Systematic Review/Meta-Analysis

Nonclostridium difficile enteric infection and the risk of developing inflammatory bowel disease: A systematic review and meta-analysis

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Abstract

Background: Inflammatory bowel disease (IBD) is a chronic inflammatory intestinal disorder. Some studies have investigated the association between non-Clostridium difficile infection (CDI) enteric infection and the risk of developing IBD with conflicting conclusions. The objective of our study was to perform a meta-analysis of available studies evaluating the possible association between non-CDI enteric infection and the risk of developing IBD.

Methods: We performed a systematic literature search of multiple online electronic databases. Inclusion criteria entailed studies about non-CDI enteric infection and IBD; A meta-analysis was conducted to evaluate relative risk (RR) and 95% confidence intervals (CIs) of combined studies for the association between non-CDI enteric infection and the risk of developing IBD. Publication bias was assessed by funnel plot analysis.

Results: Eight studies comprising 345,490 enteric infected patients, 3223 ulcerative colitis (UC) patients, and 2133 CD patients were included in the meta-analysis. Meta-analysis showed a significantly higher risk of UC in patients with enteric infection compared with noninfected patients (RR, 2.28; 95% CI, 1.85–2.8) ($I^2 = 91.3\%$, $P < 0.001$). It also showed a significantly higher risk of CD in patients with enteric infection compared with noninfected patients (RR, 1.88; 95% CI, 1.66–2.14) ($I^2 = 49\%$, $P = 0.024$).

Conclusion: Our meta-analysis has found that patients with non-CDI enteric infection were associated with an increased risk of IBD. Future studies are needed to determine the association between non-CDI enteric infection and the risk of developing IBD and elucidate the potential underlying mechanisms.

Keywords: Crohn's disease, enteric infection, inflammatory bowel disease, meta-analysis, ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic intestinal condition affecting all ages.[1,2] The disease is characterized by a remitting and relapsing course of abdominal pain, diarrhea, rectal bleeding, fever, and weight loss.[3] The highest prevalence and incidence of IBD are traditionally found in Western countries; however, during the last decades, a dramatic increase has also been observed in newly industrialized countries such as China.[4,5] IBD

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develops from a combination of genetic susceptibility and environmental factors that elicit a deleterious inflammatory response. The intestinal microbiota regulates mucosal immunity through a number of pathways, and dysbiosis is thought to be a major environmental factor in the pathogenesis and maintenance of IBD.[6-9] Among environmental factors of potential etiological importance are enteric pathogens, which have been hypothesized to trigger an already altered immune response or a defect in downregulation of the immune response, thus leading to chronic inflammation.[10]

Enteric infection is a cause of dysbiosis and is frequently identified in patients with IBD.[11] Population studies have examined the role of enteric pathogens in the development of IBD, demonstrating a possible association between enteric infections, such as Campylobacter, Salmonella, and Escherichia coli species, and an increased incidence of IBD.[10,12] An abundance of clinical, epidemiologic, and animal model studies have assessed the impact of various commensal and potentially pathogenic enteric bacteria that may trigger or exacerbate IBD. Specifically, the association between IBD and Clostridium difficile infection (CDI) has been well documented. Despite extensive recent studies examining the role of CDI in IBD, far less is known regarding the risks of acquisition and clinical impact of other enteric infections in IBD. However, similar clinical presentations and laboratory findings in relapse of IBD and enteric infection pose substantial barriers to diagnosis and treatment. A number of different enteric infections have demonstrated to cause symptoms that mimic those in exacerbation of IBD, including bacterial, viral, fungal, protozoal, and helminthic pathogens.[13]

Therefore, further understanding of the association between non-CDI enteric infection and the risk of developing IBD could eventually lead to revelations of new targets for interventions that may modulate the disease course. However, despite accumulating evidence providing common biological mechanisms involved in the pathogenesis of non-CDI enteric infection and IBD, limited and conflicting data exist on the risk of developing IBD after non-CDI enteric infection.[12,14-17] The aim of this meta-analysis was to evaluate the risk of developing IBD after non-CDI enteric infection.

