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ORIGINAL ARTICLE

Antibiotic Exposure and Risk of New-Onset Ulcerative Colitis: a Systematic Review and Meta-Analysis

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SUMMARY

Background: **Antibiotic exposure has been reported as a risk factor for the development of ulcerative colitis; however, the clinical results were controversial. Therefore, we performed a meta-analysis to evaluate the association of antibiotic exposure with the new onset of UC.**
Methods: **A comprehensive literature search for relevant studies published up to February 2024, exploring the association between antibiotic exposure and new-onset UC, was performed by using Medline and Embase, and the statistical analysis was conducted by using the Stata software.**
Results: **A total of 16 articles were included in the study, including 12 case-control studies and 4 cohort studies. The pooled analysis revealed that antibiotic exposure was associated with an increased risk of new-onset UC (summary OR = 1.28, 95% CI = 1.26 - 1.31). Subgroup analyses showed that both case-control studies and cohort studies have yielded consistent conclusions.**
Conclusions: **This meta-analysis suggests that antibiotic exposure is a risk factor for the development of UC. It is, therefore, necessary to avoid unnecessary and excessive use of antibiotics.**
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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) and has become a global health challenge over the past two decades. Although the incidence rates are stable in developed countries, they are increasing sharply in developing countries [1]. Even though the most significant risk factor for the development of UC is familial predisposition, a wide range of environmental risk factors, including antibiotic exposure, may also influence the pathogenesis of UC [2].
Recent studies have demonstrated that the frequent use of antibiotics can initiate the disruption of the gut flora and may play a role in the pathogenesis of new-onset IBD [3]. There have been a variety of observational

studies exploring the relationship between antibiotic use and new-onset IBD [4-14]; however, the role of antibiotics in the pathogenesis of IBD has not been fully clarified. While many studies have shown a positive correlation between antibiotics and IBD, a number of other studies have demonstrated no significant effect or a negative correlation; especially the association between antibiotics and UC remains conflicting. Two recent studies, a meta-analysis and a systemic review [15,16], have confirmed that antibiotic exposure is associated with Crohn's disease, but the association of antibiotic exposure with UC remained non-significant.

However, since then several large observational studies [17-21], including case-control studies and cohort studies, have been published on this topic, especially in the recent years, suggesting a positive correlation between antibiotic exposure and new-onset UC. Therefore, we conducted an exhaustive, updated meta-analysis to provide a well-powered assessment of the association of antibiotic exposure with new-onset UC.

MATERIALS AND METHODS

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. Eligible studies published up to February 2024 were retrieved by searching Medline and Embase, using the following search string: (inflammatory bowel disease or ulcerative colitis or IBD or UC) and (antibiotics or anti-bacterial or bactericidal agent or penicillin or tetracycline or fluoroquinolone or cephalosporin or metronidazole or vancomycin or doxycycline or aminoglycosides or minocycline or macrolide or sulfonamide). In addition, to avoid missing studies, the reference list of each previous systematic review and meta-analysis was also manually searched.

Study selection

Studies meeting the following inclusion criteria were included: 1) full text articles published in English; 2) case control studies or cohort studies; and 3) the odds ratios (ORs) and their 95% confidence intervals (CIs) could be retrieved or estimated from the data presented. Those reviews or systematic reviews, meta-analyses, abstracts, and those that did not provide sufficient data were excluded.

Data extraction

Two investigators worked independently to determine whether a study met the inclusion criteria and extracted the data from all the eligible studies. Disagreements were resolved by consulting a third reviewer. The following variables were recorded from each article: the name of the first author, the publication year, the country, the study type (case control study or cohort study), the odds ratio (OR) with 95% confidence intervals (95% CI), the total number of subjects, the number of subjects exposed to antibiotics, and the number of subjects newly diagnosed as UC. The quality assessment of the included articles was carried out by using the Newcastle-Ottawa scale (NOS). Two researchers conducted the quality assessment independently.

