

# World Journal of *Gastrointestinal Surgery*

Monthly Volume 17 Number 3 March 27, 2025



**EDITORIAL**

Fan YH, Wang MW, Gao YN, Li WM, Jiao Y. Genetic and environmental factors influencing Crohn's disease. *World J Gastrointest Surg* 2025; 17(3): 98526 [DOI: [10.4240/wjgs.v17.i3.98526](https://doi.org/10.4240/wjgs.v17.i3.98526)]

Pandey CK, Kumar A. Perioperative neurocognitive dysfunction and role of dexmedetomidine in radical colon cancer surgery in elderly patients. *World J Gastrointest Surg* 2025; 17(3): 100126 [DOI: [10.4240/wjgs.v17.i3.100126](https://doi.org/10.4240/wjgs.v17.i3.100126)]

Wang Y, Xun X, Luan WY, Zhang Z, Xu ZX, Lin SX, Miao YD. Hyperthermia combined with opioid therapy: Enhancing cancer pain management and reducing surgical stress in gastrointestinal cancer patients. *World J Gastrointest Surg* 2025; 17(3): 101060 [DOI: [10.4240/wjgs.v17.i3.101060](https://doi.org/10.4240/wjgs.v17.i3.101060)]

Li LQ, Jiao Y. Risk and management of adverse events in minimally invasive esophagectomy. *World J Gastrointest Surg* 2025; 17(3): 103941 [DOI: [10.4240/wjgs.v17.i3.103941](https://doi.org/10.4240/wjgs.v17.i3.103941)]

**MINIREVIEWS**

Deng SS, Zhu YP, Chen ZT, Li W. Application progress of early nutrition intervention in patients with hepatocellular carcinoma after liver transplantation. *World J Gastrointest Surg* 2025; 17(3): 100321 [DOI: [10.4240/wjgs.v17.i3.100321](https://doi.org/10.4240/wjgs.v17.i3.100321)]

Feng LF, Li XW, Zhu XQ, Jin LN. Advances in management strategies for enteral nutrition-related gastric retention in adult patients with nasogastric tubes. *World J Gastrointest Surg* 2025; 17(3): 101751 [DOI: [10.4240/wjgs.v17.i3.101751](https://doi.org/10.4240/wjgs.v17.i3.101751)]

Wu L, Wu H, Mu S, Li XY, Zhen YH, Li HY. Surgical approaches for complete rectal prolapse. *World J Gastrointest Surg* 2025; 17(3): 102043 [DOI: [10.4240/wjgs.v17.i3.102043](https://doi.org/10.4240/wjgs.v17.i3.102043)]

Zhang XD, Zhang LY, Luo JL, Yu KH, Zhu KL. Neoadjuvant therapy: Dawn of reducing the high post-surgery recurrence rate of hepatocellular carcinoma. *World J Gastrointest Surg* 2025; 17(3): 103740 [DOI: [10.4240/wjgs.v17.i3.103740](https://doi.org/10.4240/wjgs.v17.i3.103740)]

**ORIGINAL ARTICLE****Retrospective Cohort Study**

Liu M, Feng B, He N, Yan R, Qin J. Efficacy of fluorouracil combined with paclitaxel and oxaliplatin for the treatment of advanced gastric signet ring cell carcinoma. *World J Gastrointest Surg* 2025; 17(3): 94286 [DOI: [10.4240/wjgs.v17.i3.94286](https://doi.org/10.4240/wjgs.v17.i3.94286)]

Zu QQ, You Y, Chen AZ, Wang XR, Zhang SH, Chen FL, Liu M. Combined application of the preclosure technique and traction approach facilitates endoscopic full-thickness resection of gastric submucosal tumors. *World J Gastrointest Surg* 2025; 17(3): 95704 [DOI: [10.4240/wjgs.v17.i3.95704](https://doi.org/10.4240/wjgs.v17.i3.95704)]

Zhao L, Wei L, Fei XL. Impact of diabetes on recovery after radical gastrectomy for gastric cancer: A retrospective cohort study. *World J Gastrointest Surg* 2025; 17(3): 100763 [DOI: [10.4240/wjgs.v17.i3.100763](https://doi.org/10.4240/wjgs.v17.i3.100763)]

Zhao SQ, Wang SY, Ge N, Guo JT, Liu X, Wang GX, Su L, Sun SY, Wang S. Endoscopic full-thickness resection vs surgical resection for gastric stromal tumors: Efficacy and safety using propensity score matching. *World J Gastrointest Surg* 2025; 17(3): 101002 [DOI: [10.4240/wjgs.v17.i3.101002](https://doi.org/10.4240/wjgs.v17.i3.101002)]

Salehi O, Gao WL, Kenfield C, Hebbard G. Roux-en-Y jejunostomy in gastroparesis: Insight into patient perspectives and outcomes. *World J Gastrointest Surg* 2025; 17(3): 102543 [DOI: 10.4240/wjgs.v17.i3.102543]