METHODS

Literature search

We developed and adhered to a standard protocol for study identification, inclusion, and data abstraction in the conduct of this meta-analysis following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[18] We performed a systematic literature search of the following electronic databases: Medline (1950–2019), EMBASE (1947–2019), Cochrane library (1993–2019), Web of Science (1900–2019), and PubMed (1950–2019). Medical subject headings for our literature review included "Inflammatory bowel disease," "Ulcerative colitis," "Crohn's disease," "enteric infection," "Campylobacter," "Salmonella," "Escherichia coli," "enteric pathogens," "organisms," "IBD," "UC," "CD," and "gastroenteritis." Citations from identified articles were then cross-referenced for completeness.

Study selection and data abstraction

Study selection included the following criteria: (1) Studies using a case-control, nested case-control, cross-sectional, and cohort study design; (2) if the study used a case-control/cross-sectional design, the enteric infection incidence rate in IBD group and non-IBD group was examined by odds ratio (OR); if the study used a cohort study design, the IBD incidence rate in enteric infection group and no enteric infection group was examined by relative risk (RR); (3) the odds ratio or relative risk and the 95% confidence interval (CI) was reported or these data could be calculated. Exclusion criteria included the following (1) studies did not have clearly defined enteric infection; (2) studies where IBD was diagnosed within 3 months of gastroenteritis infections; (3) studies included only patients with CDI; (4) studies included pediatric patients; (5) not offering the source of cases and controls or other essential information; and (6) reviews, letters, editorials, and repeated literature were also excluded.

We performed the data extraction via a standardized data extraction form, collecting information on the author, publication year, country, period, the type of infection, number of infected patients, and IBD patients. The

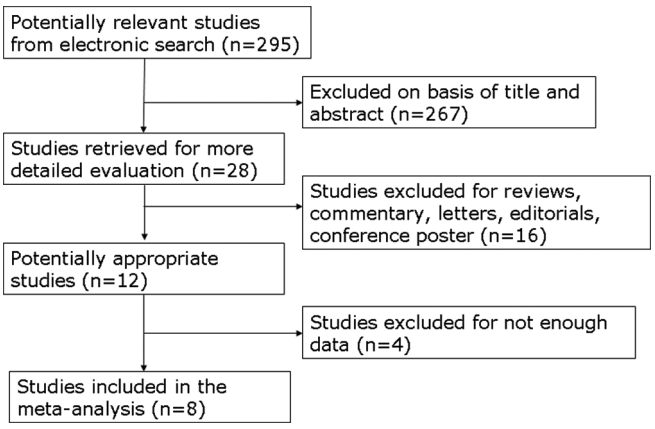

Figure 1: A flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis

outcome of the analysis was the OR and the RR. Study references and citations were collected in EndNote X4 software application. Two investigators (Cong Dai and Yu-Hong Huang) reviewed all titles, and those that appeared qualified were reviewed to assess eligibility. For manuscripts and abstracts that met our eligibility criteria, two investigators independently abstracted data using a standardized form developed for this study. Information collected included authors, title, year of publication, study design, inclusion, and exclusion criteria. Discordant results were adjudicated by the senior author. The paired agreement among the authors was 0.997. The methodological quality of each study was evaluated using the Newcastle Ottawa Scale (NOS), a tool developed to assess quality of nonrandomized studies for meta-analyses. The scale consists of eight items and scores each study on the following parameters: selection, comparability, and exposure (case control studies) or outcome (cohort studies), ranging between 0 and 9 stars. Evaluation of the validity and inter-rater reliability of NOS has been published previously. Two members of the study team (Cong Dai, Min Jiang) scored the studies separately according to the criteria laid out in the relevant NOS grading manuals.

Data synthesis and analysis

The presence of understudy heterogeneity was calculated by the Chi-square-based Q-test, and significance was set at $P < 0.10$ level. The inconsistency index (I^2) was calculated to assess the variation caused by heterogeneity. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR or RR. Otherwise, the fixed-effects model was adopted. Summary OR or RR and 95% CIs were used to describe the association between enteric infection and the risk of developing IBD. Publication bias was assessed by funnel plot analysis. Analyses were done using STATA 12.0.

