The Associations between Inflammatory Bowel Disease and a Range of Other Diseases：Umbrella Review of Systematic Reviews and Meta-analyses

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Research

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Abstract

Background

Multiple meta-analyses have reported inflammatory bowel diseases (IBD) are associated with an increased risk of diverse diseases, but the evidence quality remains unclear.

Objectives

We aimed to summarize and evaluate this existing evidence on the associations between IBD and a range of diseases a-crossed from meta-analyses.

Methods

PubMed, the Cochrane Library Database, Embase, Web of Science, CNKI Databases, Wanfang Databases and VIP Database were searched to obtain eligible literatures from inception to November 1, 2019. We appraised the methodological quality of the included meta-analyses using AMSTAR 2 tool, and evaluated the quality of evidence for each outcome using the GRADE approach.

Results

Nineteen articles covering associations between IBD and 28 types of health outcomes were included. The methodological quality of meta-analyses was rated moderate for 5.26%, low for 21.05%, and critically low for 73.68%. Overall, summary effect estimates were significant in 26 meta-analyses. The evidence quality was rated high for 3.57%, moderate for 21.43%, low for 28.57%, and very low for 46.43%. Evidence quality was high for association between IBD and an increased periodontitis risk (OR = 4.55; 95% CI, 3.00-6.19). Evidence quality was moderate for associations between IBD and an increased thyroid cancer risk (OR = 1.75; 95% CI, 1.48–2.07), myocardial infarction incidence (RR = 1.12; 95% CI, 1.05–1.21), preterm birth incidence (OR = 1.85; 95% CI, 1.67–2.05), stillbirth incidence (OR = 1.57; 95% CI, 1.03–2.38), gallstone disease prevalence (OR = 1.72; 95% CI, 1.40–2.12), and vitamin D deficiency prevalence (OR = 1.64; 95% CI, 1.30–2.08).

Conclusions

Though, associations between IBD and diverse diseases have been extensively studied, few of the reported associations have robust support. Further well-designed studies are essential to determine whether IBD increases the risk of other diseases.

Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic immune-mediated idiopathic inflammatory diseases influenced by both genetic and environmental

factors [1–3]. IBD is a global disease in the 21st century, showing accelerating incidence [4–6]. More than 6.8 million people worldwide suffer from IBD, which imparts a massive economic burden on public health [7]. As a lifelong chronic relapsing disorder with an early onset, IBD is painful and debilitating. Chronic inflammation of IBD may lead to a variety of serious complications. Multiple meta-analyses have reported that patients with IBD are at increased risk for many diseases (e.g., extra-intestinal cancers [8], nonalcoholic fatty liver disease [9], cardiovascular diseases [10]), indicating that IBD may be a contributor to both mortality and morbidity rates in patients with these diseases. Simultaneously, the global burden of these diseases is growing rapidly [11–13]. Studying and clarifying associations of IBD and diverse diseases may be of great value in the diagnosis and treatment of these conditions. Therefore, it is necessary to summarize the associations between IBD and related diseases. However, to the best of our knowledge, no study has, to date, comprehensively summarized associations between IBD and various diseases.

In addition, although many meta-analyses have revealed associations between IBD and multiple diseases, the quality of the available evidence remains unclear. The observed associations between IBD and diverse diseases could be either causal or because of confounding factors. Design scheme defects, risk of bias, small sample size effects and inconsistencies between studies could result in a downgrade of the quality of evidence. Furthermore, some findings are contradictory [14, 15]. Therefore, it is important to clarify the quality of evidence of these associations. However, no studies have been conducted yet to evaluate the quality of evidence in this regard; hence, critically apprising the body of evidence of associations between IBD and a range of diseases is needed. An umbrella review involves systematically searching, collecting and assessing the existing evidence derived from various systematic reviews and meta-analyses on any clinical health outcomes related to a particular involves [16]. An umbrella review can not only comprehensively summarize evidence of associations between IBD and diverse diseases, but can also clarify the quality of the evidence, providing clinicians with an overall picture of the subject under consideration.

This study aimed to perform an umbrella review to summarize the evidence of associations between IBD and diverse diseases derived from systematic reviews and meta-analyses, and to assess the quality of evidence of these associations.

Methods And Methods

Our study was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/, CRD42020158433), the international prospectively registered platform for systematic reviews [17]. This umbrella review was reported according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) recommendations [18].

Literature search

PubMed, Embase, the Cochrane Library Database, Web of Science, CNKI database, Wanfang database, and VIP database were independently searched by two researchers (Lijian Liu, Jinxiu Wei) from their inception to November 1, 2019 for meta-analyses and/or systematic reviews of observational studies investigating associations between IBD and diverse diseases. The search strategy involved a combination of medical subject terms, words, and free text. The search strategies of deployed in the selected literature databases are shown in Appendix 1. The references of the eligible literature were also searched by hand.

Study selection

We included only meta-analyses and/or systematic reviews with a meta-analysis of observational studies (e.g., cohort studies, case–control studies and cross–sectional studies) exploring associations between IBD and diverse diseases in humans. Eligible studies included the following aspects: (1) exposure: IBD; (2) comparator: non-IBD; (3) outcomes (s): risk/ incidence/ prevalence of diverse diseases. We included studies with specific data such as relative risk (RR), odds ratio (OR), standardized incidence ratio (SIR), standardized mortality ratio (SMR) and corresponding 95% confidence interval (95% CI). If there was more than one eligible outcome in a meta-analysis, we retrieved each of them separately. When more than one published meta-analysis studying the same association was identified, the one with the largest number of primary studies included was retained. If more than one published meta-analysis on the same association included the same number of primary studies, the one with the largest number of prospective studies or participants was included. If more than one published meta-analysis on the same association met both criteria, the one with more information available (e.g., subgroup analyses) was selected.

Meta-analyses that only contained information on cumulative risk were excluded. Studies were also excluded if not published in full form as peer-reviewed literature. We also excluded meta-analyses with incomplete or inconsistent data that had not been confirmed by the author.

Two reviewers (Liqun Li, Qianli Cen) screened all articles identified from the search independently. First, titles and abstracts of articles were screened. Second, full texts were scrutinized for applicability. Third, references of all eligible articles were hand-searched. Any disagreement between reviewers were resolved by discussion to reach a consensus and a third review (Sheng Xie) arbitrated all discrepancies.

Data extraction

For each eligible study, two reviewers (Liqun Li, Qianli Cen) independently extracted information on the name of the first author, year of publication, outcome(s), epidemiologic design and number of included studies, number of cases and controls (for case–control studies) or number of cases and participants (for cohort studies), the meta-analytic model used (fixed or random), and meta-analytic estimates and their corresponding 95% Cls. We also abstracted the results of heterogeneity, publication bias and subgroup analysis. All of the results were carefully checked by a third reviewer.

Methodological quality assessment

A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2), a reliable and valid tool [19, 20], was used to assess the risk of methodological bias observed in each article by two investigators (Lijian Liu, Jinxiu Wei). The revised AMSTAR 2 was developed from AMSTAR and contains 16 checklists in total, including seven critical domains (items 2, 4, 7, 9, 11, 13 and 15) and nine noncritical items (items 1, 3, 5, 6, 8, 10, 12, 14 and 16). AMSTAR 2 does not generate an overall score, but rather provides three (“yes”, “partial yes”, and “no”) responses to the satisfaction level of the checklists. The rating criteria of AMSTAR 2 were as follows: high quality was rated when no or one noncritical weakness was found; moderate quality was rated when more than one noncritical weakness was found; low quality was rated when one critical flaw with or without noncritical weaknesses was found; and critically low quality was rated when more than one critical flaw with

or without noncritical weaknesses was found [19]. The results were checked by a third investigator (Jianfeng Li) and discrepancies were resolved by discussion with the review group.

