生命早期的不良暴露与炎症性肠病易感性的关系

孙哲[1]，李丹[2]，郭云萍[1]，连海峰[1*]

[1]滨州医学院附属医院消化内科，山东滨州 256600；[2]滨州医学院护理学院，山东滨州 256600

[摘要] 炎症性肠病(IBD)是一组病因未明的非特异性慢性肠道炎症性疾病，包括溃疡性结肠炎(UC)和克罗恩病(CD)，发病机制复杂。近年来，IBD的发病率呈逐年上升趋势。生命早期的暴露是指胎儿期至儿童期受到的暴露，生命早期的不良暴露(如药物暴露、应激暴露、分娩方式等)可对婴儿肠道产生短期或者长期的影响，进一步影响青少年、成年甚至老年的身心健康，造成影响健康的长期效应。目前多项研究发现，生命早期的不良暴露可能通过改变肠道菌群、免疫功能、表观遗传和内脏敏感性来促进IBD的发生和发展，但其具体机制仍不明确。该文就常见的生命早期不良暴露与IBD发病风险的相关性进行综述。

[关键词] 生命早期；不良暴露；炎症性肠病

[中图分类号] R574.6 [文献标志码] A [文章编号] 0577-7402(2021)03-0311-05

[DOI] 10.11855/j.issn.0577-7402.2021.03.16

Relationship between adverse exposure in early life and susceptibility of inflammatory bowel disease

Sun Zhe[1], Li Dan[2], Guo Yun-Ping[1], Lian Hai-Feng[1*]

[1]*Department of Gastroenterology, Affiliated Hospital of Binzhou Medical University, Binzhou, Shandong 256600, China*

[2]*Nursing College, Binzhou Medical University, Binzhou, Shandong 256600,China*

[*]*Corresponding author, E-mail: lianhaifeng01@163.com*

This work was supported by the Medical and Health Technology Development Plan of Shandong Province (2018WS554)

[**Abstract**] Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is an etiology-unknown, non-specific, chronic inflammatory disorder of the intestinal tract with complex pathogenesis. Generally, patients with IBD present with repeated abdominal pain, diarrhea, mucus and blood in the stool, and even various systemic complications. More and more studies believe that it is a chronic inflammatory disease that occurs through the interaction of environment, genetics, intestinal flora, visceral sensitivity, and mental factors. In recent years, the incidence of IBD has been increasing year by year. Early-life exposure refers to the exposure from fetal period to childhood. Early-life adverse exposure (drug exposure, stress exposure, delivery methods, etc.) can have short-term or long-term effects on the intestines of infants, further affecting the physical and mental health of adolescents, adults, and even the elderly, this leads to long-term health effects. A number of studies have found that early-life adverse exposures are involved in the occurrence and progression of IBD. The occurrence of adverse exposure in early life can promote the occurrence and progression of IBD by changing the intestinal flora, immune function, epigenetic inheritance and visceral sensitivity. However, the mechanism by which early-life adverse exposure changes susceptibility to IBD remains unclear. In-depth study of the relationship between early-life adverse exposure and the occurrence of IBD can help prevent the occurrence of diseases at an early stage and reduce the burden of adulthood. This will greatly benefit the improvement of life and health and the rational use of medical resources. This article reviews the relationship between common early-life adverse exposure and the risk of IBD.

[**Key words**] early-life; adverse exposure; inflammatory bowel disease

炎症性肠病(inflammatory bowel disease，IBD)是一种易复发的慢性非特异性肠道炎症性疾病，包括溃疡性结肠炎(ulcerative colitis，UC)和克罗恩病(Crohn's disease，CD)。目前，IBD的发病机制尚不完全清楚，但越来越多的研究认为其是通过环境、遗传、肠道菌群、内脏敏感性以及精神因素等的相互作用而发生的慢性炎症性疾病[1]。生命早期的暴露是指胎儿期至儿童期受到的暴露，可对青少年甚至成年后的身心健康产生长期的影响。在生命体高度可塑阶段，生命早期的不良暴露(如药物暴露、应激暴露等)使宿主更容易感染复杂的疾病，包括IBD。然而，生命早期的不良暴露改变IBD易感性的机制尚不明确。本文就常见的生命早期不良暴露与IBD发病风险的相关性综述如下。