Shu Y, Li KJ, Sulayman S, Zhang ZY, Ababaik S, Wang K, Zeng XY, Chen Y, Zhao ZL. Predictive value of serum calcium ion level in patients with colorectal cancer: A retrospective cohort study. *World J Gastrointest Surg* 2025; 17(3): 102638 [DOI: 10.4240/wjgs.v17.i3.102638]

### Retrospective Study

Yu Y, Wang XQ, Liu G, Li L, Chen LN, Zhang LJ, Xia Q. Impact of a visual mobile terminal-based continuity of care model on caregiver competence of children with enterostomies. *World J Gastrointest Surg* 2025; 17(3): 99099 [DOI: 10.4240/wjgs.v17.i3.99099]

Chen DX, Fang KX, Chen SX, Hou SL, Wen GH, Yang HK, Shi DP, Lu QX, Zhai YQ, Li MY. Optimal timing of endoscopic biliary drainage for bile duct leaks: A multicenter, retrospective, clinical study. *World J Gastrointest Surg* 2025; 17(3): 99425 [DOI: 10.4240/wjgs.v17.i3.99425]

Liu LN, Chang YF, Wang H. Correlations of three scoring systems with the prognosis of patients with liver cirrhosis complicated with sepsis syndrome. *World J Gastrointest Surg* 2025; 17(3): 99570 [DOI: 10.4240/wjgs.v17.i3.99570]

Lou QX, Xu KP. Analgesic effect and safety of dexmedetomidine-assisted intravenous-inhalation combined general anesthesia in laparoscopic minimally invasive inguinal hernia surgery. *World J Gastrointest Surg* 2025; 17(3): 99597 [DOI: 10.4240/wjgs.v17.i3.99597]

Shi JH, Yang H, Wang ST, Wang WJ, Shi Y, Huang SS, Jiang S. Retrospective analysis on Lou Bei Er Chen decoction and acupuncture in gastroesophageal reflux disease post-gastric cancer surgery. *World J Gastrointest Surg* 2025; 17(3): 99626 [DOI: 10.4240/wjgs.v17.i3.99626]

Fang ZH, Hao AH, Qi YG. Imaging features and correlation with short-term prognosis in laparoscopic radical resection of colorectal cancer. *World J Gastrointest Surg* 2025; 17(3): 99782 [DOI: 10.4240/wjgs.v17.i3.99782]

Li J, Chen JP, Lai CH, Fu L, Ji Y. Efficacy of water infusion combined with defoamers in colonoscopy. *World J Gastrointest Surg* 2025; 17(3): 99784 [DOI: 10.4240/wjgs.v17.i3.99784]

Chen L, Li BX, Gan QZ, Guo RG, Chen X, Shen X, Chen Y. Enhanced recovery after surgery-based evidence-based care plus ice stimulation for thirst management in convalescent patients following digestive surgery under general anesthesia. *World J Gastrointest Surg* 2025; 17(3): 100185 [DOI: 10.4240/wjgs.v17.i3.100185]

Ni WJ, Xi YX, Zhou YC. Efficacy of combined psychological and physical nursing in preventing peripherally inserted central catheter-related thrombosis in gastric cancer patients. *World J Gastrointest Surg* 2025; 17(3): 100430 [DOI: 10.4240/wjgs.v17.i3.100430]

Yang JL, Yang YJ, Xu L. Effect of forearm and posterior wall anastomosis on gastroesophageal reflux in proximal gastrectomy patients. *World J Gastrointest Surg* 2025; 17(3): 100799 [DOI: 10.4240/wjgs.v17.i3.100799]

Li M, Yuan DH, Yang Z, Lu TX, Zhang L. Retrospective analysis of preoperative tumor marker levels in rectal cancer patients: Implications for diagnosis. *World J Gastrointest Surg* 2025; 17(3): 100820 [DOI: 10.4240/wjgs.v17.i3.100820]

Lin YM, Yu C, Xian GZ. Retrospective analysis of delta hemoglobin and bleeding-related risk factors in pancreaticoduodenectomy. *World J Gastrointest Surg* 2025; 17(3): 100999 [DOI: 10.4240/wjgs.v17.i3.100999]

Liu JR, Zhang J, Duan XL. Risk factors influencing sphincter preservation in laparoscopic radical rectal cancer surgery. *World J Gastrointest Surg* 2025; 17(3): 101061 [DOI: 10.4240/wjgs.v17.i3.101061]

Wu PH, Ta ZQ. Clinical effect and prognosis of laparoscopic surgery on colon cancer complicated with intestinal obstruction patients. *World J Gastrointest Surg* 2025; 17(3): 101609 [DOI: 10.4240/wjgs.v17.i3.101609]

Li HS, Zhang XF, Fu J, Yuan B. Efficacy of microwave ablation vs laparoscopic hepatectomy for primary small liver cancer: A comparative study. *World J Gastrointest Surg* 2025; 17(3): 101786 [DOI: 10.4240/wjgs.v17.i3.101786]