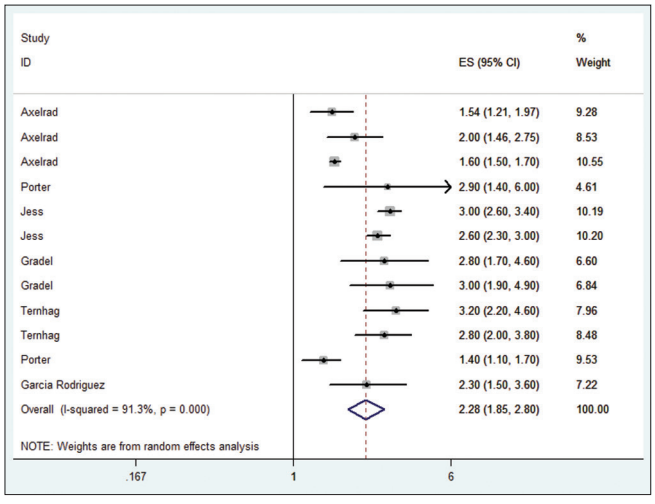

Figure 2: Forest plot of the association between non-CDI enteric infection and the risk of UC

RESULTS

Study characteristics

Our systematic review identified a total of 295 citations. After cross-referencing the index terms, titles, and abstracts, potentially relevant citations were manually evaluated for inclusion [Figure 1]. Ultimately, 12 full manuscripts and abstracts were reviewed in detail of which eight studies fulfilled inclusion criteria and were included in the meta-analysis. Study details regarding author, publication year, country, period, the type of infection, number of infected patients, and IBD patients, Newcastle Ottawa scale can be found in Table 1. A total of 345,490 patients with enteric infection, 3223 UC patients, and 2133 CD patients were included in the meta-analysis.

Meta-analyses and publication bias

Seven studies about non-CDI enteric infection and UC were included in the meta-analysis. Meta-analysis showed a significantly higher risk of UC in patients with enteric infection compared with noninfected patients (RR, 2.28; 95% CI, 1.85–2.8) (I^2 = 91.3%, $P < 0.001$) [Figure 2]. There was no evidence for publication bias using the Begg's tests (z = 0.48, $P = 0.631$) [Figure 3]. Eight studies about non-CDI enteric infection and CD were included in the meta-analysis. Meta-analysis showed a significantly higher risk of CD in patients with enteric infection compared with noninfected patients (RR, 1.88; 95% CI, 1.66–2.14) ($I^2 = 49\%$, $P = 0.024$) [Figure 4]. There was no evidence of publication bias using the Begg's tests (z = 0.55, $P = 0.583$) [Figure 5].

Subgroup analyses

In order to reduce heterogeneity, we performed subgroup analyses according to enteric pathogens (Salmonella and Campylobacter). Three studies about Salmonella infection and UC were included in the meta-analysis. The meta-analysis

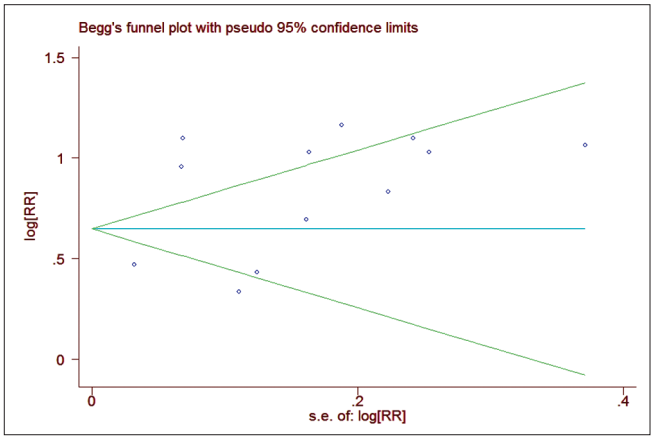

Figure 3: Funnel plot to assess publication bias from studies about non-CDI enteric infection and UC