Statistical analysis

Statistical analysis was performed by using STATA 11.0 (Stata Corporation, College Station, TX, USA). The antibiotics exposure and risk of new-onset UC was assessed by pooled estimates of odds ratios (ORs) as well as the 95% CIs.

A p-value less than 0.05 was considered statistically significant. The chi-squared (χ^2) test was performed to evaluate the between-study heterogeneity. The fixed-effects model (Mantel-Haenszel) was used when there was no heterogeneity. Influence analysis was performed by omitting each study to find potential outliers. Potential publication bias was evaluated with the Begg's and the Egger's test. Subgroup analysis was conducted according to the study type (case control study or cohort study).

RESULTS

Literature search results and study characteristics

A total of 39,387 studies were retrieved from Medline and Embase, 32,100 of which were excluded after reading the titles and abstracts. After reading the full texts, 16 articles were included in the study (4 cohort studies and 12 case-control studies). The detailed literature search procedure is presented in Figure 1. The detailed baseline characteristics of the studies are summarized in Table 1.

Pooled analysis of antibiotic exposure and the risk of new-onset UC

Sixteen studies, including 12 case-control studies and 4 cohort studies, provided OR estimates for the association between the antibiotic exposure and the risk of new-onset UC. More than 71,105 cases and 1,637,904 controls were included in the analysis. The pooled analysis revealed that antibiotic exposure was associated with an increased risk of new-onset UC (summary OR = 1.28, 95% CI = 1.26 - 1.31, Figure 2). Subgroup analyses according to the study type were conducted. Both the case-control studies and the cohort studies suggested a positive correlation between the antibiotic exposure and the new-onset UC (Figure 2). A between-study heterogeneity existed in these analyses, therefore, the ORs were calculated with random-effects models.

Sensitivity analysis

An influence analysis was conducted to evaluate the influence of each individual study on the pooled OR, regarding the antibiotic exposure and the new-onset UC risk, by sequential omission of the individual study. The

Table 1. Baseline characteristics of the included studies.

Study	Year	Country	Design	UC Cases		Controls		Quality score
				Antibiotics	No antibiotics	Antibiotics	No antibiotics	
Gearry 2010	2010	New Zealand	case control	OR				7
Shaw 2010	2010	Canada	case control	3	6	139	221	7
Margolis 2010	2010	USA	cohort	68	31	57,658	36,622	8
Hviid 2011	2011	Denmark	cohort	45	22	489,946	566,565	8
Castiglione 2012	2012	Italy	case control	231	296	260	302	3
Virta 2012	2012	Finland	case control	207	155	756	692	8
Ng 2014	2014	Asia-Pacific	case control	OR				7
Niu 2016	2016	China	case control	215	256	754	1,007	6
Troelsen 2019	2019	UK	case control	417	44	1,665	179	6
Canova 2020	2020	UK	case control	27	36	320	380	8
Nguyen 2020	2020	Sweden	case control	9,364	6,587	40,707	37,642	9
Lee 2021	2021	Malaysia	case control	12	32	11	57	8
Shimodaira 2022	2022	Japan	case control	1,010	1,410	4,879	9,076	6
Jawad 2023	2023	Denmark	cohort	705	114	6,575	1,234	7
Narula 2023	2023	Canada	cohort	14	414	947	132,390	7
Oh 2023	2023	Korea	case control	43,566	5,818	210,576	36,344	6

OR means that this article only provides OR values without detailed numbers.