Evidence quality assessment

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was employed to rate the quality of evidence across every outcome [21, 22]. From here, the evidence quality could be further downgraded by five factors (study limitations, inconsistency of results, indirectness of evidence, imprecision and potential publication bias), or upgraded by three factors (large magnitude of effect, dose response and confounders). When there was a serious or very serious defect for downgrading factors, the evidence quality was lowered by one or two level(s), respectively. When there was large effect (RR/OR of either > 2.0) or very large effect (RR/OR of either > 5.0), the evidence quality was increased by one or two level(s), respectively. When there was evidence of a gradient dose response, the evidence quality was upgraded by one level. If there was evidence that the influence of all plausible confounding would reduce a demonstrated effect or suggest a spurious effect, the evidence quality was upgraded by one level. The primary evidence quality of observational studies was considered as “low”; the evidence quality was rated as “very low” by downgrading one level or more; the evidence quality was rated as “moderate” and “high “by upgrading one or two levels, respectively. Ultimately, the evidence quality of the outcomes was categorized as high, moderate, low or very low [21, 22]. The GRADE assessment was independently conducted by two reviewers (Jinjing Tan, Yalu Chen), and the results were checked by a third investigator (Yuanyuan Liu). Discordant decisions were resolved by a team researcher (Sheng Xie).

Data synthesis

If the included meta-analyses did not present the results of pooled meta-analysis (RRs, ORs, SMRs, or SIRs), I^2, Egger’s test, or publication bias, we extracted the necessary data from primary studies to recalculate them as possible as we could. Publication bias was estimated by using Egger’s test (significant at $p < 0.10$) [23]. Cochrane Q test (significant at $p < 0.10$) and I^2 statistics were used to assess the heterogeneity [24]. For I^2 statistics, a value of more than 50% was considered to indicate significant heterogeneity. A random-effects model was employed to calculate the relative summary risk estimates when significant heterogeneity was observed [25]. Otherwise, a fixed-effects model was used. All statistical analysis was conducted using Stata version 15.0 (IBM Corp., Armonk, NY, USA).

Results

Description of the included meta-analyses

A total of 9,310 records were found through an initial database review. After screening the titles and abstracts, 64 articles were kept as full-text articles for additional review. Ultimately, 19 articles covering associations between IBD and 28 types of health outcomes were included (Fig. 1). The included meta-analyses were published in English between 2014 and 2019. Various disease outcomes included cancers (n=7) [26-31], cardiovascular and cerebrovascular diseases (n=8) [32-35], obstetrical diseases (n=4)[36], neuropsychiatric disease (n=1) [38], otolaryngology and stomatology diseases (n=2) [41,43] and others (n=6) [37,39-40,42,44] (Table 1). A total of 249 individual study estimates were included among the 19 articles. Among the 249

individual studies, 204 (81.93%) were cohort studies, 36 (14.46%) were case–control studies, and nine (3.61%) were cross-sectional studies. Three to 23 studies estimates were pooled in per meta-analysis, while the median study estimate count was eight. The number of primary studies that pooled in 60.71% of meta-analyses was less than 10. Five meta-analyses did not provide the total number of participants [34, 44], while 13 meta-analyses did not provide the total number of cases [26, 33-36, 41, 43, 44]. Among the meta-analyses that indicated the number of cases or participants, the median number of participants was 352,977 (811–940,572,339), and the median number of cases was 4,984 (117–120,312). A total of 22 meta-analyses included more than 1,000 participants, 10 meta-analyses included more than 1,000 cases and two meta-analyses included less than 300 cases.

Heterogeneity between studies and publication bias

Table 1 shows the heterogeneity between studies. Eighteen meta-analyses (64.29%) reported significant heterogeneity between studies with $p < 0.10$ or $I^2 > 50\%$. There was moderate heterogeneity (I^2=50%–75%) in five (17.85%) meta-analyses and high heterogeneity ($I^2 > 75\%$) in eleven (39.28%) meta-analyses. Two meta-analyses were reanalyzed because they did not present the results of publication bias [32, 41]. Only one meta-analysis indicated the existence of publication bias [36].

Methodological quality of included meta-analyses

The assessment results of the AMSTAR2 are shown in Supplemental Table 3 and Fig. 6. Seventeen (89.47%) meta-analyses did not report explicit statements or protocols. Thirteen (68.42%) meta-analyses did not use comprehensive literature search strategies. Thirteen (68.42%) meta-analyses did not provide a list of exclude studies and justify the exclusions. Five (26.31%) meta-analyses did not use a satisfactory technique for assessing the risk of bias in the primary studies. None of the meta-analyses reported the details of funding sources for the included studies. Overall, the methodological qualities of the included meta-analyses were rated as moderate for 5.26% (n=1), low for 21.05% (n=4), and critically low for 73.68% (n=14).

Associations and quality of evidence between IBD and various diseases

A total of 28 associations between IBD and different types of diseases were found (Table 1). Amongst these associations, the random meta-analytic model was used in 23 estimates (82.14%), and the fixed meta-analytic model was used in five estimates (17.86%). Ten (35.71%) meta-analytic summary effect estimates were adjusted, while 18 (64.29%) meta-analytic summary effect estimates were unadjusted. Overall, the summary effect estimates were significant in 92.86% estimates.

The result of evidence quality for each association is summarized in Table 2 and Supplemental Table 4. In total, the evidence quality was graded as high for 3.57% (n=1), moderate for 21.43% (n=6), low for 28.57% (n=8), and very low for 46.43% (n=13). Large heterogeneity between studies is the main reason leading to a downgrade in the evidence quality. Fig. 3-5 and supplemental table 1-2 shows the subgroup results stratifying by the types of IBD, gender, ethnicity, age and other.

The associations between IBD and cancers

Moderate quality of evidence shows that there was positive associations between IBD and risk of thyroid cancer (OR=1.75; 95% CI, 1.48-2.07) (Table 2 and Supplemental Table 4) [29]. Low quality of evidence shows that IBD was associated with an increased risk of cervical cancer [27], intrahepatic cholangiocarcinoma [30], melanoma [31] and extrahepatic cholangiocarcinoma [30]. There was an association between IBD and increased risk of prostate cancer [26] and colorectal cancer [28], but the evidence quality was very low.

By stratifying based on the type of IBD, CD was significantly associated with an elevated risk of cervical cancer, while UC was not [27]. UC was increased the risk of thyroid cancer, while CD was not [29] (Fig. 3A-B). By stratifying based on ethnicity, IBD was associated with a higher risk of extrahepatic cholangiocarcinoma in Asians, but not in Non-Asians [30]; with an increased risk of melanoma in North Americans, but not in Europeans [31](Fig. 5). By stratifying based on age, IBD was associated with a higher risk of colorectal cancer in patients of age 30 years, but not in the patients age ≥ 30 years (Supplemental Table 1) [28]. By stratifying based on study design, IBD was associated with an increased risk of thyroid cancer and melanoma in population-based studies, but not in hospital based studies [29, 31] (Supplemental Table 2). By stratifying based on the number of patients, IBD was associated with an increased risk of thyroid cancer in the studies with ≥ 10,000 patients, but not in those with 10,000 patients[29]. Further, IBD increased risk of thyroid cancer in the patients who use immunosuppressants, but not in those who never use immunosuppressants [29].

The associations between IBD and cardio-cerebro-vascular diseases

Moderate quality of evidence shows that IBD was associated with an increased incidence of myocardial infarction (RR=1.12; 95% CI, 1.05-1.21) [34] (Table 2 and Supplemental Table 4). There are positive associations between IBD and stroke incidence [32], ischemic heart disease risk [33], cerebrovascular disease incidence [34], coronary heart disease incidence [34], venous thromboembolic risk [35], but the quality of evidence is low to very low. There are no clear associations between IBD and cardiovascular disease mortality and arterial thromboembolism [35], but the quality of evidence is low and very low.

By stratifying based on the type of IBD, UC was associated with and increased incidence of stroke, while CD did not [32] (Fig. 3A-B). By stratifying based on gender, IBD was associated with increased stroke incidence [32], ischemic heart disease risk [33], cerebrovascular disease incidence both in Male and Female [34] (Fig. 4). By stratifying based on ethnicity, IBD was associated with increased stroke incidence both in Asians and non-Asians [32] (Fig. 5). By stratifying based on the length of follow-up, IBD increased risk of ischemic heart disease in the patients who were follow-up for less than 5 years, but not in those who were follow-up for more than 5 years [33](Supplemental Table 2). By stratifying based on study design, IBD was associated with an increased risk of arterial thromboembolism in general patients, but not in hospitalized patients [35] (Supplemental Table 2). Further, IBD was associated with an increased risk mesenteric ischemia, but not associated with an increased risk peripheral artery disease [35].