Table 1: Characteristics of included studies

Study	Year	Country	Period	Type	Years of follow-up or patient-years	Infection
Axelrad	2018	Sweden	1964-2014	case-control	Max: 50 years	Salmonella
Axelrad	2018	Sweden	1964-2014	case-control	Max: 50 years	Campylobacter
Axelrad	2018	Sweden	2002-2014	case-control	Max: 12 years	all GE
Porter	2017	United States	2001-2009	cohort study	470060	all GE
Springmann	2014	Canada	1998-2005	case-control	Max: 7 years	all GE
Jess	2011	Denmark	1992-2008	cohort study	94264447	Salmonella
Jess	2011	Denmark	1992-2008	cohort study	94264447	Campylobacter
Gradel	2009	Denmark	1991-2003	cohort study	12 years	Salmonella
Gradel	2009	Denmark	1991-2003	cohort study	12 years	Campylobacter
Ternhag	2008	Sweden	1997-2004	retrospective cohort study	Max: 7 years	Salmonella
Ternhag	2008	Sweden	1997-2004	retrospective cohort study	Max: 7 years	Campylobacter
Porter	2008	United States	1999-2006	case-control	7 years	all GE
Garcia Rodriguez	2006	United Kingdom	1992-2001	cohort study	325743	all GE

Study	Number of infected patients	Number of non-infected patients	UC	CD	UC-Risk	CD-Risk	Quality assessment		
							Selection	Comparability	Outcome
Axelrad	787	418822	74	44	1.54 (1.21-1.97)	1.95 (1.41-2.69)	3	2	3
Axelrad	362	418822	46	23	2.0 (1.46-2.75)	2.35 (1.49-3.70)	3	2	3
Axelrad	20790	459931	1672	1050	1.6 (1.5-1.7)	1.7 (1.6-1.8)	3	2	3
Porter	82107	26022	49	58	2.9 (1.4-6.0)	1.1 (0.5-2.5)	4	2	3
Springmann	1318	694		409	-	0.97 (0.38-2.44)	4	1	3
Jess	41628	-	487	161	3.0 (2.6-3.4)	2.2 (1.7-2.7)	3	1	3
Jess	49420	-	487	161	2.6 (2.3-3.0)	2.2 (1.8-2.7)	3	1	3
Gradel	6463	26116	79	29	2.8 (1.7-4.6)	2.5 (1.0-6.3)	3	2	2
Gradel	6685	26116	79	29	3.0 (1.9-4.9)	3.3 (1.6-7.0)	3	2	2
Ternhag	34664	9766	29	14	3.2 (2.2-4.6)	1.4 (0.8-2.3)	3	2	2
Ternhag	57425	9766	42	27	2.8 (2.0-3.8)	1.6 (1.0-2.3)	3	2	2
Porter	828	13837	115	88	1.4 (1.1-1.7)	1.5 (1.2-2.0)	4	1	2
Garcia Rodriguez	43013	51000	64	40	2.3 (1.5-3.6)	3.1 (1.7-5.7)	3	2	2

showed a significantly higher risk of UC in patients with Salmonella infection compared with noninfected patients (RR, 2.51; 95% CI, 1.71–3.67) (I^2 = 87.2%, P < 0.001) [Supplementary Figure S1]. Three studies about Campylobacter infection and UC were included in the meta-analysis. The meta-analysis showed a significantly higher risk of UC in patients with Campylobacter infection compared with noninfected patients (RR, 2.56; 95% CI, 2.29–2.86) (I^2 = 3.8%, P = 0.374) [Supplementary Figure S2].

The three studies about Salmonella infection and CD showed a significantly higher risk of CD in patients with Salmonella infection compared with noninfected patients (RR, 2.03; 95% CI, 1.71–2.42) (I^2 = 0.0%, P = 0.454) [Supplementary Figure S3]. The Three studies about Campylobacter infection and CD showed a significantly higher risk of CD in patients with Campylobacter infection compared with noninfected patients (RR, 2.15; 95% CI, 1.83–2.54) (I^2 = 12.4%, P = 0.331) [Supplementary Figure S4].