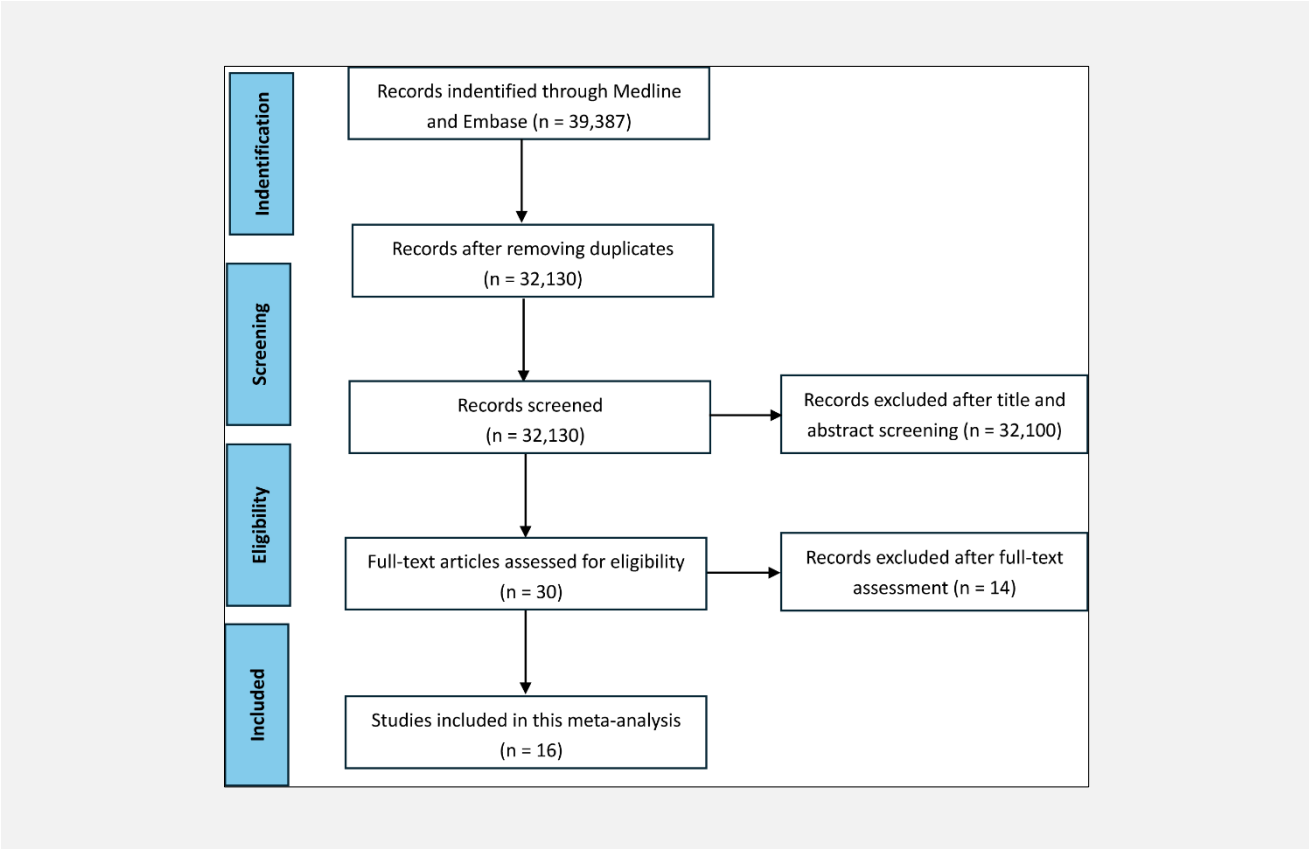

Figure 1. Flow chart for study selection.