Shin DW, Cho YA, Moon SH, Kim TH, Park JW, Lee JW, Choe JY, Kim MJ, Kim SE. High cellular prion protein expression in cholangiocarcinoma: A marker for early postoperative recurrence and unfavorable prognosis. *World J Gastrointest Surg* 2025; 17(3): 101940 [DOI: 10.4240/wjgs.v17.i3.101940]

Yang QS, Zhang M, Ma CS, Teng D, Li A, Dong JD, Wang XF, Liu FB. Analysis of risk factors for bile leakage after laparoscopic exploration and primary suture of common bile duct. *World J Gastrointest Surg* 2025; 17(3): 102190 [DOI: 10.4240/wjgs.v17.i3.102190]

Lu XY, Tan XD. Clinical outcomes of interlocking main pancreatic duct-jejunal internal bridge drainage in middle pancreatectomy: A comparative study. *World J Gastrointest Surg* 2025; 17(3): 102428 [DOI: 10.4240/wjgs.v17.i3.102428]

Xiao NJ, Chu JG, Ning SB, Wei BJ, Xia ZB, Han ZY. Successful management of bleeding ectopic small bowel varices secondary to portal hypertension: A retrospective study. *World J Gastrointest Surg* 2025; 17(3): 102589 [DOI: 10.4240/wjgs.v17.i3.102589]

Hu XS, Wang Y, Pan HT, Zhu C, Zhou S, Chen SL, Liu HC, Pang Q, Jin H. Initial experience with ultrafine choledochoscopy combined with low-dose atropine for the treatment of Oddi intersphincter stones. *World J Gastrointest Surg* 2025; 17(3): 102998 [DOI: 10.4240/wjgs.v17.i3.102998]

Yuan J, Liu Q, Wu BY. Therapeutic effectiveness and influencing factors of laparoscopic appendectomy with mesoappendix dissection in the treatment of acute appendicitis. *World J Gastrointest Surg* 2025; 17(3): 103516 [DOI: 10.4240/wjgs.v17.i3.103516]

Eray IC, Topal U, Gumus S, Isiker K, Yavuz B, Aydin I. Comparative analysis of Ferguson hemorrhoidectomy combined with doppler-guided hemorrhoidal artery ligation and Ferguson hemorrhoidectomy in hemorrhoidal disease treatment. *World J Gastrointest Surg* 2025; 17(3): 103953 [DOI: 10.4240/wjgs.v17.i3.103953]

### Clinical Trials Study

Zhu LL, Shen RZ. Follow-up of elderly gastric cancer post-radical surgery: Trauma, complications, and prognosis. *World J Gastrointest Surg* 2025; 17(3): 100143 [DOI: 10.4240/wjgs.v17.i3.100143]

### Observational Study

Hu G, Ma J, Qiu WL, Mei SW, Zhuang M, Xue J, Liu JG, Tang JQ. Patient selection and operative strategies for laparoscopic intersphincter resection without diverting stoma. *World J Gastrointest Surg* 2025; 17(3): 95983 [DOI: 10.4240/wjgs.v17.i3.95983]

### Randomized Controlled Trial

Tan XQ, Huang XL. Effects of postoperative quantitative assessment strategy-based nursing in patients with colorectal cancer. *World J Gastrointest Surg* 2025; 17(3): 100302 [DOI: 10.4240/wjgs.v17.i3.100302]

### SYSTEMATIC REVIEWS

Isah AD, Wang X, Shaibu Z, Yuan X, Dang SC. Systematic review and meta-analysis comparing extraperitoneal and transperitoneal routes of colostomy-related complications. *World J Gastrointest Surg* 2025; 17(3): 98947 [DOI: 10.4240/wjgs.v17.i3.98947]

**SCIENTOMETRICS**

Wang XY, Chen HY, Sun Q, Li MH, Xu MN, Sun T, Huang ZH, Zhao DL, Li BR, Ning SB, Fan CX. Global trends and research hotspots in esophageal strictures: A bibliometric study. *World J Gastrointest Surg* 2025; 17(3): 100920 [DOI: 10.4240/wjgs.v17.i3.100920]

**CASE REPORT**

Chen JT, Li YP, Guo SQ, Huang JS, Wang YG. Nonsurgical treatment of postoperative intestinal obstruction caused by heterotopic ossification of the mesentery: A case report. *World J Gastrointest Surg* 2025; 17(3): 99015 [DOI: 10.4240/wjgs.v17.i3.99015]

Wang CD, Liu RD, Liu MJ, Song J. Lung metastasis following temporary discontinuation of lenvatinib and tislelizumab in hepatocellular carcinoma: A case report. *World J Gastrointest Surg* 2025; 17(3): 100951 [DOI: 10.4240/wjgs.v17.i3.100951]

Xu F, Kong J, Dong SY, Xu L, Wang SH, Sun WB, Gao J. Laparoscopic microwave ablation for giant cavernous hemangioma coexistent with diffuse hepatic hemangiomatosis: Two case reports. *World J Gastrointest Surg* 2025; 17(3): 101697 [DOI: 10.4240/wjgs.v17.i3.101697]