The associations between IBD and obstetrical diseases

Moderate quality of evidence shows that IBD was associated with an increased incidence of preterm birth (OR=1.85; 95% CI, 1.67-2.05) and incidence of stillbirth (OR=1.57; 95% CI, 1.03-2.38) [36] (Table 2 and Supplemental Table 4). There are positive associations between IBD and incidence of small for gestational age birth weight and congenital anomalies, but the quality of evidence is low and very low. By stratifying

based on the type of IBD, both UC and CD were associated with an increased incidence of preterm birth [36] (Fig. 3A-B).

The associations between IBD and neuropsychiatric diseases

There are positive associations between IBD and risk of Parkinson's disease, but the quality of evidence are very low [38] (Table 2 and Supplemental Table 4). By stratifying based on the type of IBD, both UC and CD were associated with an increased risk of Parkinson's disease [38] (Fig. 3A-B). By stratifying based on gender, IBD was increased risk of Parkinson's disease both in Male and Female (Fig. 4). By stratifying based on age, IBD was increased risk of Parkinson's disease in patients either younger than 65 years old or elder than 65 years old [38] (Supplemental Table 1).

Association between IBD and otolaryngology and stomatology diseases

High quality of evidence shows that IBD increased the risk of periodontitis (OR=4.55; 95% CI, 3.00-6.19) [41]. Low quality of evidence shows that IBD was associated with an increased risk of rosacea [43] (Table 2 and Supplemental Table 4). By stratifying based on ethnicity, IBD was associated with increased risk of rosacea both in Asians and Europeans [43] (Fig.5).

Association between IBD and other diseases

Moderate quality of evidence shows that IBD increased the prevalence of gallstone disease (OR=1.72; 95% CI, 1.40-2.12) [40] and vitamin D deficiency (OR=1.64; 95% CI, 1.30-2.08)[42]. Very low quality of evidence indicates that IBD was associated with an increased risk of sexual dysfunction [37] and osteoporotic fracture [39] (Table 2 and Supplemental Table 4).

By stratifying based on the type of IBD, both CD and UC increased the risk of herpes zoster infection and the prevalence of vitamin D deficiency [44]; CD was associated with an increased prevalence of gallstone disease, but UC was not [40]. By stratifying based on gender, IBD was increased risk of sexual dysfunction both in male and ffemale [37] (Fig. 4). By stratifying based on ethnicity, IBD was increased the risk of herpes zoster infection both in Causations and Asians [44] (Fig. 5). By stratifying based on age, IBD was associated with an increased risk of sexual dysfunction only in male less than 50 years old and female less than 40 years old [37] ; with increased prevalence of vitamin D deficiency in adult, but not in pediatric [42]. IBD was only associated with an increased risk of vertebral fracture, but not associated with risk of hip, wrist and humeral fracture [39].

Discussion

Principal findings

Our umbrella review systematically summarized and evaluated existing evidence from meta-analyses on associations between IBD and diverse diseases. This umbrella review included 19 published meta-analyses that investigated on the association between IBD and 28 types of health outcomes. 64.29% of meta-analyses reported significant heterogeneity between studies. Only one meta-analysis indicated the existence of publication bias. The methodological qualities of the included meta-analyses were rated as moderate for 5.26% (n=1), low for 21.05% (n=4), and critically low for 73.68% (n=14). The evidence quality of the

associations between IBD and various diseases was graded as high for 3.57% (n=1), moderate for 21.43% (n=6), low for 28.57% (n=8), and very low for 46.43% (n=13).

Possible explanations

We found that IBD was associated with an increased risk of 26 types of different diseases. This result supports that the human body is an interconnected organic unit whose organs might be related to each other by their pathophysiology, such as the theory of the brain and intestine axis and the theory of the liver and intestine axis [45]. Identifying and removing risk factors can play an important role in the prevention and prediction of diseases. Therefore, comprehensively recognizing associations between IBD and diverse diseases may contribute to human health. However, 64.29% meta-analytic summary effect estimates were unadjusted for confounders (e.g., smoking and drinking). Nevertheless, the influence of confounding factors on the results cannot be ruled out.

This study shows that IBD, both UC and CD increased risk of periodontitis with high quality of evidence, demonstrating that IBD contributes to the prevalence of periodontitis. Both IBD and periodontitis are immune-mediated inflammatory diseases influenced by genetic and environmental factors [46-48]. The immune responses of IBD are involved in the course of periodontitis [46-48]. The cytokines and mediators of inflammation might play an important role in linking association between IBD and periodontitis [49-51].

IBD was associated with an increased risk of thyroid cancer, incidence of myocardial infarction, incidence of preterm birth, incidence of stillbirth, prevalence of gallstone disease and prevalence of vitamin D deficiency with moderate quality of evidence. It indicates that IBD may play an important role in the pathogeny and development of these diseases. Chronic systemic inflammation may be a major mechanism explained the association between IBD and these diseases. Related research shows thyroid cancer and IBD may share a similar denominator in pathogenesis [52]. Reliable genetic data indicate that the extraintestinal manifestations and complications of IBD and the genetic risk loci of gallstones widely overlap, and the pathogenicity overlap between them has expanded from shared risk genes to unique shared biological pathways [53]. Inflammation triggers atherosclerosis-related processes, from plaque formation to thrombus rupture, leading to coronary heart disease [54].

The associations with low or very low quality of evidence between IBD and those diseases (e.g. prostate cancer, stroke, ischemic heart disease) indicate that these associations should be assessed with caution. Although quality of evidence for these associations were graded “low” or “very low,” they might still provide ideas for clinicians. Most of the evidence quality was downgrade by inconsistency of meta-analyses. Therefore, these associations warrant further investigation.

Subgroup analyses shows that UC was increased the risk of thyroid cancer and the incidence of stroke, while CD was not; CD was associated with an increased prevalence of gallstone disease and risk of cervical cancer, but UC was not. These differences might be interpreted by not the same pathogeneses of UC and CD [46,55]. It also may be confused by confounders, which may exaggerate or minimize the effects. The risks of thyroid cancer, stroke, ischemic heart disease, sexual dysfunction and Parkinson’s disease, and the incidence of coronary heart disease and cerebrovascular disease were increased in both male and female participants with IBD, demonstrating that associations between IBD and these diseases might not be a gender-specific problem.

Subgroup analyses shows that IBD was associated with an increased risk of extrahepatic cholangiocarcinoma in Asians, but not in non-Asians; IBD was related to an increased risk of melanoma in North Americans, but not Europeans. These findings indicate that ethnicity plays an important role in the association between IBD and these diseases. Different environmental exposures and genetic susceptibilities among various geographic areas may explain these differences [3, 47].

By stratifying based on age, IBD was associated with a higher risk of colorectal cancer in patients at the age of 30 years old, but not in the patients at the age ≥ 30 years old; with an increased risk of sexual dysfunction only in male less than 50 years old and female less than 40 years old; with increased prevalence of vitamin D deficiency in adult, but not in pediatric. These results demonstrate that age play an important role in the association between IBD and those diseases [56]. However, the included studies are affected by the sample size, and the conclusions drawn are not necessarily correct.

A previous study reported that disease behaviour remained stable in 91% of patients with IBD, after a median follow-up of six years [57]. This information might be able to explain why patients with IBD followed up with for a short duration were associated with an increased risk of ischemic heart disease, whereas patients followed up for a long period were not associated with such risk[33].

The methodological qualities of 94.74% of the included meta-analyses were low or critically low per AMSTAR2, suggesting that the results of these meta-analyses might be inconclusive. Twenty meta-analyses reported significant heterogeneity between studies. All of the included studies explored potential sources of heterogeneity by subgroup analyses. The sources of heterogeneity partly were type of IBD[27-29, 31, 34, 42, 43], disease activity and severity of IBD[33], the age of patient[33, 37, 42, 44], different ethnicity[30, 43, 44], different length of time of follow-up[33], study setting[35], and study design[30, 35]. However, some heterogeneity could not be readily explained in certain studies [26, 36], indicating that some associations between IBD and the risk of other diseases may be inflated or falsely positives.

A minority of meta-analyses reported notable publication bias. However, 60.71% of meta-analyses included less than 10 primary studies, which indicates that the results in this regard may not be reliable. Furthermore, associations between IBD and the risk of other diseases may be found among thousands of individuals, but only a small proportion of associations are recorded, and an even smaller fraction is finally published [58]. Moreover, in practice, positive results are probably easier to publish, while negative results may not be published [59]. These phenomena could lead to publication biases in the results.