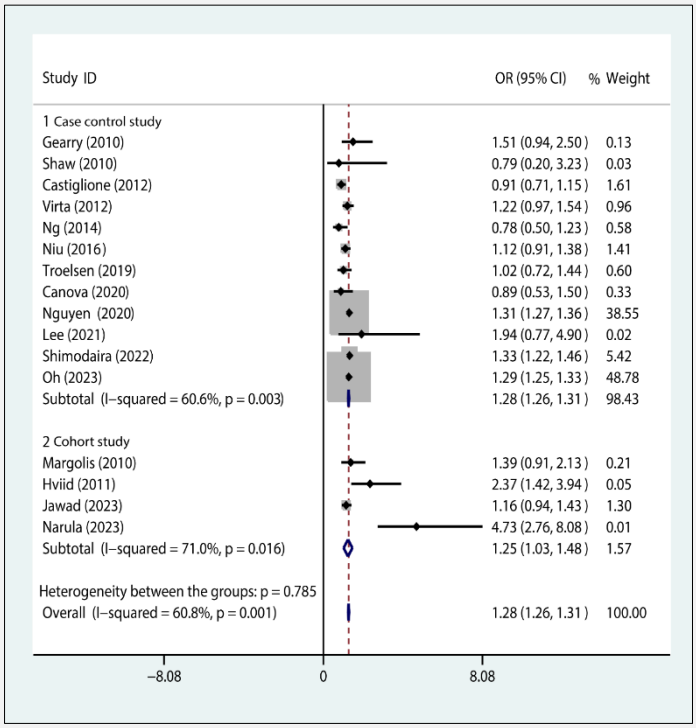

Figure 2. Forrest plots for antibiotic exposure and risk of new-onset UC.

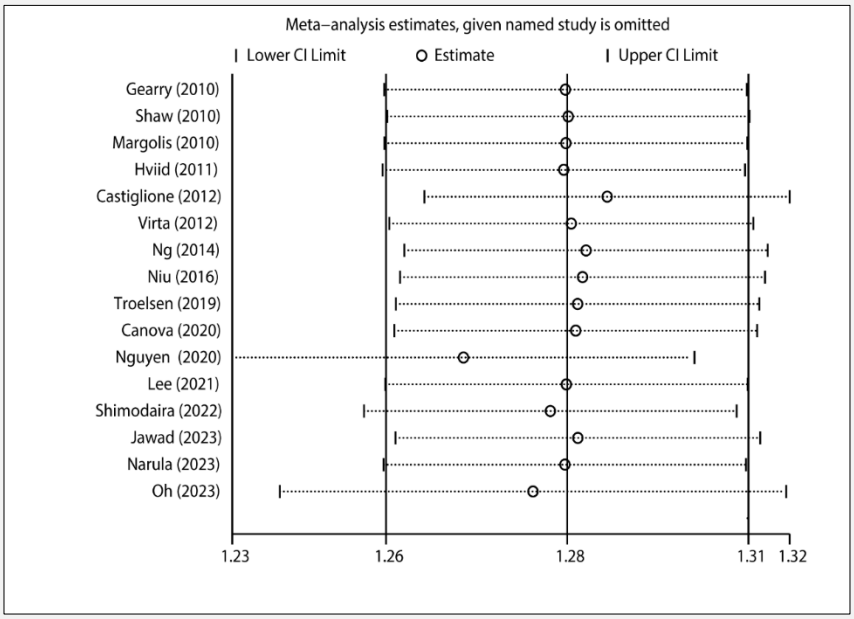

Figure 3. Influence analysis of antibiotic exposure and the risk of new-onset UC.