Tian ZS, Ma XP, Ruan HX, Yang Y, Zhao YL. Rare large sigmoid hamartomatous polyp in an elderly patient with atypical Peutz-Jeghers syndrome: A case report. *World J Gastrointest Surg* 2025; 17(3): 102174 [DOI: 10.4240/wjgs.v17.i3.102174]

**LETTER TO THE EDITOR**

Deng HZ, Liu YF, Zhang HW. Role of two-dimensional shear wave elastography in predicting post-hepatectomy liver failure: A step forwards in hepatic surgery. *World J Gastrointest Surg* 2025; 17(3): 98454 [DOI: 10.4240/wjgs.v17.i3.98454]

Rao AG, Nashwan AJ. Enhancing endoscopic retrograde cholangiopancreatography safety: Predictive insights into gastric retention. *World J Gastrointest Surg* 2025; 17(3): 98898 [DOI: 10.4240/wjgs.v17.i3.98898]

Munini M, Fodor M, Corradi A, Frena A. Clinical benefits and controversies of jejunostomy feeding in patients undergoing gastrectomy for gastric cancer. *World J Gastrointest Surg* 2025; 17(3): 100384 [DOI: 10.4240/wjgs.v17.i3.100384]

Pavlidis ET, Galanis IN, Pavlidis TE. Current opinions on the use of prophylactic antibiotics in patients undergoing laparoscopic cholecystectomy. *World J Gastrointest Surg* 2025; 17(3): 101938 [DOI: 10.4240/wjgs.v17.i3.101938]

Xie Y, Xie H, Wang RL. Enhancing palliative care in malignant obstructive jaundice: A critical care perspective on endoscopic biliary stenting. *World J Gastrointest Surg* 2025; 17(3): 103431 [DOI: 10.4240/wjgs.v17.i3.103431]

**ABOUT COVER**

Peer Reviewer of *World Journal of Gastrointestinal Surgery*, Adrienn Biró, MD, PhD, Assistant Professor, Surgeon, Department of Surgery, Somogy County Kaposi Mor Teaching Hospital, Kaposvár 7400, Hungary.  
b.adrienn5@gmail.com

**AIMS AND SCOPE**

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS, World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

**INDEXING/ABSTRACTING**

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGS* as 1.8; JIF without journal self cites: 1.7; 5-year JIF: 1.9; JIF Rank: 126/292 in surgery; JIF Quartile: Q2; and 5-year JIF Quartile: Q3.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Zi-Hang Xu, Production Department Director: Xiang Li, Cover Editor: Jia-Ru Fan.

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Surgery*

**ISSN**

ISSN 1948-9366 (online)

**LAUNCH DATE**

November 30, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Eva Lieto

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

**PUBLICATION DATE**

March 27, 2025

**COPYRIGHT**

© 2025 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Genetic and environmental factors influencing Crohn's disease

Ye-Hui Fan, Ming-Wei Wang, Yu-Ning Gao, Wen-Mao Li, Yan Jiao

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade B, Grade B, Grade D

**Novelty:** Grade B, Grade B, Grade C

**Creativity or Innovation:** Grade B, Grade B, Grade C

**Scientific Significance:** Grade B, Grade B, Grade C

**P-Reviewer:** Kotlyarov S; Shamseldeen AM

**Received:** June 28, 2024

**Revised:** December 14, 2024

**Accepted:** January 6, 2025

**Published online:** March 27, 2025

**Processing time:** 241 Days and 5.4 Hours



**Ye-Hui Fan**, Department of The First Operation Room, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

**Ming-Wei Wang**, Ministry of Health Key Laboratory of Radiobiology, School of Public Health of Jilin University, Changchun 130000, Jilin Province, China

**Yu-Ning Gao**, Department of Gastrointestinal Surgery, Changchun Central Hospital, Changchun 130000, Jilin Province, China

**Wen-Mao Li**, Department of Rehabilitation, The Second Hospital of Jilin University, Changchun 130000, Jilin Province, China

**Yan Jiao**, Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

**Corresponding author:** Yan Jiao, MD, PhD, Doctor, Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, The First Hospital of Jilin University, No. 1 Xinmin Street, Changchun 130021, Jilin Province, China. [lagelangri1@126.com](mailto:lagelangri1@126.com)

### Abstract

This editorial discusses Pellegrino and Gravina's essay. Crohn's disease (CD) is a complex and multifactorial disease that is influenced by a combination of genetic and environmental factors. While genetic factors play a key role in the development of the disease, environmental factors also play a significant role in influencing the risk of developing CD. By looking at present understanding of CD pathogenesis, we emphasize the important factors involved in the development of this illness, such as nucleotide-binding oligomerization domain-2, smoking, and vitamin D. Understanding the interplay between genetic and environmental factors is crucial for developing effective strategies for preventing and treating this chronic inflammatory bowel disease.

**Key Words:** Crohn's disease; Pathogenesis; Nucleotide-binding oligomerization domain-2; Smoking; Vitamin D

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** The link and complicated mechanisms between Crohn's disease (CD), nucleotide-binding oligomerization domain-2, smoking, and vitamin D is complex and poorly understood. In addition to genetic and environmental factors, the interaction between the two is also thought to play a role in the development of CD. Furthermore, the consequences of CD differ from person to person, emphasizing the importance of individual therapy. Individualized treatment, including surgery and medications, is important.