[基金项目] 山东省医药卫生科技发展计划(2018WS554)

[作者简介] 孙哲，硕士研究生，主要从事炎症性肠病的基础与临床研究。E-mail：m18654343063@163.com

[通信作者] 连海峰，E-mail：lianhaifeng01@163.com

1 早期抗生素使用

在儿童时期，抗生素的使用非常常见，关于幼年期抗生素使用与IBD发病风险的研究越来越多。一项Meta分析显示，与成人相比，儿童使用抗生素与IBD的关联性更高，除青霉素外，其他抗生素均与IBD的发生关系密切[2]。加拿大的一项IBD流行病学调查比较了36例IBD患者与360名健康对照者出生后第1年抗生素的使用情况，结果显示，58%的IBD患者出生后第1年使用了1种或多种抗生素，而仅39%的健康对照者出生后第1年使用了1种或多种抗生素[3]。Shaw等[4]发现，5岁前患有中耳炎(作为抗生素使用的替代指标)的儿童患IBD的概率为对照组的3倍。以上研究为早期抗生素使用增加IBD发病风险提供了进一步支持。

产后早期是肠道菌群发育最活跃的时期，肠道菌群的丰度和(或)多样性在生命前3年会发生快速且大规模的变化[5-6]。在获得像成人一样稳定的肠道菌群之前，菌群发育被破坏极易对身体健康造成不良后果[7-9]。而早期接触抗生素可改变肠道定植菌，这种改变可能伴随着潜在致病菌的过度生长，从而增加了IBD的发病风险[10-11]。肠道菌群改变可对肠道免疫系统产生间接影响[12]。健康人体中肠道优势菌群与机体免疫系统处于一种动态平衡，可有效维持肠道正常生理功能并抑制肠道疾病的发生与发展，而早期接触抗生素会导致有益菌群减少或延缓其在肠道内的定植，干扰免疫系统的成熟，导致免疫系统功能障碍，诱发易感个体发生IBD。有研究发现，给4~13日龄小鼠注射万古霉素造成早期肠道菌群失调后，成年后小鼠的内脏敏感性增加，且腰骶髓Trpv1和α-2A肾上腺素受体mRNA表达水平均降低，并最终导致脊髓的内脏疼痛信号增强，提示生命早期破坏肠道菌群可能会对内脏敏感性甚至脑-肠轴产生持续到成年的长期影响[13]。目前认为，内脏高敏感是IBD患者腹痛的主要病理生理机制。

2 早期应激事件

生命早期应激包括躯体疾病、母爱剥夺、忽视、虐待等不良经历，可影响下丘脑-垂体-肾上腺(HPA)轴的发育，增强全身免疫反应以及改变肠道菌群。

2.1 早期胃肠道感染史 早期胃肠道炎症会在肠道菌群形成的关键时期降低微生物的丰度，从而影响婴儿肠道菌群成熟，并增加IBD的发病风险[14]。有研究者建立了新生及成年大鼠的肠道炎症模型(NI和AI模型)，发现在幼年期发生过结肠炎的大鼠会通过改变表观遗传对AI造成一定影响：(1)NI致使肾上腺素、去甲肾上腺素的表达增加，诱导白介素(IL)-1β启动子的组蛋白超乙酰化，成年后大鼠再次受到炎症刺激会增加IL-1β的表达，产生放大的免疫反应[15]。(2)NI+AI组大鼠miR-155组蛋白超乙酰化，miR-155过表达会显著抑制成年大鼠肠道中E-钙黏蛋白的表达，破坏紧密连接，从而导致持续性上皮损伤，使肠道通透性增加，而肠道上皮完整性遭到破坏是IBD的一个重要易感因素[16]。(3)NI可上调蓝斑酪氨酸羟化酶，增加脑脊液中去甲肾上腺素的表达，将组蛋白乙酰转移酶(HAT)引入脑源性神经营养因子(brain-derived neurotrophic factor，BDNF)基因以增强其转录，可导致内脏高敏感[17]。Shanks等[18]发现，新生大鼠低剂量内毒素暴露史可导致HPA轴活动的长期变化，血浆皮质醇浓度持续增高，并对免疫调节产生长远影响，如增加应激对淋巴细胞增殖抑制的敏感性等。有研究者认为，免疫耐受决定疾病的易感性，而HPA轴活性决定了疾病的严重程度[19]。根据欧洲儿科胃肠病学、肝病学和营养协会(ESPGHAN)修订的标准，尽管儿童时期的结肠炎经常表现出非典型的CD或UC症状，但也被归于儿童炎症性肠病(PIBD)。国内团队阐明了儿童结肠炎与成人IBD黏膜免疫缺陷的基础都是cAMP反应缺陷导致肠道高炎症状态、$CD39^+$上皮T细胞缺乏及血小板聚集，后两者可增加内皮通透性，加重过敏反应，并且首次发现cAMP抑制剂双嘧达莫可促进黏膜愈合，改善结肠炎的预后[20]。