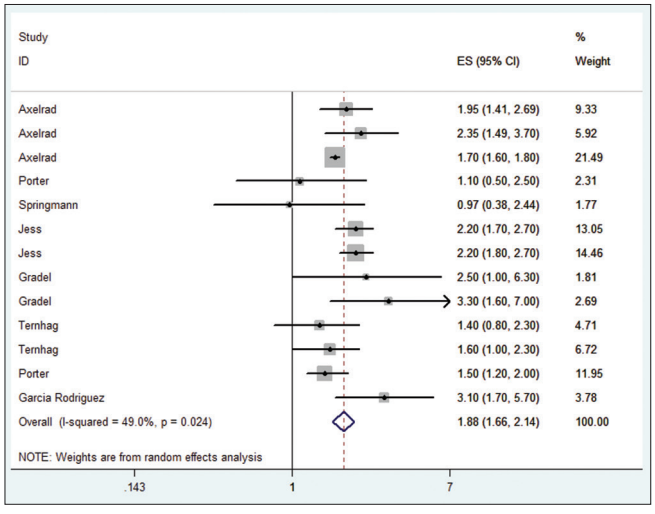

Figure 4: Forest plot of the association between non-CDI enteric infection and the risk of CD

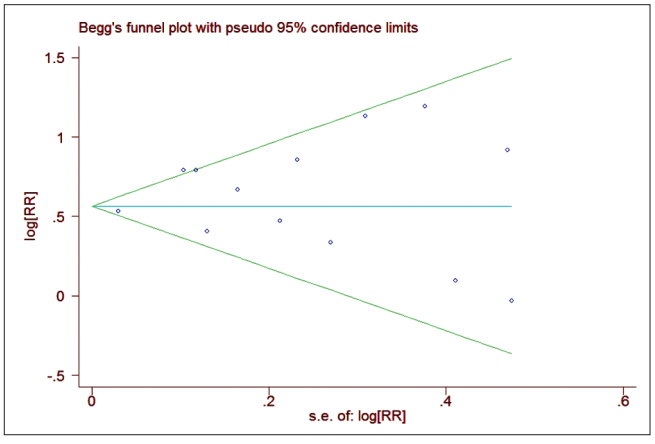

Figure 5: Funnel plot to assess publication bias from studies about non-CDI enteric infection and CD

Quality assessment

The quality of the included studies ranged from 7 to 9 according to the NOS [Table 1].

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis investigating the risk of developing IBD after non-CDI enteric infection. This systematic review demonstrated an increased risk of IBD in patients with non-CDI enteric infection. The pathogenesis of IBD represents the evolving understanding of a complex interaction between environmental factors, microbial insults, ethnicity, genetic susceptibility, and a dysregulated immune system; whereby among genetically susceptible individuals, IBD may arise subsequent to an enteric infection owing to an alteration of the gut epithelial barrier resulting in exposure to commensal and/or pathogenic microflora and disturbed adaptive and innate immune responses leading to disease.[19-22]

Although IBD will often have a more serious course, the first symptoms are likely to occur months or years before it is diagnosed. This was also corroborated by an increasing risk of IBD in the period up to the enteric infections in exposed as compared with unexposed individuals. There are numerous data suggesting a role for enteric infections in promoting gastrointestinal microbial dysbiosis and, subsequently, the intestinal inflammation that characterizes IBD.[11,23-27] At the same time, the emerging understanding of differential genetic predisposition and immunopathologic triggers associated with the IBD subtype may explain the differences in risk associated with IBD after enteric infection.[10,28]

However, some studies from epidemiological observations found that exposure to infections experienced during early childhood may play a protective role in IBD.[29] Protective effects against T helper type 1 (Th-1)-mediated autoimmune diseases have since been reported with some consistency using various potential indicators of infection exposure.[29,30] The mechanism is that early exposure to infections helps establish the immunological balance between proinflammatory and tolerance-inducing responses to antigenic stimuli and thus contributes to the maintenance of physiological inflammation from subsequent contact.[31] Also, some studies have also demonstrated that inflammatory phenotypes such as CD are likely due to defects in tolerance-inducing mechanisms, and that inducing tolerance in patients with CD could attenuate symptoms of disease.[32,33]