**Citation:** Fan YH, Wang MW, Gao YN, Li WM, Jiao Y. Genetic and environmental factors influencing Crohn's disease. *World J Gastrointest Surg* 2025; 17(3): 98526

**URL:** <https://www.wjgnet.com/1948-9366/full/v17/i3/98526.htm>

**DOI:** <https://dx.doi.org/10.4240/wjgs.v17.i3.98526>

## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that affects millions of individuals worldwide[1]. This debilitating condition is characterized by inflammation of the lining of the digestive tract, leading to a range of symptoms including abdominal pain, diarrhea, weight loss, and fatigue[2]. The exact cause of CD remains unknown, but it is believed to result from a complex interplay of genetic, environmental, and immune factors[3]. About 60%-70% of CD patients may experience complications such as abdominal abscess, intestinal obstruction, intestinal perforation, intestinal fistula, intestinal leakage, and gastrointestinal bleeding in the later stage, requiring one or even multiple surgical treatments[4]. A key feature of CD is dysregulation of the immune response, with an exaggerated inflammatory response to intestinal bacteria believed to play a central role in the development of the disease[5]. Genetic factors also contribute to the risk of developing CD, with certain genetic variations known to increase susceptibility to this condition[6]. Environmental factors such as diet, smoking, and the composition of the gut microbiota are also thought to play a role in triggering or exacerbating inflammation in individuals predisposed to CD[7]. The colonic bacterial composition in CD is altered compared to healthy individuals, and this dysbiosis, an imbalance in the microbial community, appears to contribute to both the onset and the exacerbation of inflammation in the gut. **Table 1** summarized the potential factors influencing CD.

## GENETIC FACTORS

Genetic factors have long been recognized as playing a key role in the development of CD. In fact, having a first-degree relative with CD can increase the risk of developing the disease by up to 20 times. Variants in the nucleotide-binding oligomerization domain-2 (*NOD2*) gene, involved in the immune response to bacteria in the gut, could increase risk of developing CD.

*NOD2* mutations are associated with some phenotypes of CD, such as fibrous stenosis or penetrating lesions[8]. *NOD2* gene deficiency leads to intestinal inflammatory gene expression and dysfunction of goblet cells in the intestinal mucosa in mice. These abnormalities are related to excessive production of kinesin by intestinal mucosal intraepithelial lymphocytes. In addition, scholars also detected an increase in the number of pro-inflammatory microorganisms *Bacteroides* in the gut. The mice with *NOD2* mutation have autophagy dysfunction and increased bacterial lipopolysaccharide, which leads to the activation of Toll like receptors, the massive release of a variety of inflammatory related factors and the waterfall like effect, and finally causes intestinal inflammatory response[9].

The identification of these genetic risk factors has helped to improve our understanding of the underlying mechanisms that drive the development of CD. For example, studies have shown that mutations in the *NOD2* gene can lead to an abnormal immune response in the gut, leading to inflammation and damage to the intestinal lining. Other genetic variants have been linked to abnormalities in the gut microbiome, the community of bacteria that live in the intestines and play a crucial role in regulating the immune system.

## GENETIC VARIANTS TO IMPROVE THE EFFECTIVENESS OF DIAGNOSIS AND TREATMENT

Over the last few decades, CD-associated genetic variants largely affect immune responses, intestinal barrier function, and microbial interactions. Variants in the *IL23R* gene, which play a crucial role in the regulation of T-cell responses, are also strongly associated with CD. The involvement of *IL23R* in immune cell regulation suggests a potential therapeutic target. *ATG16 L1* and *IRGM* are involved in autophagy, a process critical for the immune response to pathogens. Mutations in these genes can lead to impaired autophagy and contribute to CD pathogenesis. Variants in *TNF* Superfamily Member 15 have been linked to an increased risk of CD, particularly in European and Asian populations, suggesting a role in the regulation of inflammation. While genetic testing for CD is not yet routine in clinical practice, it holds potential in early diagnosis. Identifying patients at high genetic risk could enable earlier intervention, potentially altering the disease course. Moreover, genetic variants such as those affecting drug metabolism can influence a patient's