然而，并非所有的胃肠道感染都会增加IBD的发病风险。流行病学调查结果显示，幽门螺杆菌(*Helicobacter pylori*，Hp)感染与IBD的发病风险呈负相关[21]。在Hp流行地区的人群中，Hp感染最常发生于生命早期。因为大多数儿童感染后没有明显的临床症状，故儿童的Hp感染发病率很可能被低估。生命早期Hp感染对IBD的保护机制可能为[21-23]：(1)抗Hp抗体已被证实对随后的弯曲杆菌感染有一定的抵抗力，两种细菌之间存在抗原交叉反应，可降低发生慢性肠道炎症的可能性；(2)Hp感染的儿童与未感染的同龄儿童、Hp感染的成人相比，肠道菌群丰度显著增加，更加有助于维持肠道黏膜的完整性。

2.2 早期负性生活事件 目前研究越来越多地关注童年时期经历的负性生活事件，认为这是成年后IBD发展的重要危险因素之一，但关于早期负性生活事件与IBD发展之间的生物学联系尚知之甚少。婴儿期、儿童期及青春期是个体发育的关键时期，更容易受到各种负性压力的影响。因此，将仍未发育成熟的大肠或肠道暴露于不利的环境因素中，可

能会对个体产生长期的影响[24]。最近研究发现，成年期低社会经济地位个体炎症基因的表达会升高，而合并早期负性生活压力会进一步加重炎症反应，提示童年经历过创伤事件会进一步增加成年期低社会经济地位个体炎症性疾病的易感性[25]。Lacey等[26]认为，童年逆境可能会增高成年后C反应蛋白的水平，导致免疫系统的长期过度反应。

童年时期父母离异会使亲子关系遭到破坏，增加儿童成年后的心理痛苦，所以幼年时期的家庭模式异常与成年后IBD发生的心理社会途径有关[26-27]。另有研究表明，早期父母离异加重成年后炎症反应可能与HPA轴的变化有关，皮质醇水平长期升高会降低机体对糖皮质激素的敏感性，加剧炎症反应[27]。在经历慢性压力的人群中，压力会诱导自主神经活性增强，这可能是去甲肾上腺素水平升高导致慢性炎症的另一个机制[27-29]。

在动物模型中，母婴分离(MS)会导致HPA轴对应激的长期过度反应，中枢促肾上腺皮质激素释放激素(CRF)出现异常分泌[30-31]。有研究发现，相比对照组，MS成年大鼠更易出现内脏高敏感、排便过多、肠黏膜功能障碍、HPA轴反应增强以及焦虑样行为，而且粪便菌群也会发生显著改变[32-34]。McKernan等[35]在MS大鼠结肠黏膜中观察到Toll样受体(TLR)3、TLR4和TLR5 mRNA的表达水平明显增高，考虑与炎症性疾病的易感性有关。啮齿类动物早期负性压力会改变基因组的DNA甲基化，导致基因表达发生永久改变，CRF启动子的cAMP参与了CRF的转录激活，该区域的低甲基化会增强MS大鼠的应激反应[36]。Lennon等[24]的研究发现，MS可加重IL-10$^{-/-}$小鼠的自发性结肠炎，提示MS导致的结肠通透性增加是肠道炎症加重的关键因素。