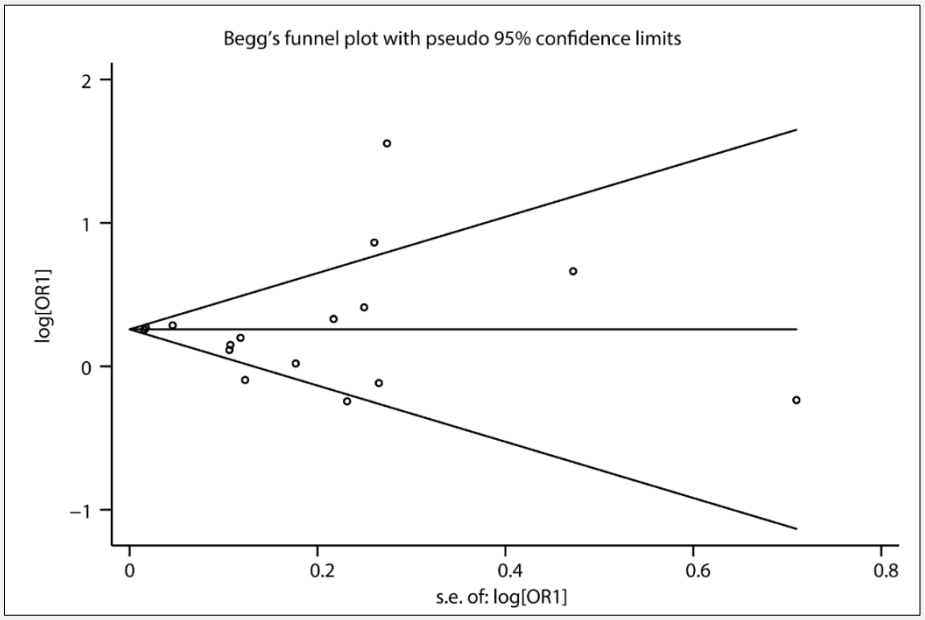

Figure 4. Begger's test for the analysis of the antibiotic exposure and risk of new-onset UC.

result showed that no individual trial could significantly affect the pooled OR (Figure 3).

Publication bias

Potential publication bias was quantitatively assessed in the analysis of the antibiotic exposure and the new-onset UC risk by Begg's and Egger's tests. The p-values assessed by both Begg's test and Egger's test were greater than 0.05 (Begg's test, p = 0.62; Egger's test, p = 0.82), indicating no potential publication bias among these studies (Figure 4).

DISCUSSION

Previous meta-analyses have found that antibiotic exposure is associated with an increased risk of new-onset IBD [15,16], but subgroup analyses have found that antibiotic exposure is only significantly associated with an increased risk of CD. Although there is an increasing trend in the increased occurrence of UC, there is no statistical significance. Our meta-analysis focuses on the relationship between antibiotic exposure and newly diagnosed UC and found that antibiotic exposure was significantly associated with an increased risk of new-onset UC. The pooled results from both the case-control studies and the cohort studies confirmed this issue.

Compared with previous meta-analyses, this meta-analysis included a number of newly published studies [17-21], and several of them have a large number of study objects, therefore, this updated meta-analysis provides a more reliable evaluation of antibiotic exposure and new-onset UC. The results from this meta-analysis must be more solid and reliable. In fact, several recent studies with a large number of study objects have provided the same results. For example, the most recent published study by Oh [21], with the largest number of study objects until now (68,633 new-onset IBD patients versus 343,165 matched controls), showed that antibiotic prescriptions significantly increased the odds of developing IBD (IBD, OR = 1.24, 95% CI:1.21 - 1.27; UC, OR = 1.26, 95% CI: 1.22 - 1.29; CD, OR = 1.18, 95% CI: 1.11 - 1.26). Another case-control study published in 2022 [18], which included 2,420 UC patients, also found an increased OR in new-onset UC in the association with antibiotic use, and the risk associated with the antibiotics was independent of the number or the type of antibiotics. The result from a newly published cohort study [20] was also consistent with this meta-analysis. Many other included studies also provided the same results as our meta-analysis.

Our robust finding provides a fundamental epidemiological basis for identifying antibiotic exposure as an environmental trigger for UC, suggesting that antibiotic use, due to a rapid change in economic growth and lifestyle, may be associated with the recent increase in the incidence of UC in the newly developing countries [23]. The effect of antibiotic exposure on the progression of

new-onset UC could be a result of alterations in the gut flora. Although there is a study that shows that gut microbiota in UC is more similar to that of healthy individuals than in CD [24], most studies believe that there is a significant change in the gut microbiota of UC patients [25,26] and that the crosstalk between microbial dysbiosis and gut mucosal immunity plays a crucial role in the occurrence of UC [27]. This is confirmed by DSS-induced experimental colitis models, which suggest that an antibiotic perturbation of the gut microbiota worsens experimental models of colitis [28].