**Table 1** The potential factors influencing Crohn's disease

Pathogenesis	Factors	Description
Genetic factors	<i>NOD2</i>	<i>NOD2</i> is involved in recognizing bacterial components and activating innate immune responses. Mutations in <i>NOD2</i> are one of the most well-established genetic risk factors for CD, particularly influencing the response to intestinal bacteria
	ATG16 L1	ATG16 L1 is critical for autophagy, the process by which cells degrade and recycle components. Variants in this gene impair autophagy, which can increase susceptibility to CD by disrupting immune tolerance and promoting chronic inflammation
	TLRs	TLRs are part of the innate immune system, helping to recognize pathogens and initiate immune responses. Dysregulated TLR signaling can lead to an exaggerated immune response to gut microbiota, contributing to CD
Environmental factors	Smoking	Smoking is a well-established environmental risk factor for CD. It alters immune responses and microbiome composition, and is associated with more severe disease progression and complications, such as strictures and fistulas
	Diet	A diet high in processed foods, fats, and sugar, and low in fiber, can promote gut inflammation and dysbiosis, which may trigger or exacerbate CD. Diets rich in omega-3 fatty acids and fiber may have protective effects
	Vitamin D	Low levels of vitamin D have been associated with an increased risk of developing CD and may affect immune function. Vitamin D plays a role in regulating the immune system and maintaining the intestinal barrier
Gut microbiota	Bacteria	Dysbiosis, or an imbalance in gut bacterial composition, is linked to CD. Pathogenic bacteria like <i>Escherichia coli</i> may promote inflammation, while beneficial bacteria like <i>Faecalibacterium prausnitzii</i> have anti-inflammatory effects
	Fungi	The gut mycobiome (fungal microbiota) has been found to differ in CD patients compared to healthy controls. Dysregulated fungal populations may interact with bacteria, affecting immune responses and intestinal barrier function
	Virus	Viral infections, particularly those that affect the gut, may trigger or exacerbate CD in genetically susceptible individuals. Viruses like enteric adenoviruses and Epstein-Barr virus have been implicated in IBD pathogenesis
	Parasite	Parasitic infections may modulate immune responses, potentially either triggering or protecting against inflammation. Some studies suggest that exposure to certain parasites may be protective against CD
Immune factors	Innate immunity	Innate immunity involves the body's first line of defense, including pattern recognition receptors. Dysregulation in innate immunity leads to an inappropriate immune response to normal gut bacteria, contributing to chronic inflammation in CD
	Acquired immunity	The acquired immune response involves T cells and antibodies. In CD, an imbalance of Th1 and Th17 responses can drive inflammation, while Tregs may be insufficient to control it. Abnormal cytokine production is a key feature of CD
Non-coding RNA	miRNA	miRNAs are small RNA molecules that regulate gene expression post-transcriptionally. In CD, altered miRNA expression can affect immune cell differentiation and response, potentially contributing to inflammation and disease progression
	lncRNA	lncRNAs are involved in the regulation of gene expression, chromatin remodeling, and immune cell differentiation. Their dysregulation in CD may impact immune function and contribute to intestinal inflammation
	siRNA	siRNAs regulate gene silencing and play a role in modulating immune responses. They have been explored as potential therapeutic agents for targeting specific genes involved in CD pathogenesis
	circRNA	circRNAs are a type of non-coding RNA that form closed loops. They are involved in regulating gene expression and protein activity. In CD, altered circRNA expression may influence immune responses and gut barrier integrity

*NOD2*: Nucleotide-binding oligomerization domain-2; ATG16 L1: Autophagy related 16 like 1; TLRs: Toll-like receptors; CD: Crohn's disease; Tregs: Regulatory T cells; IBD: Inflammatory bowel disease.

response to medications and their risk of adverse effects.

## ENVIRONMENT FACTORS

Several environmental risk factors have been identified, including smoking, diet, and stress. Smoking is one of the most well-established environmental risk factors for CD, with smokers being twice as likely to develop the disease compared to non-smokers. Studies have shown that smoking can disrupt the balance of bacteria in the gut and increase inflammation, contributing to the development of CD.

Smoking as one environmental factor has long been recognized as a risk factor for several health conditions, including heart disease, lung cancer, and respiratory problems. Recently, smoking has been of particular interest in relation to CD. Several studies have suggested that smoking may have a significant impact on the development and progression of CD [10,11]. For instance, research has shown that smoking can increase the risk of developing CD in individuals with a genetic predisposition to the condition [12]. Additionally, smokers with CD may experience more severe symptoms, require more aggressive treatment, and have a higher risk of complications compared to non-smokers with the condition. Chronic smokers, particularly those who have smoked for many years, are at an increased risk of developing CD, with

studies indicating that smoking may accelerate disease onset and increase the severity of symptoms. Smoking duration and intensity are important factors in modulating disease outcomes, with heavy smokers experiencing more frequent flare-ups and complications compared to non-smokers. Both active smoking and passive exposure to tobacco smoke have been associated with increased disease risk. However, the risk is significantly higher in active smokers. While the exact mechanisms remain unclear, smoking-induced changes in the gut's immune system and microbiota are believed to play a key role in the pathogenesis of CD.

Diet is another important environmental factor that can influence the development of CD. Research has shown that a diet high in processed foods, sugar, and saturated fats can increase inflammation in the gut and disrupt the balance of bacteria, contributing to the development of the disease. In contrast, a diet high in fruits, vegetables, and fiber has been shown to reduce inflammation and promote a healthy gut microbiome, reducing the risk of developing CD.