3 分娩方式

新生儿出生标志着从无菌的胎儿环境过渡到富含各种微生物的复杂环境中，经阴道分娩的婴儿获得的新菌群类似于母亲阴道或肠道的微生物群，而剖宫产婴儿的肠道菌群包含了大量的环境细菌，因此新生儿的第一次微生物接触可能决定了出生后早期的肠道菌群[37]。因分娩方式不同导致的菌群差异可能会造成细菌相关疾病的易感性不同。产后期是婴儿建立黏膜稳定性的脆弱阶段，因此剖宫产婴儿肠道上皮表面微生物菌群的差异及菌群定植功能受损可能会在以后的生命过程中导致黏膜的炎症状态。一项Meta分析显示，剖宫产是成人及儿童CD发病的危险因素，但与UC的发病风险无关，提示CD与UC的发病机制并不相同[38]。然而，德国一项病例对照研究(收集了1096例CD患者、763例UC患者和878名健康对照者)发现，分娩方式与IBD发病无明显关联，但早产与IBD的发病有关。值得注意的是，该研究中大部分入组者出生时剖宫产并未普及，这在一定程度上反映了该研究中实际通过剖宫产分娩的参与者数量相对较少[39]。因此，为明确分娩方式与IBD易感性的关系，在接下来几十年里需要对经剖宫产出生的儿童和该队列中的IBD病例进行前瞻性研究，以得出更准确的结论。

4 母乳喂养

母体母乳中含有分泌型IgA(sIgA)，sIgA可通过强化肠上皮屏障抑制肠道内的微生物及抗原激活自身免疫。在新生儿出生10 d内，肠道固有层中几乎检测不到可以产生IgA的浆细胞，且产生IgA的浆细胞数量可能需要几年时间才能达到健康成人的水平[40]。婴儿早期sIgA由母乳提供，非母乳喂养的婴儿缺乏母体sIgA对肠道黏膜屏障的保护作用[41]。大多数学者认为，母乳喂养在免疫介导的疾病中起着重要作用[42-43]。

然而，有研究发现，母乳喂养与CD或UC发病风险的关系并不一致，多项研究均未能确定两者之间的关联性[44-46]。丹麦的一项研究发现，母乳喂养对IBD有保护作用[47]；Guo等[48]的调查结果显示母乳喂养可降低CD的手术风险；Corrao等[49]的研究发现，CD女性人群归因危险度最高的因素是婴儿期缺乏母乳喂养。

5 总结与展望

生命早期的不良暴露可通过改变肠道菌群、免疫功能、表观遗传及内脏敏感性等促进IBD的发生发展，其机制错综复杂。本文提到的生命早期不良暴露有限，未来仍需进行更多的临床试验，以及多中心、大样本、前瞻性的流行病学研究，更加细致地发掘、验证IBD的易感因素，以更好地防治IBD。

【参考文献】

[1] Lamb CA, Kennedy NA, Raine T, *et al*. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults[J]. Gut, 2019, 68(Suppl 3): s1-s106.

[2] Ungaro R, Bernstein CN, Gearry R, *et al*. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis[J]. Am J Gastroenterol, 2014, 109(11): 1728-1738.

[3] Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease[J]. Am J Gastroenterol, 2010, 105(12): 2687-2692.

[4] Shaw SY, Blanchard JF, Bernstein CN. Association between

early childhood otitis media and pediatric inflammatory bowel disease: an exploratory population-based analysis[J]. J Pediatr, 2013, 162(3): 510-514.

[5] Tun HM, Bridgman SL, Chari R, *et al*. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring[J]. JAMA Pediatr, 2018, 172(4): 368-377.

[6] Sokol H, Leducq V, Aschard H, *et al*. Fungal microbiota dysbiosis in IBD[J]. Gut, 2017, 66(6): 1039-1048.

[7] Milani C, Duranti S, Bottacini F, *et al*. The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota[J]. Microbiol Mol Biol Rev, 2017, 81(4): e00036-17.

[8] Dunn AB, Jordan S, Baker BJ, *et al*. The maternal infant microbiome: considerations for labor and birth[J]. MCN Am J Matern Child Nurs, 2017, 42(6): 318-325.

[9] Wegh CAM, Schoterman MHC, Vaughan EE, *et al*. The effect of fiber and prebiotics on children's gastrointestinal disorders and microbiome[J]. Expert Rev Gastroenterol Hepatol, 2017, 11(11): 1031-1045.

[10] Zhao Y, Zhou Y, Zhu Q, *et al*. Determination of antibiotic concentration in meconium and its association with fetal growth and development[J]. Environ Int, 2019, 123: 70-78.

