disease. *J Clin Microbiol*. 2003;41:2915-2923.
98. Feller M, Huwiler K, Stephan R, et al. Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis [see comment]. *Lancet Infect Dis*. 2007;7:607-613.
99. Quirke P. Mycobacterium avium subspecies paratuberculosis is a cause of Crohn's disease. *Gut*. 2001;49:757-760.
100. Selby W, Pavli P, Crotty B, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology*. 2007;132:2313-2319.
101. Wakefield AJ, Ekblom A, Dhillon AP, Pittilo RM, Pounder RE. Crohn's disease: pathogenesis and persistent measles virus infection. *Gastroenterology*. 1995;108:911-916.
102. Wakefield AJ, Pittilo RM, Sim R, et al. Evidence of persistent measles virus infection in Crohn's disease. *J Med Virol*. 1993;39:345-353.
103. Chadwick N, Bruce IJ, Schepelmann S, Pounder RE, Wakefield AJ. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcription followed by the polymerase chain reaction. *J Med Virol*. 1998;55:305-311.
104. Haga Y, Funakoshi O, Kuroe K, et al. Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction [see comment]. *Gut*. 1996;38:211-215.
105. Lizuka M, Nakagomi O, Chiba M, Ueda S, Masamune O. Absence of measles virus in Crohn's disease. *Lancet*. 1995;345:199.
106. Ekblom A, Daszak P, Kraaz W, Wakefield AJ. Crohn's disease after in-utero measles virus exposure [see comment]. *Lancet*. 1996;348:515-517.
107. Ekblom A, Wakefield AJ, Zack M, Adami HO. Perinatal measles infection and subsequent Crohn's disease [see comment]. *Lancet*. 1994;344:508-510.
108. 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.
109. Jones P, Fine P, Piracha S. Crohn's disease and measles [comment]. *Lancet*. 1997;349:473.
110. Pardi DS, Tremaine WJ, Sandborn WJ, Loftus EV Jr, Poland GA, Melton LJ 3rd. Perinatal exposure to measles virus is not associated with the development of inflammatory bowel disease. *Inflamm Bowel Dis*. 1999;5:104-106.
111. Nielsen LLW, Nielsen NM, Melbye M, Sodermann M, Jacobsen M, Aaby P. Exposure to measles in utero and Crohn's disease: Danish register study. *BMJ*. 1998;316:196-197.
112. Thompson NP, Pounder RE, Wakefield AJ, Montgomery SM. Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet*. 1995;345:1071-1074.
113. Morris DL, Montgomery SM, Thompson NP, Ebrahim S, Pounder RE, Wakefield AJ. Measles vaccination and inflammatory bowel disease: a national British cohort study. *Am J Gastroenterol*. 2000;95:3507-3512.
114. 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.
115. Feeney M, Clegg A, Winwood P, Snook J. A case-control study of measles vaccination and inflammatory bowel disease. *Lancet*. 1997;350:764-766.
116. Korzenik JR. Past and current theories of etiology of IBD: toothpaste, worms, and refrigerators. *J Clin Gastroenterol*. 2005;39(4 suppl 2):S59-65.
117. Hunter MM, McKay DM. Helminths as therapeutic agents for inflammatory bowel disease. *Aliment Pharmacol Ther*. 2004;19:167-177.
118. Summers RW, Elliott DE, Urban JF, Thompson R, Weinstock JV. Trichuris suis therapy in Crohn's disease. *Gut*. 2005;54:87-90.
119. Summers RW, Elliott DE, Urban JF, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology*. 2005;128:825-832.
120. Garcia Rodriguez LA, Ruigomez A, Panes J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology*. 2006;130:1588-1594.
121. Gradel KO, Nielsen HL, Schonheyder HC, Ejlersten T, Kristensen B, Nielsen H. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis [see comment]. *Gastroenterology*. 2009;137:495-501.
122. Darfeuille-Michaud A, Boudeau J, Bulois P, et al. High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease. *Gastroenterology*. 2004;127:412-421.
123. Peeters H, Bogaert S, Laukens D, et al. CARD15 variants determine a disturbed early response of monocytes to adherent-invasive Escherichia coli strain LF82 in Crohn's disease. *Int J Immunogenet*. 2007;34:181-191.
124. Lapaquette P, Glasser AL, Huett A, Xavier RJ, Darfeuille-Michaud A. Crohn's disease-associated adherent-invasive E. coli are selectively favoured by impaired autophagy to replicate intracellularly. *Cell Microbiol*. 2010;12:99-113.
125. Standaert-Vitse A, Sendid B, Joossens M, et al. Candida albicans colonization and ASCA in familial Crohn's disease. *Am J Gastroenterol*. 2009;104:1745-1753.
126. Kalkanci A, Tuncer C, Degertekin B, et al. Detection of Candida albicans by culture, serology and PCR in clinical specimens from patients with ulcerative colitis: re-evaluation of an old hypothesis with a new perspective. *Folia Microbiol (Praba)*. 2005;50:263-267.
127. McKenzie H, Main J, Pennington CR, Parratt D. Antibody to selected strains of Saccharomyces cerevisiae (baker's and brewer's yeast) and Candida albicans in Crohn's disease. *Gut*. 1990;31:536-538.
128. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*. 2005;54:1481-1491.
129. 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.
130. Soderholm JD, Yang P-C, Ceponis P, et al. Chronic stress induces mast cell-dependent bacterial adherence and initiates mucosal inflammation in rat intestine. *Gastroenterology*. 2002;123:1099-1108.
131. Mazzon E, Sturniolo GC, Puzzolo D, Frisina N, Fries W. Effect of stress on the paracellular barrier in the rat ileum. *Gut*. 2002;51:507-513.