Vitamin D plays an important role in the pathogenesis by participating in the regulation of intestinal immune function [13]. Most patients with CD are complicated with vitamin D deficiency, and the reduction of vitamin D is significantly correlated with the incidence of CD [14]. The 1,25-dihydroxyvitamin D<sub>3</sub> can significantly increase the secretion of antimicrobial peptides by Paneth cells in the intestinal mucosa through binding with vitamin D receptor, and promote the development and differentiation of regulatory T cells and type 2 helper T cells [15]. Vitamin D also affects the function of natural killer T cells and reduces the production of related cytokines such as Th17 cells. In addition, vitamin D can protect patients with CD by increasing the number and abundance of beneficial bacteria and regulating the polymorphism of bacteria in the gut [16]. And vitamin D supplementation can reduce the recurrence rate of CD. The threshold for vitamin D deficiency commonly used in clinical practice is typically below 20 ng/mL (50 nmol/L), which is consistent with the definition of deficiency from organizations like the Institute of Medicine and the Endocrine Society. Levels between 20-30 ng/mL are considered insufficient, while levels above 30 ng/mL are generally considered sufficient for bone and immune health. Most studies implicating vitamin D in CD have linked deficiency levels (under 20 ng/mL) with poorer disease outcomes, such as higher disease activity, increased flare-ups, and poorer response to treatment. Vitamin D deficiency may be associated with the development of CD [17].

There are also some other environmental factors such as smoking e-cigarettes, exposure to various food toxicants, *etc.* The use of e-cigarettes is increasingly common, and while it is considered less harmful than traditional smoking, emerging evidence suggests it may still have a detrimental effect on gut health. E-cigarette vapors contain various chemicals, such as nicotine, formaldehyde, and acrolein, which can alter the gut microbiota, increase oxidative stress, and trigger inflammatory responses. Nicotine, in particular, may exacerbate CD by promoting Th17-mediated inflammation and impairing mucosal immunity. The long-term effects of vaping on CD are not fully understood but may include the potential to exacerbate existing disease or trigger the onset in susceptible individuals. Exposure to environmental pollutants, including particulate matter (PM<sub>2.5</sub>), NO<sub>2</sub>, and O<sub>3</sub>, has been associated with an increased risk of inflammatory bowel diseases, including CD. These pollutants can promote systemic inflammation, affect the gut immune response, and disrupt the microbiome.

---

## EFFECT OF UNHEALTHY DIET, AND LIFESTYLE

Diets high in sugar, processed foods, and refined carbohydrates (*e.g.*, white bread, sugary drinks, and sweets) have been shown to promote inflammation in the body. These foods can trigger or worsen flare-ups of CD by aggravating the gut's immune response. Diets rich in unhealthy fats, particularly trans fats and saturated fats, have been linked to increased intestinal inflammation. Excess fat intake can promote the production of pro-inflammatory cytokines, which increase gut inflammation and can contribute to the severity of Crohn's symptoms.

---

## CLINICAL IMPLICATIONS

Despite these findings, the link between CD, *NOD2*, smoking, and vitamin D is complex and poorly understood. In addition to genetic and environmental factors, the interaction between the two is also thought to play a role in the development of CD. Similarly, environmental factors may influence the expression of certain genes that increase the risk of developing the disease. Furthermore, the consequences of CD differ from person to person, emphasizing the importance of individual therapy. The complicated mechanisms underlying the link between CD, *NOD2*, smoking, and vitamin D need to be studied further for therapeutic applications. Individualized management, including surgery and medicines, is significant [18].

---

## CONCLUSION

While genetic factors play a key role in the development of the disease, environmental factors also play a significant role in influencing the risk of developing CD. By looking at present understanding of CD pathogenesis, we emphasize the important factors involved in the development of this illness, such as *NOD2*, smoking, and vitamin D. Understanding the interplay between genetic and environmental factors is crucial for preventing and treating this chronic inflammatory bowel disease.

## FOOTNOTES

**Author contributions:** Jiao Y designed the overall concept and outline of the manuscript; Jan YH contributed to the discussion and design of the manuscript; Fan YH, Wang MW, Gao YN, and Li WM contributed to the writing, and editing the manuscript, illustrations, and review of literature.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**Country of origin:** China