Comparison with other studies

Our umbrella review supports some recommendations of existing guidelines, and adds evidence in several respects. We found that patients with IBD had a high risk of periodontitis with a high quality of evidence [41]. Considering the association between IBD and the risk of periodontitis may helpful for the diagnosis and treatment of periodontitis. However, a guideline recommending this association was not found. Thus, this evidence may be added to relevant guidelines in the future. A practical guideline stated increased disease activity of IBD has the greatest adverse effects upon a pregnancy [60], which was supported by our results that IBD increased the risks of preterm birth and stillbirth with a moderate level of evidence quality [36]. The guideline of Crohn's disease by the American College of Gastroenterology (ACG) stated that gallstone disease

and metabolic bone diseases (associated with vitamin D deficiency) are complications of Crohn's disease [61], which was also supported by our results. However, the moderate quality of evidence for associations between IBD and an increased risk of thyroid cancer and incidence of myocardial infarction are not stated in the guideline yet [61]. This evidence might be helpful in future disease prevention and treatment efforts and could be added to the guidelines in the future.

Prevention again venous thromboembolism (strong recommendation, low quality of evidence) in patients with IBD are included in some guidelines [60,62]. The Canadian Association of Gastroenterology has also reached a consensus on the risk, prevention, and treatment of venous thromboembolism in patients with IBD [63]. Both venous and arterial thromboembolisms are the complications of Crohn's disease [61]. However, we found that IBD was associated with an increased risk of venous thromboembolism with a very low evidence quality [35], while IBD was not associated with an increased risk of arterial thromboembolism also per a very low quality of evidence [35]. The type of IBD may be one of the causes leading to this difference. Further research should be conducted to confirm whether IBD is associated with an arterial thromboembolic risk.

Additionally, guidelines recommended that patients with IBD should undergo cancer (cervical cancer, melanoma, colorectal cancer, and prostate cancer) screening, herpes zoster infection prevention, osteopenia monitoring, and fracture risk assessment [61,62,64-66]. These recommendations were confirmed by our results with low or very low qualities evidence. Although the quality of evidence of these associations was low, they still may provide guidance for clinicians.

So far, we have not found a review of the relationship between IBD and other diseases after searching. However, through our efforts, we have found studies on other diseases related to IBD, and the results show that the quality of the evidence is relatively low.

Strengths, weaknesses, and future studies

There are several strengths in our umbrella review. At first, this umbrella review firstly summarized and re-evaluated the evidence of associations between IBD and diverse diseases from published meta-analyses of observational studies. Previous studies have demonstrated the strengths of umbrella reviews [67-69]. Second, we identified the methodological quality of SRs/Mets by AMSTAR2, and evaluated the evidence quality of each outcome by GRADE. These two appraisal tools are critical and valid, being used worldwide [20-22]. Confirming the evidence is important for the recommendation of guidelines [71,72]. Using GRADE approach to re-evaluate the quality of evidence, this umbrella review adds evidence about associations between IBD and diverse diseases for clinical decision-makers and developers of guideline. Moreover, this umbrella review used systematic methods, including a comprehensive search of seven literature databases, an independent study selection, extraction and assessment by two reviewers. Although the selection and evaluation of the included studies may be subjective, a third investigator checked the results and a fourth investigator arbitrated all disagreement, which may have reduced the reduce subjectivity. Lastly, we found some deficiencies in existing published meta-analyses through this umbrella review, which may contribute to future research improvements. We also found some evidence of an association between IBD and other diseases (diseases for which there were original studies but which have not yet been meta-analyzed, such as diabetes [72]) were absent, which should be considered in future studies.

However, there were several weaknesses in our umbrella review. First, we only included meta-analyses and systematic reviews with meta-analyses. Some primary studies which did not develop to meta-analyses were not been completely included in this umbrella review [72-74], which might induce conclusion bias of this study. Second, we assessed heterogeneity by I^2 which was influenced by sample size and the accuracy of the GRADE assessment might be affected. Moreover, although AMSTAR 2 and GRADE are both validated tools, the use of other tools (e.g., Risk of Bias in Systematic Reviews) could have led to different conclusions regarding the quality of the methodology and the evidence [75]. Finally, the included primary studies were observational prospective or retrospective investigations, which are prone to confounding bias and retrospective bias.

Therefore, a large body of well-designed prospective studies should be carried out to better evaluate associations between IBD and the risk of multisystem diseases, especially those associations showing low or very low qualities of evidence. Future prospective studies should focus confounder information (e.g., family history) to better map the association between IBD and other diseases. In this umbrella review, the methodological qualities of 90% of the included meta-analyses were low or critically low. Meta-analyses should be conducted using a standard method in future studies, providing reliable evidence.

Conclusions

In conclusion, associations between IBD and diverse diseases have been widely studied by published meta-analyses, and most summary meta-analytic estimates yielded nominally significant results. However, only the association between IBD and the risk of periodontitis experienced robust support without hints of bias. Therefore, associations with low or very low quality need to be interpreted with caution. Well-designed prospective studies and meta-analyses are required to confirm these associations. In addition, careful planning and close monitoring should be adopted to discover and minimize the risk of diverse diseases in patients with IBD.

Declarations

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Ethical approval

Not applicable.

Declaration of interests

None.

Author Contributions

Liqun Li, Qianli Cen and Lijian Liu contributed equally to this work. Qianli Cen wrote the protocol. Lijian Liu and Jinxiu Wei independently searched the databases and conducted the AMSTAR2 classification. Liqun Li and Qianli Cen screened the articles according to the eligibility and exclusion criteria, and extracted the data. Jinjing Tan and Yalu Chen conducted GRADE classifications. Jianfeng Li checked the result of AMSTAR2 classification, and Yuanyuan Liu checked the data and results. Liqun Li and Guangwen Chen conducted statistical analyses. Li Liqun, Cen Qianli and Lijian Liu wrote the draft of the paper. Jinxiu Wei, Tan Jinjing and Yuanyuan Liu revised the paper. Xie Sheng was contributed in concept design, guidance and arbitrating all discrepancies, and was also responsible for the final content. All authors approved the final manuscript and attested that it has not been previously published.