[11] Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life[J]. Allergol Int, 2017, 66(4): 515-522.

[12] Lai NY, Mills K, Chiu IM. Sensory neuron regulation of gastrointestinal inflammation and bacterial host defence[J]. J Intern Med, 2017, 282(1): 5-23.

[13] O'Mahony SM, Felice VD, Nally K, *et al*. Disturbance of the gut microbiota in early-life selectively affects visceral pain in adulthood without impacting cognitive or anxiety-related behaviors in male rats[J]. Neuroscience, 2014, 277: 885-901.

[14] Sabino J, Torres J, Colombel JF, *et al*. Neonatal life events and the risk of inflammatory bowel disease[J]. Gastroenterology, 2019, 157(5): 1440-1441.

[15] Zhong XS, Winston JH, Luo X, *et al*. Neonatal colonic inflammation epigenetically aggravates epithelial inflammatory responses to injury in adult life[J]. Cell Mol Gastroenterol Hepatol, 2018, 6(1): 65-78.

[16] Kline KT, Lian H, Zhong XS, *et al*. Neonatal injury increases gut permeability by epigenetically suppressing E-cadherin in adulthood[J]. J Immunol, 2020, 204(4): 980-989.

[17] Aguirre JE, Winston JH, Sarna SK. Neonatal immune challenge followed by adult immune challenge induces epigenetic-susceptibility to aggravated visceral hypersensitivity[J]. Neurogastroenterol Motil, 2017, 29(9): e13081.

[18] Shanks N, Windle RJ, Perks PA, *et al*. Early-life exposure to endotoxin alters hypothalamic-pituitary-adrenal function and predisposition to inflammation[J]. Proc Natl Acad Sci U S A, 2000, 97(10): 5645-5650.

[19] Kubo KY, Suzuki A, Iinuma M, *et al*. Vulnerability to stress in mouse offspring is ameliorated when pregnant dams are provided a chewing stick during prenatal stress[J]. Arch Oral Biol, 2019, 97: 150-155.

[20] Huang B, Chen Z, Geng L, *et al*. Mucosal profiling of pediatric-onset colitis and IBD reveals common pathogenics and therapeutic pathways[J]. Cell, 2019, 179(5): 1160-1176.

[21] Castaño-Rodríguez N, Kaakoush NO, Lee WS, *et al*. Dual role of *Helicobacter* and *Campylobacter* species in IBD: a systematic review and meta-analysis[J]. Gut, 2017, 66(2): 235-249.

[22] Brawner KM, Kumar R, Serrano CA, *et al*. *Helicobacter pylori* infection is associated with an altered gastric microbiota in children[J]. Mucosal Immunol, 2017, 10(5): 1169-1177.

[23] Tepler A, Narula N, Peek RM Jr, *et al*. Systematic review with meta-analysis: association between *Helicobacter pylori* CagA seropositivity and odds of inflammatory bowel disease[J]. Aliment Pharmacol Ther, 2019, 50(2): 121-131.

[24] Lennon EM, Maharshak N, Elloumi H, *et al*. Early life stress triggers persistent colonic barrier dysfunction and exacerbates colitis in adult IL-$10^{-/-}$ mice[J]. Inflamm Bowel Dis, 2013, 19(4): 712-719.

[25] Levine ME, Cole SW, Weir DR, *et al*. Childhood and later life stressors and increased inflammatory gene expression at older ages[J]. Soc Sci Med, 2015, 130: 16-22.

[26] Lacey RE, Kumari M, McMunn A. Parental separation in childhood and adult inflammation: the importance of material and psychosocial pathways[J]. Psychoneuroendocrinology, 2013, 38(11): 2476-2484.

[27] Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan[J]. Brain Behav Immun, 2013, 27(1): 8-12.

[28] Slopen N, Loucks EB, Appleton AA, *et al*. Early origins of inflammation: An examination of prenatal and childhood social adversity in a prospective cohort study[J]. Psychoneuroendocrinology, 2015, 51: 403-413.

[29] Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful[J]. Immunol Res, 2014, 58(2-3): 193-210.

[30] Amini-Khoei H, Haghani-Samani E, Beigi M, *et al*. On the role of corticosterone in behavioral disorders, microbiota composition alteration and neuroimmune response in adult male mice subjected to maternal separation stress[J]. Int Immunopharmacol, 2019, 66: 242-250.