**ORCID number:** Ye-Hui Fan 0000-0002-3041-7224; Yan Jiao 0000-0001-6914-7949.

**S-Editor:** Li L

**L-Editor:** A

**P-Editor:** Guo X

## REFERENCES

- 1 **Torres J**, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017; **389**: 1741-1755 [PMID: 27914655 DOI: 10.1016/S0140-6736(16)31711-1]
- 2 **Claytor J**, Kumar P, Ananthakrishnan AN, Colombel JF, Agrawal M, Ungaro RC. Mild Crohn's Disease: Definition and Management. *Curr Gastroenterol Rep* 2023; **25**: 45-51 [PMID: 36753033 DOI: 10.1007/s11894-023-00863-y]
- 3 **Kane SV**. Some Thoughts About Crohn's Disease. *Gastroenterol Clin North Am* 2022; **51**: xv [PMID: 35595426 DOI: 10.1016/j.gtc.2022.04.001]
- 4 **Cockburn E**, Kamal S, Chan A, Rao V, Liu T, Huang JY, Segal JP. Crohn's disease: an update. *Clin Med (Lond)* 2023; **23**: 549-557 [PMID: 38065612 DOI: 10.7861/clinmed.2023-0493]
- 5 **Leibovitz H**, Lee SH, Raygoza Garay JA, Espin-Garcia O, Xue M, Neustaeter A, Goethel A, Huynh HQ, Griffiths AM, Turner D, Madsen KL, Moayyedi P, Steinhart AH, Silverberg MS, Deslandres C, Bitton A, Mack DR, Jacobson K, Cino M, Aumais G, Bernstein CN, Panaccione R, Weiss B, Halfvarson J, Xu W, Turpin W, Croitoru K; Crohn's and Colitis Canada (CCC) Genetic, Environmental, Microbial (GEM) Project Research Consortium. Immune response and barrier dysfunction-related proteomic signatures in preclinical phase of Crohn's disease highlight earliest events of pathogenesis. *Gut* 2023; **72**: 1462-1471 [PMID: 36788016 DOI: 10.1136/gutjnl-2022-328421]
- 6 **Mills SC**, von Roon AC, Tekkis PP, Orchard TR. Crohn's disease. *BMJ Clin Evid* 2011; **2011**: 0416 [PMID: 21524318]
- 7 **Roda G**, Ng SC, Kotze PG, Argollo M, Panaccione R, Spinelli A, Kaser A, Peyrin-Biroulet L, Danese S. Author Correction: Crohn's disease. *Nat Rev Dis Primers* 2020; **6**: 51 [PMID: 32561754 DOI: 10.1038/s41572-020-0193-x]
- 8 **Ashton JJ**, Seaby EG, Beattie RM, Ennis S. NOD2 in Crohn's Disease-Unfinished Business. *J Crohns Colitis* 2023; **17**: 450-458 [PMID: 36006803 DOI: 10.1093/ecco-jcc/jjac124]
- 9 **Butera A**, Di Paola M, Pavarini L, Strati F, Pindo M, Sanchez M, Cavalieri D, Boirivant M, De Filippo C. Nod2 Deficiency in mice is Associated with Microbiota Variation Favouring the Expansion of mucosal CD4+ LAP+ Regulatory Cells. *Sci Rep* 2018; **8**: 14241 [PMID: 30250234 DOI: 10.1038/s41598-018-32583-z]
- 10 **Yamamoto T**, Keighley MR. Smoking and disease recurrence after operation for Crohn's disease. *Br J Surg* 2000; **87**: 398-404 [PMID: 10759731 DOI: 10.1046/j.1365-2168.2000.01443.x]
- 11 **Mahid SS**, Minor KS, Stevens PL, Galandiuk S. The role of smoking in Crohn's disease as defined by clinical variables. *Dig Dis Sci* 2007; **52**: 2897-2903 [PMID: 17401688 DOI: 10.1007/s10620-006-9624-0]
- 12 **Inamdar S**, Volfson A, Rosen L, Sunday S, Katz S, Sultan K. Smoking and early infliximab response in Crohn's disease: a meta-analysis. *J Crohns Colitis* 2015; **9**: 140-146 [PMID: 25518060 DOI: 10.1093/ecco-jcc/jju018]
- 13 **Rafferty T**, O'Sullivan M. Optimal vitamin D levels in Crohn's disease: a review. *Proc Nutr Soc* 2015; **74**: 56-66 [PMID: 25497215 DOI: 10.1017/S0029665114001591]
- 14 **Wallace C**, Gordon M, Sinopoulou V, Limketkai BN. Vitamin D for the treatment of inflammatory bowel disease. *Cochrane Database Syst Rev* 2023; **10**: CD011806 [PMID: 37781953 DOI: 10.1002/14651858.CD011806.pub2]
- 15 **Schardey J**, Globig AM, Janssen C, Hofmann M, Manegold P, Thimme R, Hasselblatt P. Vitamin D Inhibits Pro-Inflammatory T Cell Function in Patients With Inflammatory Bowel Disease. *J Crohns Colitis* 2019; **13**: 1546-1557 [PMID: 31051495 DOI: 10.1093/ecco-jcc/jjz090]
- 16 **Basson A**. Vitamin D and Crohn's disease in the adult patient: a review. *JPEN J Parenter Enteral Nutr* 2014; **38**: 438-458 [PMID: 24154811 DOI: 10.1177/0148607113506013]
- 17 **White JH**. Vitamin D deficiency and the pathogenesis of Crohn's disease. *J Steroid Biochem Mol Biol* 2018; **175**: 23-28 [PMID: 28025175 DOI: 10.1016/j.jsbmb.2016.12.015]
- 18 **Pellegrino R**, Gravina AG. Machine learning as a tool predicting short-term postoperative complications in Crohn's disease patients undergoing intestinal resection: What frontiers? *World J Gastrointest Surg* 2024; **16**: 2755-2759 [PMID: 39351543 DOI: 10.4240/wjgs.v16.i9.2755]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [office@baishideng.com](mailto:office@baishideng.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