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Tables

Table 1 Description of the 19 included meta-analyses

Studies	Outcomes	No of studies	No of participants / cases	Meta-analytic model used	Type of metric	Effect size (95%CI)	P value of Q test	I^2	P value of Egger's Test / funnel plots	Whether publication bias exists?
Associations between IBD and cancers										
Chen,2019[26]	Prostate cancer risk	1CCS,9 CS	282935 / NR	Random	OR	**1.78 (1.32, 2.41)**	0.000	88%	0.10	No
Wang,2014[27]	Cervical cancer risk	7 CS	83,866 / 253	Fixed	SIR	**1.20 (1.00, 1.45)**	0.049	24%	0.55	No
Lutgens,2013[28]	Colorectal cancer risk	11 CS	544,552 / 334	Random	SIR	**1.70 (1.20, 2.20)**	NR	64%	Symmetry	No
Cao,2018[29]	Thyroid cancer risk	8 CCS	4,652,390 / 4,984	Fixed	OR	**1.75 (1.48, 2.07)**	0.31	15%	Symmetry	No
Huai,2014[30]	Intrahepatic cholangiocarcinoma risk	4 CCS,1CS	222,248 / 4,939	Random	OR[a]	**2.61 (1.72, 3.95)**	0.01	73%	0.12	No
	Extrahepatic cholangiocarcinoma risk	2 CCS,1 CS	126,413 / 2,803	Random	OR[a]	**1.47 (1.10, 1.97)**	0.28	22%	0.12	No
Singh,2014[31]	Melanoma risk	12 CS	172,837 / 179	Random	OR[a]	**1.37 (1.10, 1.70)**	0.18	26%	0.43	No
Associations between IBD and cardio-cerebro-vascular diseases										
Yuan,2016[32]	Stroke incidence	8 CS	1,162,318 /18,762	Random	RR[a]	**1.32 (1.20, 1.44)**	0.00	85%	NR	No
Feng,2017[33]	Ischemic heart disease risk	12 CS	5,645,367 / NR	Random	RR[a]	**1.24 (1.14, 1.35)**	<0.01	87%	0.29	No
Sun,2018[34]	Cerebrovascular disease incidence	6 CS	NR / NR	Random	RR	**1.25 (1.08, 1.44)**	< 0.01	91%	0.1	No
	Coronary heart disease incidence	6 CS	NR / NR	Random	RR	**1.17 (1.07, 1.27)**	< 0.01	83%	0.1	No
	Myocardial infarction incidence	4 CS	NR / NR	Fixed	RR	**1.12 (1.05, 1.21)**	0.75	0%	0.1	No
Fumery,2014[35]	Venous thromboembolic risk	9 CS,1 CCS	940,572,339 / NR	Random	RR	**1.96 (1.67, 2.30)**	<0.01	99%	0.93	No
	Arterial thromboembolism risk	8 CS,1 CCS	22,472,601 / NR	Random	RR	1.15 (0.91, 1.45)	<0.01	97%	0.93	No
	Cardiovascular disease mortality	15 CS	69,383 / NR	Random	SMR	1.03 (0.93, 1.14)	<0.01	70%	0.47	No
Associations between IBD and obstetrical diseases										
O'Toole,2015[36]	Preterm birth incidence	23 CS	13,033/ NR	Random	OR	**1.85 (1.67, 2.05)**	0.05	31%	0.93	No
	Small for gestational age birth weight incidence	13 CS	4,144,549 / 118,523	Random	OR	**1.36 (1.16, 1.60)**	0.01	56%	Symmetry	No
	Congenital anomalies incidence	11 CS	3,336,345 / 120,312	Random	OR	**1.29 (1.05, 1.58)**	0.05	46%	Asymmetry	Yes
	Stillbirth incidence	10 CS	2,973,200 / 12,326	Random	OR	**1.57 (1.03, 2.38)**	0.17	30%	Symmetry	No
Associations between IBD and neuropsychiatric diseases										

Studies	Outcomes	No of studies	No of participants / cases	Meta-analytic model used	Type of metric	Effect size (95%CI)	P value of Q test	I^2	P value of Egger's Test / funnel plots	Whether publication bias exists?
Zhu,2019[38]	Parkinson's disease risk	3 CS,1 CCS	187,791,256 / 43,244	Random	RR[a]	**1.41 (1.19, 1.66)**	0.003	83%	0.62	No
Associations between IBD and otolaryngology and stomatology diseases										
Han,2019[43]	Rosacea risk	2 CCS,4 CSS	4,726,070 / NR	Fixed	RR[a]	**1.66 (1.50, 1.84)**	0.09	48%	> 0.05	No
Papageorgiou,2017[41]	Periodontitis prevalence	4 CS	811 / NR	Random	OR	**4.55 (3.00, 6.19)**	NR	0%	NR	No
Associations between IBD and other diseases										
Zhao,2019[37]	Sexual dysfunction risk	5 CCS,2 CS,1 CSS	352,977 / 35,885	Random	RR	**1.56 (1.28, 1.89)**	0.00	80%	0.24	No
Szafors,2018[39]	Osteoporotic fractures risk	9 CS	245,761 / 7,295	Random	RR[a]	**1.38 (1.11, 1.73)**	<0.01	89%	0.241	No
Zhang,2015[40]	Gallstone disease prevalence	2 CCS,6 CS	7,829 / 790	Fixed	OR	**1.72 (1.40, 2.12)**	0.23	25%	0.81	No
Del Pinto,2015[42]	Vitamin D deficiency prevalence	9 CCS,1 CS,4 CSS	1,891 / 625	Random	OR	**1.64 (1.30, 2.08)**	0.37	7%	0.11	No
Ning, 2019[44]	Herpes zoster infection risk (CD)	7 CS	NR / NR	Random	RR[a]	**1.74 (1.57, 1.92)**	< 0.01	84%	0.33	No
	Herpes zoster infection risk (UC)	6 CS	NR /NR	Random	RR[a]	**1.40 (1.31, 1.50)**	0.00	72%	0.45	No

Abbreviation CS=cohort study; CCS=case-control study; CSS=cross-sectional study; NR=not report; RR=relative risk; OR=odds ratio; SMR=standardized mortality ratio ; SIR=standardized incidence ratio; CD=Crohn's disease; IBD=inflammatory bowel disease UC=ulcerative colitis; No*=the original meta-analysis stated no evidence of publication bias; a=adjusted.

Table 2 Results of evidence quality for 29 outcomes classified by GRADE

Level of evidence	Outcomes		
	Increased risk/ incidence/ prevalence of	No association with	Decrease risk of
High	Periodontitis[41]	-	-
Moderate	Thyroid cancer[29], Myocardial infarction[34], Preterm birth[36], Stillbirth[36], Gallstone disease[40], Vitamin D deficiency[42].	-	-
Low	Cervical cancer[27], Melanoma[31],Intrahepatic cholangiocarcinoma[30], Extrahepatic cholangiocarcinoma[30], Coronary heart disease[34], Small for gestational age birth weight[36], Rosacea[43].	Cardiovascular disease mortality[35]	-
Very low	Prostate cancer[26], Colorectal cancer[28], Stroke[32], Ischemic heart disease[33], Cerebrovascular disease[34], Venous thromboembolic[35], Congenital anomalies[36], Sexual dysfunction[37], Parkinson's disease[38], Osteoporotic fracture[39],Herpes zoster infection (UC)[44], Herpes zoster infection (CD)[44].	Arterial thromboembolism[35]	-

Abbreviation CD=Crohn's disease; UC= ulcerative colitis.