Our study has confirmed the association between enteric infection (especially about Salmonella and Campylobacter) and the risk of developing IBD. However, the association can be affected by some factors in the included studies. First, the threshold for diagnosing enteric infection (Salmonella/Campylobacteris) probably lowered with increasing severity of gastroenteritis, and the higher hospitalization rate for IBD patients likely reflects a more severe gastroenteritis in this patient group. Second, there is likely to be higher vigilance around hospitalized patients with enteric infection, especially if their gastroenteritis continues beyond a few days. This will prompt further investigations (endoscopy examinations) and thus increase the likelihood of diagnosing IBD. Third, it may be difficult to distinguish between IBD and enteric infection involving severe mucosal damage,[34,35] and some included studies cannot rule out that the latter may have been diagnosed as IBD close to the enteric infection in some patients. Likewise, it is possible that undiagnosed IBD patients may have more frequent notification of enteric infections. Fourth, antibiotic use could be a confounding factor. A previous meta-analysis has shown a modest association between antibiotic use and IBD development (OR, 1.57; 95% CI, 1.27–1.94).[36] Antibiotic use increased the odds of CD development (OR, 1.74; 95% CI, 1.35–2.23) but not UC (OR, 1.08; 95% CI, 0.91–1.27). Because early antibiotic exposure may impact the long-term composition of the gut microbiome, several investigators have examined the impact of antibiotic exposure early in life. For example, Shaw *et al*. observed that the odds of antibiotic exposure in the first year of life was 2.9 times greater among children subsequently diagnosed with IBD than among matched controls.[37] Furthermore, there was evidence of a dose response with a stronger association among those with more courses of antibiotics, but no specific class of antibiotics has been consistently associated with the incidence of CD. For example, while both *et al* Margolis and Card *et al*. observed associations with tetracylcines,[38,39] Kronman *et al* did not.[40] Rather, Kronman *et al* observed an association with broad-spectrum penicillins, but only in the first 3 months after treatment. In contrast, Card *et al*. observed no association with broad-spectrum penicillins. It seems unlikely that the association is related to a specific immunologic property of the antibiotics. One possibility is that the antibiotics alter the gut microbiota in a way that is specific to different populations. Although there is an association between antibiotic use and the development of IBD, a possible triggering role of antibiotics in the onset of IBD should be interpreted with caution.

At the same time, our meta-analysis has several limitations. First, some included studies lacked of culture data or specific pathogen diagnoses for most gastroenteritis events and most gastroenteritis cases occurred in the inpatient setting, possibly limiting generalizability. Also, diagnosed enteric infection (Salmonella/Campylobacter gastroenteritis) represents only a minor fraction of the real number of infections. A Danish study found up to 570 times higher incidence of Salmonella antibodies in blood donors as compared with reported gastroenteritis cases.[41] Therefore, we had limited power to assess risk of IBD associated with specific pathogens and urge caution when interpreting these findings. Second, the studies did not consider other risk factors for IBD, such as diet, vaccinations, smoking history, and previous antibiotic exposures. For example, the inverse effects of dietary consumption of vegetables and fruits and positive associations with fatty foods are potential confounders.[42]

Third, there may be detection bias in this meta-analysis. The assumption of detection bias is further supported by the fact that the true incidences of enteric infections (Salmonella and Campylobacter infections) in the population are markedly higher than what is observed based on physician-requested stool culturing, which implies that the likelihood of detecting enteric infections will depend on the number of stool tests performed.[43] In accordance with the clinical criteria for diagnosing IBD, which include the requirement for a negative stool examination, individuals with negative stool tests were five times more likely than those with positives tests to be diagnosed with IBD within the first year following the stool tests. At the same time, patients who were diagnosed with IBD within the first year after their first stool test were more likely than those who did not develop IBD to have had additional stool tests performed.[44] Additionally, the markedly higher percentage of detection methods such as colonoscopies, CT, and MRI scans in stool test-negative than in stool test-positive individuals corroborates the idea that the initial peak in IBD incidence soon after negative stool tests reflects the influence of detection bias.

In conclusion, our meta-analysis has found that patients with non-CDI enteric infection were associated with an increased risk of developing IBD. Therefore, patients with non-CDI enteric infection should be aware of the potential risk for developing IBD. Also, these patients should be regularly evaluated for gastrointestinal tract with related examinations such as gastroscopy, colonscopy, capsule endoscopy, and abdominal imaging. Future studies are needed to determine the association between non-CDI enteric infection and the risk of developing IBD, and elucidate the potential underlying mechanisms.

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Conflicts of interest

There are no conflicts of interest.