There are several limitations to our meta-analysis. First, a between-study heterogeneity existed in the pooled analysis, presenting recall bias and under-powered studies with varying study designs. We performed subgroup analyses and sensitivity analyses to assess the high heterogeneity levels; however, no individual study could significantly affect the pooled results. Second, the frequency and the duration of the antibiotic exposure vary in each study, and the time from antibiotic exposure to the diagnosis of UC also varies. Third, due to limited data in the literature, we were unable to conduct a subgroup analysis based on the types of antibiotics. However, some literature mentions that broad-spectrum antibiotics have a greater impact on UC [19,21]. Fourth, publication bias may exist in this paper, even though the Begg's test and the Egger's test did not show it, since negative results are generally not published. Moreover, most of the studies included in our meta-analysis reported retrospective outcomes and are thus prone to recall bias.

CONCLUSION

In summary, our findings confirmed the significant role of antibiotic exposure in the newonset of UC. We suggest the careful use of antibiotics in patients with a high risk of developing UC, especially in early life. Antibiotics are a double-edged sword, our study verified that antibiotic exposure could increase the risk of developing UC. Therefore, it is necessary to avoid unnecessary and excessive use of antibiotics.

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Declaration of Interest:
The authors report no competing financial interests.

References:

1. Ananthakrishnan AN, Kaplan GG, Ng SC. Changing Global Epidemiology of Inflammatory Bowel Diseases: Sustaining Health Care Delivery Into the 21st Century. Clin Gastroenterol Hepatol 2020;18(6):1252-60. (PMID: 32007542)

2. Sun Y, Yuan S, Chen X, et al. The Contribution of Genetic Risk and Lifestyle Factors in the Development of Adult-Onset Inflammatory Bowel Disease: A Prospective Cohort Study. Am J Gastroenterol 2023;118(3):511-22. (PMID: 36695739)

3. Han A, Yang M, Chen B, et al. Microbiome and its relevance to indigenous inflammatory bowel diseases in China. Gene 2024: 909:148257. (PMID: 38367851)

4. Gearry RB, Richardson AK, Frampton CM, Dodgshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. J Gastroenterol Hepatol 2010; 25(2):325-33. (PMID: 20074146)

5. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am J Gastroenterol 2010;105(12):2687-92. (PMID: 20940708)

6. Margolis DJ, Fanelli M, Hoffstad O, Lewis JD. Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease. Am J Gastroenterol 2010;105(12):2610-6. (PMID: 20700115)

7. Hviid A, Svanstrom H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. Gut 2011;60(1):49-54. (PMID: 20966024)

8. 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 Crohns Coliti 2012;6(3):324-9. (PMID: 22405169)

9. Virta L, Auvinen A, Helenius H, Huovinen P, Kolho K-L. Association of repeated exposure to antibiotics with the development of pediatric Crohn's disease--a nationwide, register-based finnish case-control study. Am J Epidemiol 2012;175(8):775-84. (PMID: 22366379)

10. Ng SC, Tang W, Leong RW, et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. Gut 2015;64(7):1063-71. (PMID: 25217388)

11. Niu J, Miao J, Tang Y, et al. Identification of Environmental Factors Associated with Inflammatory Bowel Disease in a Southwestern Highland Region of China: A Nested Case-Control Study. PLoS One 2016;11(4):e0153524. (PMID: 27070313)

12. Troelsen FS, Jick S. Antibiotic Use in Childhood and Adolescence and Risk of Inflammatory Bowel Disease: A Case-Control Study in the UK Clinical Practice Research Datalink. Inflamm Bowel Dis 2020;26(3):440-7. (PMID: 31265060)

13. Canova C, Ludvigsson JF, Di Domenicantonio R, Zanier L, Barbiellini Amidei C, Zingone F. Perinatal and Antibiotic Exposures and the Risk of Developing Childhood-Onset Inflammatory Bowel Disease: A Nested Case-Control Study Based on a Population-Based Birth Cohort. Int J Environ Res Public Health 2020;17(7): 2409. (PMID: 32252276)