Figures

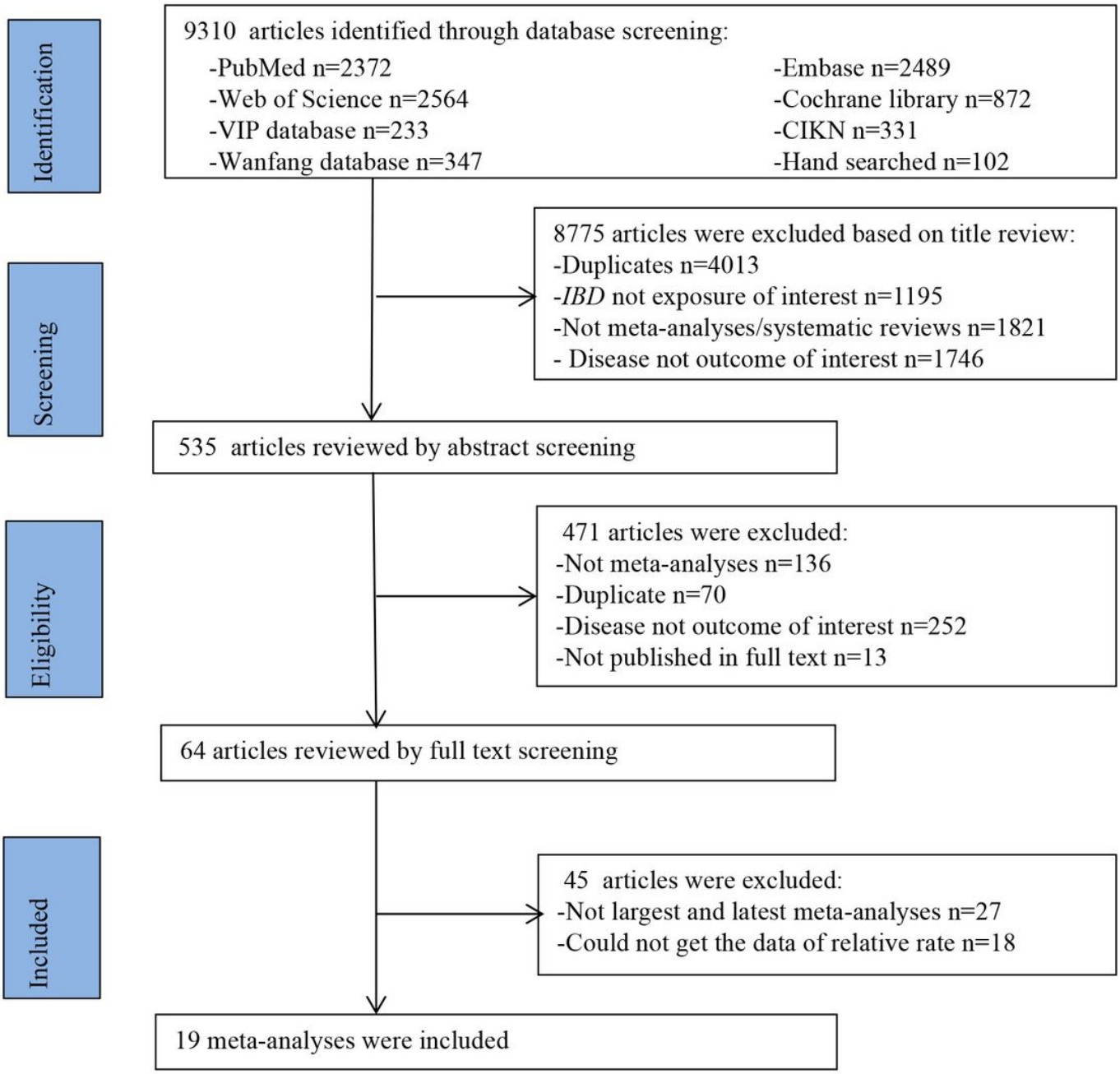


Fig.1 Flowchart of study selection process for umbrella review

Figure 1

Flowchart of study selection process for umbrella review

Association of IBD with	No of studies	Method	Effect size (95% CI)	Effect size (95% CI)	I^2 (%)	Evidence for publication bias
Prostate cancer risk [26]	10	Random		OR, 1.78 (1.32, 2.41)	88	No
Cervical cancer risk [27]	7	Fixed		SIR, 1.20 (1.00, 1.45)	24	No
Colorectal cancer risk [28]	11	Random		SIR, 1.70 (1.20,2.20)	64	No
Thyroid cancer risk [29]	8	Fixed		OR, 1.75 (1.48, 2.07)	15	No
Intrahepatic cholangiocarcinoma risk [30]	5	Random		OR[a], 2.61 (1.72, 3.95)	73	No
Extrahepatic cholangiocarcinoma risk [30]	3	Random		OR[a], 1.47 (1.10, 1.97)	22	No
Melanoma risk [31]	12	Random		OR[a], 1.37 (1.10, 1.70)	26	No
Stroke incidence [32]	8	Random		RR[a], 1.31 (1.61, 1.47)	87	No
Ischemic heart disease risk [33]	12	Random		RR[a], 1.24 (1.14, 1.35)	87	No
Cerebrovascular disease incidence [34]	6	Random		RR, 1.25 (1.08, 1.44)	91	No
Coronary heart disease incidence [34]	6	Random		RR, 1.17 (1.07, 1.27)	83	No
Myocardial infarction incidence [34]	4	Fixed		RR, 1.12 (1.05, 1.21)	0.0	No
Venous thromboembolic risk [35]	10	Random		RR, 1.96 (1.67, 2.30)	99	No
Arterial thromboembolism risk [35]	9	Random		RR, 1.15 (0.91, 1.45)	97	No
Cardiovascular disease mortality risk [35]	15	Random		SMR,1.03 (0.93, 1.14)	70	No
Preterm birth incidence [36]	23	Random		OR, 1.85 (1.67, 2.05)	31	No
SGA birth weight incidence [36]	13	Random		OR, 1.36 (1.16, 1.60)	56	No
Congenital anomalies incidence [36]	11	Random		OR, 1.29 (1.05, 1.58)	46	Yes
Stillbirth incidence [36]	10	Random		OR, 1.57（1.03, 2.38）	30	No
Sexual function risk [37]	8	Random		RR, 1.56 (1.28, 1.89)	80	No
Parkinson's disease risk [38]	4	Random		RR[a], 1.41 (1.19, 1.66)	83	No
Osteoporotic fractures risk [39]	9	Random		RR[a], 1.38 (1.11, 1.73)	89	No
Gallstone disease prevalence [40]	8	Fixed		OR, 1.72 (1.40, 2.12)	25	No
Periodontitis prevalence [41]	4	Random		OR, 4.55 (3.00, 6.19)	0.0	No
Vitamin D deficiency prevalence [42]	14	Random		OR, 1.64 (1.30, 2.08)	7	No
Rosacea risk [43]	6	Fixed		RR[a], 1.66 (1.50, 1.84)	48	No
Herpes zoster infection risk [44]	NR	NR		NR	NR	NR

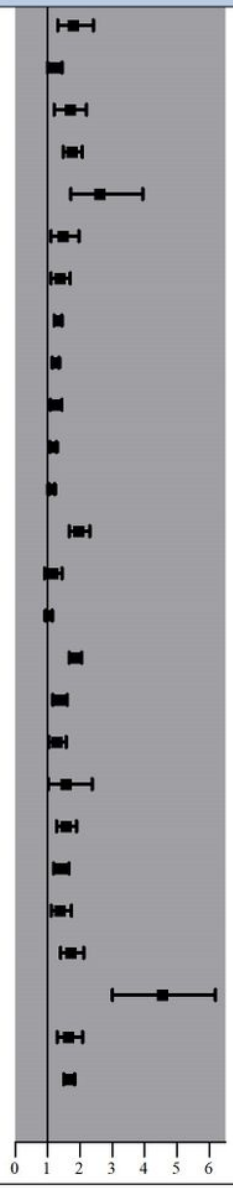
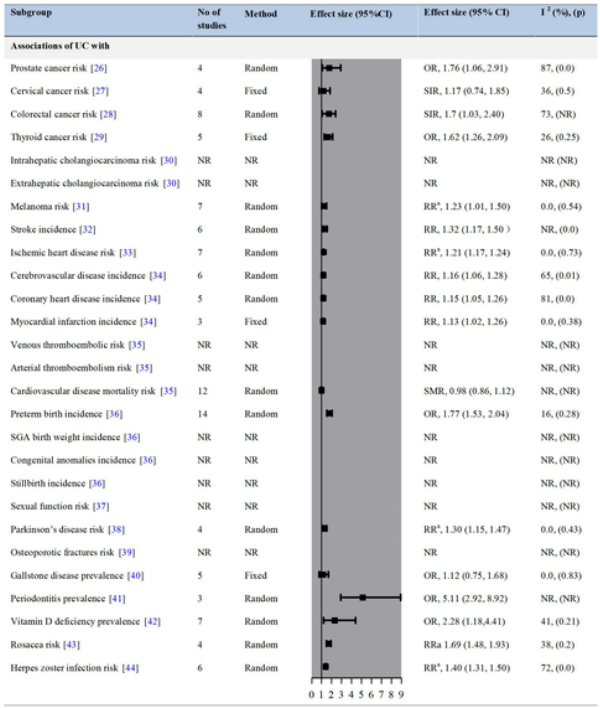


Fig.2 Summary effect estimates with 95% confidence intervals from 28 meta-analyses of associations between IBD and risk of other diseases

Abbreviation: IBD=inflammatory bowel disease; SGA=small for gestational age; NR=not report; RR=relative risk; OR=odds ratio; SMR=standardized mortality ratio; SIR=standardized incidence ratio; a=adjusted.