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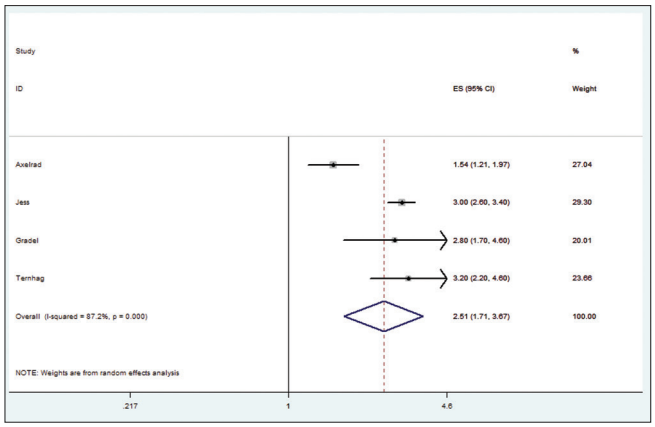
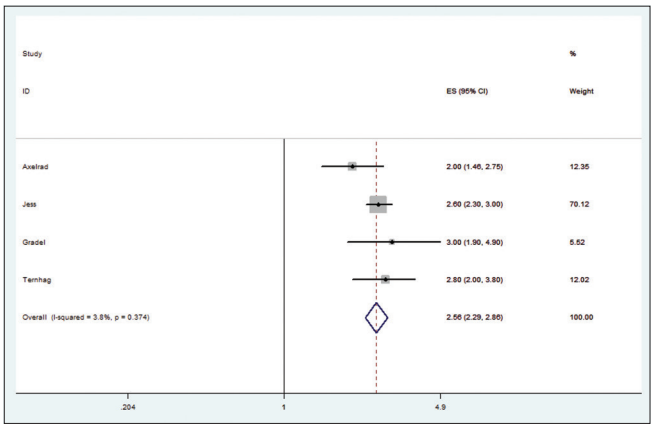
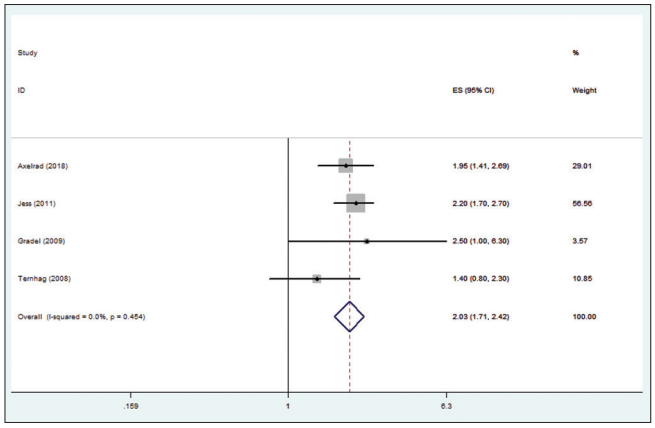


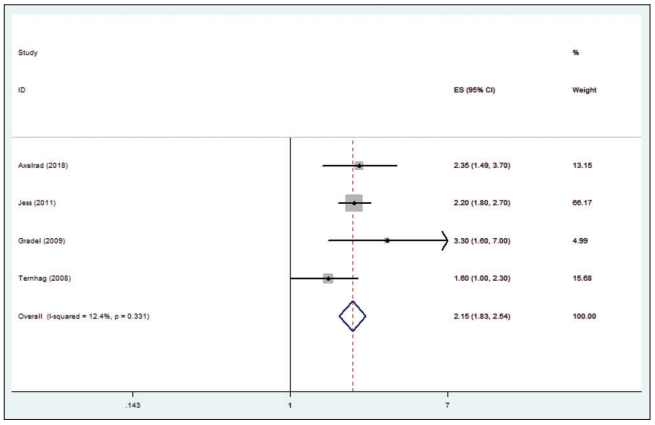
Supplementary Figure S1: Forest plot of the association between Salmonella infection and the risk of UC



Supplementary Figure S2: Forest plot of the association between Campylobacter infection and the risk of UC



Supplementary Figure S3: Forest plot of the association between Salmonella infection and the risk of CD



Supplementary Figure S4: Forest plot of the association between Campylobacter infection and the risk of CD