14. Nguyen LH, Ortqvist AK, Cao Y, et al. Antibiotic use and the development of inflammatory bowel disease: a national case-control study in Sweden. Lancet Gastroenterol Hepatol 2020;5(11):986-95. (PMID: 32818437)

15. Theochari NA, Stefanopoulos A, Mylonas KS, Economopoulos KP. Antibiotics exposure and risk of inflammatory bowel disease: a systematic review. Scand J Gastroenterol 2018;53(1):1-7. (PMID: 29022402)

16. Dar SH, Maniya MT, Merza N, et al. The association of antibiotic exposure with new-onset inflammatory bowel disease: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2023;47(6):102129. (PMID: 37116651)

17. Lee WS, Song ZL, Wong SY, et al. Environmental risk factors for inflammatory bowel disease: A case control study in Southeast Asian children. J Paediatr Child Health 2022;58(5):782-90. (PMID: 34761458)

18. Shimodaira Y, Watanabe K, Iijima K. The risk of antibiotics and enterocolitis for the development of inflammatory bowel disease: a Japanese administrative database analysis. Sci Rep 2022;12(1): 7604. (PMID: 35534662)

19. Jawad AB, Jansson S, Wewer V, Malham M. Early Life Oral Antibiotics Are Associated With Pediatric-Onset Inflammatory Bowel Disease-A Nationwide Study. J Pediatr Gastroenterol Nutr 2023;77(3):366-72. (PMID: 37346028)

20. Narula N, Wong ECL, Pray C, et al. Associations of Antibiotics, Hormonal Therapies, Oral Contraceptives, and Long-Term NSAIDS With Inflammatory Bowel Disease: Results From the Prospective Urban Rural Epidemiology (PURE) Study. Clin Gastroenterol Hepatol 2023;21(10): 2649-59.e16. (PMID: 36528284)

21. Oh SJ, Kim HJ, Lee CK; Big Data Research Group (BDRG) of the Korean Society of Gastroenterology. A dose-dependent increase in the risk of inflammatory bowel disease after exposure to broad-spectrum antibiotics: A national population study in Korea. Aliment Pharmacol Ther 2023;58(2):191-206. (PMID: 37154240)

22. Rethlefsen ML, Page MJ. PRISMA 2020 and PRISMA-S: common questions on tracking records and the flow diagram. J Med Libr Assoc 2022;110(2):253-7. (PMID: 35440907)

23. Singh N, Bernstein CN. Environmental risk factors for inflammatory bowel disease. United European Gastroenterol J 2022;10 (10):1047-1053. (PMID: 36262056)

24. Pittayanon R, Lau JT, Leontiadis GI, et al. Differences in Gut Microbiota in Patients With vs. Without Inflammatory Bowel Diseases: A Systematic Review. Gastroenterology 2020;158(4): 930-46.e1. (PMID: 31812509)

25. Zakerska-Banaszak O, Tomczak H, Gabryel M, et al. Dysbiosis of gut microbiota in Polish patients with ulcerative colitis: a pilot study. Sci Rep 2021;11(1):2166. (PMID: 33495479)

26. Barberio B, Facchin S, Patuzzi I, et al. A specific microbiota signature is associated to various degrees of ulcerative colitis as assessed by a machine learning approach. Gut Microbes 2022;14 (1):2028366. (PMID: 35129058)

27. Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. Lancet 2023;402(10401):571-84. (PMID: 37573077)

28. Fenneman AC, Weidner M, Chen LA, Nieuwdorp M, Blaser MJ. Antibiotics in the pathogenesis of diabetes and inflammatory diseases of the gastrointestinal tract. Nat Rev Gastroenterol Hepatol 2023;20(2):81-100. (PMID: 36258032)