[31] Biggio F, Talani G, Locci V, *et al*. Low doses of prenatal ethanol exposure and maternal separation alter HPA axis function and ethanol consumption in adult male rats[J]. Neuropharmacology, 2018, 131: 271-281.

[32] Butkevich IP, Mikhailenko VA. Long-term effects of neonatal pain and stress on reactivity of the nociceptive system[J]. Bull Exp Biol Med, 2016, 161(6): 755-758.

[33] Rincel M, Olier M, Minni A, *et al*. Pharmacological restoration of gut barrier function in stressed neonates partially reverses long-term alterations associated with maternal separation[J]. Psychopharmacology (Berl), 2019, 236(5): 1583-1596.

[34] O'Mahony SM, Hyland NP, Dinan TG, *et al*. Maternal separation as a model of brain-gut axis dysfunction[J]. Psychopharmacology (Berl), 2011, 214(1): 71-88.

[35] McKernan DP, Nolan A, Brint EK, *et al*. Toll-like receptor mRNA expression is selectively increased in the colonic mucosa of two animal models relevant to irritable bowel syndrome[J]. PLoS One, 2009, 4(12): e8226.

[36] Chen J, Evans AN, Liu Y, *et al*. Maternal deprivation in rats is associated with corticotrophin-releasing hormone (CRH) promoter hypomethylation and enhances CRH transcriptional responses to stress in adulthood[J]. J Neuroendocrinol, 2012,

24(7): 1055-1064.

[37] Sakwinska O, Foata F, Berger B, *et al*. Does the maternal vaginal microbiota play a role in seeding the microbiota of neonatal gut and nose?[J]. Benef Microbes, 2017, 8(5): 763-778.

[38] Li Y, Tian Y, Zhu W, *et al*. Cesarean delivery and risk of inflammatory bowel disease: a systematic review and meta-analysis[J]. Scand J Gastroenterol, 2014, 49(7): 834-844.

[39] Sonntag B, Stolze B, Heinecke A, *et al*. Preterm birth but not mode of delivery is associated with an increased risk of developing inflammatory bowel disease later in life[J]. Inflamm Bowel Dis, 2007, 13(11): 1385-1390.

[40] Brugman S, Perdijk O, van Neerven RJ, *et al*. Mucosal immune development in early life: setting the stage[J]. Arch Immunol Ther Exp (Warsz), 2015, 63(4): 251-268.

[41] Renz H, Brandtzaeg P, Hornef M. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation[J]. Nat Rev Immunol, 2011, 12(1): 9-23.

[42] Oddy WH. Breastfeeding, childhood asthma, and allergic disease[J]. Ann Nutr Metab, 2017, 70(Suppl 2): 26-36.

[43] Güngör D, Nadaud P, Dreibelbis C, *et al*. Infant milk-feeding practices and diagnosed celiac disease and inflammatory bowel disease in offspring: a systematic review [J]. Am J Clin Nutr, 2019, 109(Suppl_7): 838S-851S.

[44] Khalili H, Ananthakrishnan AN, Higuchi LM, *et al*. Early life factors and risk of inflammatory bowel disease in adulthood[J]. Inflamm Bowel Dis, 2013, 19(3): 542-547.

[45] Castiglione F, Diaferia M, Morace F, *et al*. Risk factors for inflammatory bowel diseases according to the "hygiene hypothesis": a case-control, multi-centre, prospective study in Southern Italy[J]. J Crohns Colitis, 2012, 6(3): 324-329.

[46] Jakobsen C, Paerregaard A, Munkholm P, *et al*. Environmental factors and risk of developing paediatric inflammatory bowel disease - a population based study 2007-2009[J]. J Crohns Colitis, 2013, 7(1): 79-88.

[47] 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]. J Crohns Colitis, 2011, 5(6): 577-584.

[48] Guo AY, Stevens BW, Wilson RG, *et al*. Early life environment and natural history of inflammatory bowel diseases[J]. BMC Gastroenterol, 2014, 14: 216.

[49] Corrao G, Tragnone A, Caprilli R, *et al*. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC)[J]. Int J Epidemiol, 1998, 27(3): 397-404.

(收稿日期：2020-08-03；修回日期：2020-10-15)
(责任编辑：熊晓然，纪方方)