Figure 2

Summary effect estimates with 95% confidence intervals from 28 meta-analyses of associations between IBD and risk of other diseases



Subgroup	No of studies	Method	Effect size (95%CI)	Effect size (95% CI)	I^2 (%), (p)
Associations of UC with					
Prostate cancer risk [26]	4	Random		OR, 1.76 (1.06, 2.91)	87, (0.0)
Cervical cancer risk [27]	4	Fixed		SIR, 1.17 (0.74, 1.85)	36, (0.5)
Colorectal cancer risk [28]	8	Random		SIR, 1.7 (1.03, 2.40)	73, (NR)
Thyroid cancer risk [29]	5	Fixed		OR, 1.62 (1.26, 2.09)	26, (0.25)
Intrahepatic cholangiocarcinoma risk [30]	NR	NR		NR	NR (NR)
Extrahepatic cholangiocarcinoma risk [30]	NR	NR		NR	NR, (NR)
Melanoma risk [31]	7	Random		RR[a], 1.23 (1.01, 1.50)	0.0, (0.54)
Stroke incidence [32]	6	Random		RR, 1.32 (1.17, 1.50)	NR, (0.0)
Ischemic heart disease risk [33]	7	Random		RR[a], 1.21 (1.17, 1.24)	0.0, (0.73)
Cerebrovascular disease incidence [34]	6	Random		RR, 1.16 (1.06, 1.28)	65, (0.01)
Coronary heart disease incidence [34]	5	Random		RR, 1.15 (1.05, 1.26)	81, (0.0)
Myocardial infarction incidence [34]	3	Fixed		RR, 1.13 (1.02, 1.26)	0.0, (0.38)
Venous thromboembolic risk [35]	NR	NR		NR	NR, (NR)
Arterial thromboembolism risk [35]	NR	NR		NR	NR, (NR)
Cardiovascular disease mortality risk [35]	12	Random		SMR, 0.98 (0.86, 1.12)	NR, (NR)
Preterm birth incidence [36]	14	Random		OR, 1.77 (1.53, 2.04)	16, (0.28)
SGA birth weight incidence [36]	NR	NR		NR	NR, (NR)
Congenital anomalies incidence [36]	NR	NR		NR	NR, (NR)
Stillbirth incidence [36]	NR	NR		NR	NR, (NR)
Sexual function risk [37]	NR	NR		NR	NR, (NR)
Parkinson's disease risk [38]	4	Random		RR[a], 1.30 (1.15, 1.47)	0.0, (0.43)
Osteoporotic fractures risk [39]	NR	NR		NR	NR, (NR)
Gallstone disease prevalence [40]	5	Fixed		OR, 1.12 (0.75, 1.68)	0.0, (0.83)
Periodontitis prevalence [41]	3	Random		OR, 5.11 (2.92, 8.92)	NR, (NR)
Vitamin D deficiency prevalence [42]	7	Random		OR, 2.28 (1.18,4.41)	41, (0.21)
Rosacea risk [43]	4	Random		RRa 1.69 (1.48, 1.93)	38, (0.2)
Herpes zoster infection risk [44]	6	Random		RR[a], 1.40 (1.31, 1.50)	72, (0.0)

Fig.3A Summary effect estimates with 95% confidence of associations between type of IBD (UC) and risk of other diseases Abbreviation: UC= ulcerative colitis; SGA=small for gestational age; NR=not report; RR=relative risk; OR=odds ratio; SMR=standardized mortality ratio; SIR=standardized incidence ratio; a=adjusted.

Subgroup	No of studies	Method	Effect size (95%CI)	Effect size (95%CI)	I^2 (%), (p)
Associations of CD with					
Prostate cancer risk [26]	4	Random		OR, 1.29 (1.04, 1.61)	88, (0.0)
Cervical cancer risk [27]	3	Fixed		SIR, 1.63 (1.13, 2.35)	0.0, (0.01)
Colorectal cancer risk [28]	3	Random		SIR, 1.7 (1.01, 2.5)	0.0, (NR)
Thyroid cancer risk [29]	6	Fixed		OR, 1.41 (0.91, 2.18)	0.0, (0.65)
Intrahepatic cholangiocarcinoma risk [30]	NR	NR		NR	NR, (NR)
Extrahepatic cholangiocarcinoma risk [30]	NR	NR		NR	NR, (NR)
Melanoma risk [31]	7	Random		RR[a], 1.80 (1.17, 2.75)	30, (0.19)
Stroke incidence [32]	6	Random		RR, 1.17 (0.95, 1.45)	NR, (0.0)
Ischemic heart disease risk [33]	7	Random		RR[a], 1.24 (1.04, 1.48)	90, (<0.001)
Cerebrovascular disease incidence [34]	7	Random		RR, 1.27 (1.07, 1.51)	85, (0.0)
Coronary heart disease incidence [34]	5	Random		RR, 1.08 (1.03, 1.12)	0.0, (0.45)
Myocardial infarction incidence [34]	3	Fixed		RR, 1.14 (1.03, 1.26)	0.0, (0.83)
Venous thromboembolic risk [35]	NR	NR		NR	NR, (NR)
Arterial thromboembolism risk [35]	NR	NR		NR	NR, (NR)
Cardiovascular disease mortality risk [35]	10	Random		SMR, 1.12 (0.94, 1.32)	NR, (NR)
Preterm birth incidence [36]	14	Random		OR, 1.77 (1.52, 2.06)	14, (0.3)
SGA birth weight incidence [36]	NR	NR		NR	NR, (NR)
Congenital anomalies incidence [36]	NR	NR		NR	NR, (NR)
Stillbirth incidence [36]	NR	NR		NR	NR, (NR)
Sexual function risk [37]	NR	NR		NR	NR, (NR)
Parkinson's disease risk [38]	4	Random		RR[a], 1.28 (1.08, 1.52)	22, (0.28)
Osteoporotic fractures risk [39]	NR	NR		NR	NR, (NR)
Gallstone disease prevalence [40]	3	Fixed		OR, 2.05 (1.61, 2.63)	0.0, (0.54)
Periodontitis prevalence [41]	4	Random		OR, 3.96 (2.39, 6.54)	NR, (NR)
Vitamin D deficiency prevalence [42]	12	Random		OR, 1.63 (1.24, 2.13)	0.0, (0.7)
Rosacea risk [43]	4	Random		RR[a], 2.08 (1.26, 3.46)	68, (0.04)
Herpes zoster infection risk [44]	7	Random		RR[a], 1.74 (1.57, 1.92)	84, (<0.01)

Fig.3B Summary effect estimates with 95% confidence of associations between type of IBD (CD) and risk of other diseases Abbreviation: CD=Crohn's Disease ulcerative; SGA=small for gestational age; NR=not report; RR=relative risk; OR=odds ratio; SMR=standardized mortality ratio; SIR=standardized incidence ratio; a=adjusted.

Figure 3

Fig.3A Summary effect estimates with 95% confidence of associations between type of IBD (UC) and risk of other diseases Fig.3B Summary effect estimates with 95% confidence of associations between type of IBD (CD) and risk of other diseases

Associations of IBD with (Stratified by gender)	No of studies	Method	Effect size (95%CI)	Effect size (95%CI)	I^2 (%), (P)
Male					
Colorectal cancer risk [28]	3	Random		SIR, 1.90 (0.80,3.0)	84,(NR)
Thyroid cancer risk [29]	2	Fixed		OR, 2.05 (1.38, 3.05)	NR, (0.26)
Stroke incidence [32]	5	Random		RR[a], 1.23 (1.04, 1.45)	72, (0.01)
Ischemic heart disease risk [33]	NR	Random		RR[a], 1.19 (1.03, 1.38)	NR, (0.0)
Cerebrovascular disease incidence [34]	NR	Random		RR, 1.34 (1.11, 1.61)	NR, (NR)
Coronary heart disease incidence [34]	NR	Random		RR, 1.13 (1.09, 1.17)	NR, (NR)
Sexual dysfunction risk [37]	7	Random		RR, 1.41 (1.09, 1.81)	80, (<0.001)
Parkinson's disease risk [38]	2	Random		RR[a], 1.53 (1.09, 2.15)	NR, (NR)
Female					
Colorectal cancer risk [28]	3	Random		SIR, 1.40 (0.80, 2.10)	61, (NR)
Thyroid cancer risk [29]	2	Fixed		OR, 1.48 (1.11, 1.97)	NR, (0.79)
Stroke incidence [32]	5	Random		RR[a], 1.46 (1.12, 1.91)	90, (0.0)
Ischemic heart disease risk [33]	NR	Random		RR[a], 1.35 (1.21, 1.51)	NR, (0.0)
Cerebrovascular disease incidence [34]	NR	Random		RR, 1.77 (1.20, 2.59)	NR, (NR)
Coronary heart disease incidence [34]	NR	Random		RR, 1.27 (1.12, 1.45)	NR, (NR)
Sexual dysfunction risk [37]	5	Random		RR, 1.76 (1.28, 2.42)	70, (0.011)
Parkinson's disease risk [38]	2	Random		RR[a], 1.49 (1.29, 1.72)	NR, (NR)

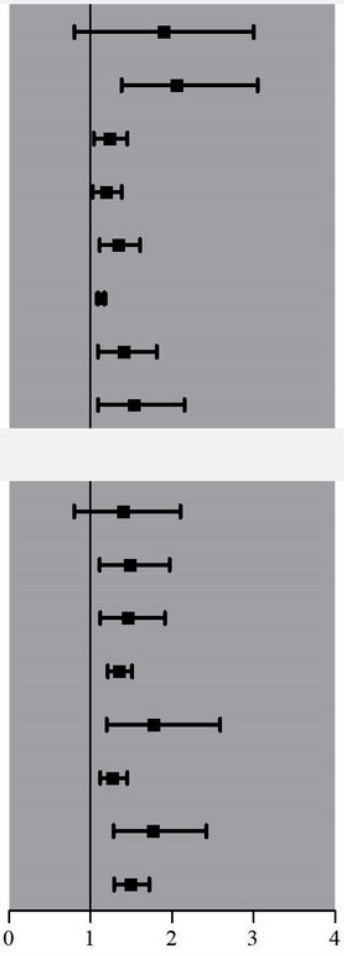


Fig.4 Summary effect estimates with 95% confidence of associations between gender of IBD patients and risk of other diseases

Abbreviation: NR=not report; RR=relative risk; OR=odds ratio; SIR=standardized incidence ratio; a=adjusted.

Figure 4

Summary effect estimates with 95% confidence of associations between gender of IBD patients and risk of other diseases

Associations of IBD with (Stratified by ethnicity)	No of studies	Method	Effect size (95%CI)	Effect size (95%CI)	I^2(%), (P)
Caucasian					
Prostate cancer risk [26]	7	Random		OR, 1.60 (1.17, 2.19)	90, (0.0)
Thyroid cancer risk [29]	2	Fixed		OR, 1.87 (1.34, 2.61)	NR, (0.29)
Herpes zoster infection risk (CD) [44]	4	Random		RR[a], 1.71 (1.62, 1.80)	0.0, (0.4)
Herpes zoster infection risk (UC) [44]	3	Random		RR[a], 1.43 (1.17, 1.74)	87, (<0.001)
Asian					
Prostate cancer risk [26]	3	Random		OR, 1.78 (1.32 ,2.41)	88, (0.0)
Thyroid cancer risk [29]	4	Fixed		OR, 1.55 (1.1, 2.08)	NR, (0.39)
Intrahepatic cholangiocarcinoma risk [30]	1	Random		RR[a], 1.70 (1.39, 2.08)	NA, (NA)
Extrahepatic cholangiocarcinoma risk [30]	1	Random		RR[a], 1.50 (1.14,1.97)	NA, (NA)
Stroke incidence [32]	3	Random		RR[a], 1.59 (1.11, 2.30)	NR, (0.01)
Rosacea risk [43]	4	Random		RR[a], 2.25 (1.69, 2.99)	20, 0.29
Herpes zoster infection risk (CD) [44]	3	Random		RR[a], 1.79 (1.45, 2.20)	93, (<0.001)
Herpes zoster infection risk (UC) [44]	3	Random		RRa, 1.38 (1.33, 1.43)	0.0, (0.43)
Non-Asian					
Intrahepatic cholangiocarcinoma risk [30]	4	Random		RR[a], 3.08 (2.24, 4.23)	14, (0.32)
Extrahepatic cholangiocarcinoma risk [30]	2	Random		RR[a], 1.46 (0.74, 2.87)	63, (0.11)
Stroke incidence [32]	5	Random		RR[a], 1.21 (1.10, 1.32)	NR, (0.0)
European					
Melanoma risk [31]	8	Random		RR[a], 1.21 (0.98, 1.50)	NR, (NR)
Rosacea risk [43]	2	Random		RR[a], 1.58 (1.42, 1.77)	0.0, (0.37)
North American					
Melanoma risk [31]	4	Random		RR[a], 1.92 (1.12, 3.28)	NR, (NR)

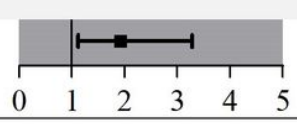


Fig.5 Summary effect estimates with 95% confidence of associations between ethnicity of IBD patients and risk of other diseases Abbreviation: CD=Crohn's Disease ulcerative; UC= ulcerative colitis; NR=not report; RR=relative risk; OR=odds ratio; a=adjusted.

Figure 5

Summary effect estimates with 95% confidence of associations between ethnicity of IBD patients and risk of other diseases

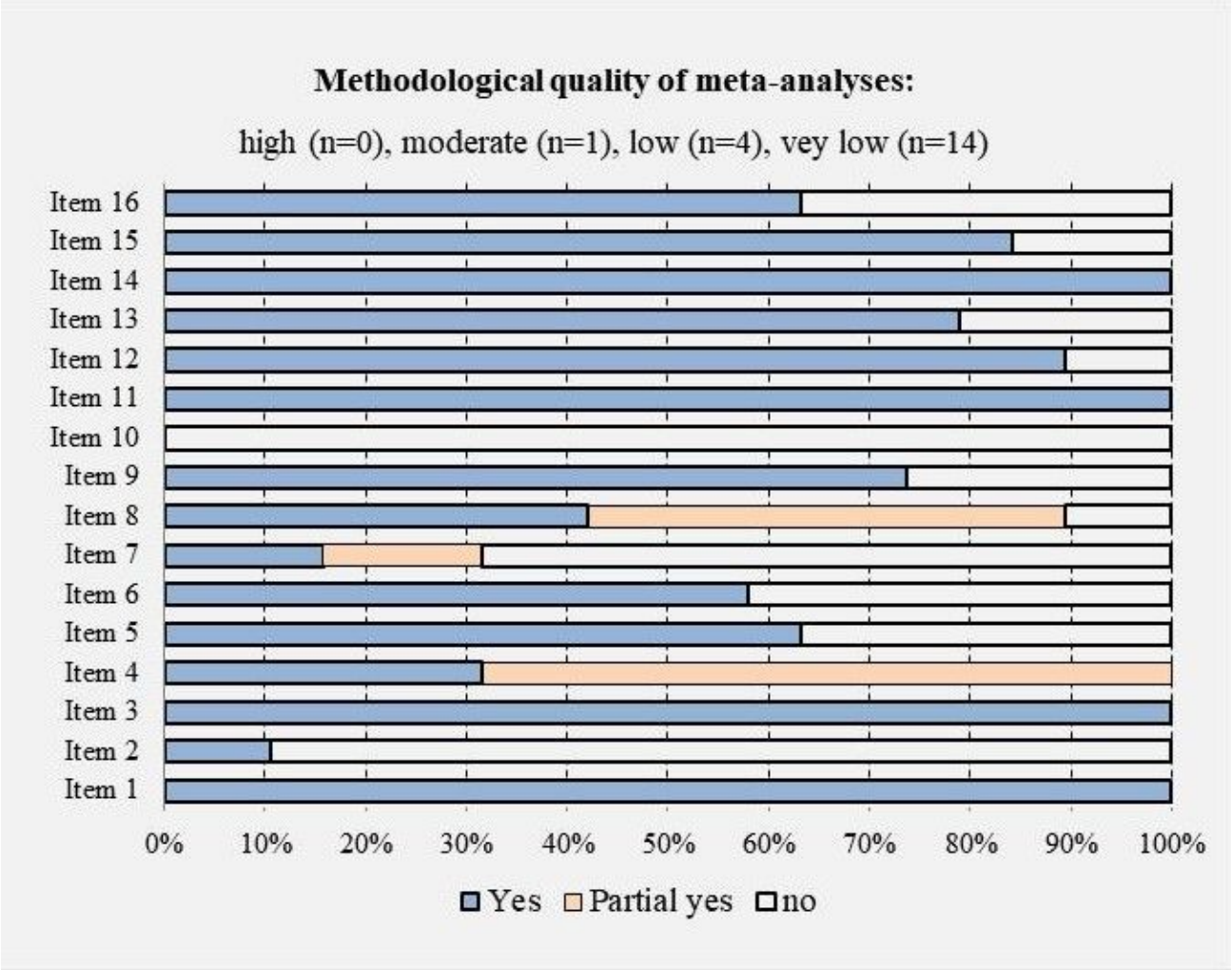


Fig.6 Quality assessment of the included studies with AMSTAR
The graph is showing a summary (n = 19 meta-analyses) of the evaluation on each of the AMSTAR2 domains.

Figure 6

Quality assessment of the included studies with AMSTAR

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.doc
- MOOSEChecklist.doc
- SupplementalTable14.docx