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Umbrella review of risk factors for inflammatory bowel disease: a study protocol

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ABSTRACT

Introduction Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disorder that arises from complex interactions between genetics, environment and gut microbiota. It encompasses Crohn's disease, ulcerative colitis and IBD-unclassified. The protracted course of IBD imposes a significant burden on patients' quality of life, economic productivity, social functioning, as well as treatment, hospitalisation and surgery. This study aims to conduct an umbrella review of meta-analyses to systematically evaluate the methodology's quality, potential biases and validity of all epidemiological evidence focused on risk factors for IBD while providing an overview of the evidence concerning IBD risk factors.

Methods and analysis We will systematically search, extract and analyse data from reported systematic reviews and meta-analyses that specifically focus on the risk factors of IBD, following the guidelines outlined in Preferred Reporting Items for Overviews of Reviews. Our search will encompass PubMed, Embase, Web of Science and the Cochrane Database of Systematic Reviews from the initial period up until April 2023 (last update), targeting systematic reviews and meta-analyses based on non-interventional studies. Inclusion criteria allow for systematic reviews and meta-analyses evaluating IBD risk factors across all countries and settings, regardless of ethnicity or sex. The identified risk factors will be categorised according to the health ecological model into innate personal traits, behavioural lifestyles, interpersonal networks, socioeconomic status and macroenvironments. To assess methodological quality for each meta-analysis included in our study, two authors will employ a measurement tool to assess the methodological quality of systematic reviews (AMSTAR)-2, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria along with evidence classification criteria.

Ethics and dissemination Ethical approval is not required for this umbrella review. We will seek to submit the results for publication in a peer-reviewed journal or present it at conferences.

PROSPERO registration number CRD42023417175.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We will systematically search, extract and analyse the data from reported systematic reviews and meta-analyses which focus on the risk factors of inflammatory bowel disease.
⇒ We will search PubMed, Embase, Web of Science and the Cochrane Database of Systematic Reviews from the initial through April 2023 (last update) for systematic reviews and meta-analyses of non-interventional studies.
⇒ To assess methodological quality for each meta-analysis included in our study, two authors will employ AMSTAR-2, Grading of Recommendations, Assessment, Development and Evaluation criteria along with evidence classification criteria.
⇒ This study will solely extract and analyse existing data from systematic reviews and meta-analyses, omitting data from original studies not included in these reviews and analyses.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic idiopathic inflammatory disease at the intersection of complex interactions between genetics, environment and gut microbiota, which comprising Crohn's disease (CD) and ulcerative colitis (UC).[1 2] In addition, IBD-unclassified (IBD-U) refers to a type of disease characterised by neither 'ulcerative colitis' nor 'Crohn's disease', which is more common in children with early-onset IBD.[3] It is estimated that more than 10 000 residents in the USA and about 20 000 in Europe have IBD.[4 5] IBD was previously more common in high-income countries in the West and rarely reported in Asia, Africa and Latin America.[6] At the turn of the 21st century, IBD has become a global disease with rising prevalence in the newly industrialised countries of Asia, South America and the Middle East.[7] In China, the incidence of IBD has increased along with economic development and lifestyle changes, resulting in a substantial increase in disease burden.[8] The long course of IBD leads to a significant burden of treatment, hospitalisation, surgery and a significant impact on patients' quality of life, economic productivity and social functioning.[9 10] Given the

increasing incidence and severe disease burden of IBD and the high cost of treatment, it is necessary to better understand the potential risk factors of IBD and to adopt effective prevention strategies.

The pathogenesis of IBD is believed to be multifactorial, with the involvement of both genetic and environmental factors contributing to the initiation and progression of this disease.[11–13] Over the past few decades, the heritability of IBD has been recognised: in 2001, the first CD-related gene was discovered.[14 15] Subsequent research observed 163 risk alleles associated with IBD in white populations.[16] Furthermore, it is widely acknowledged that the aetiology of IBD involves a complex interplay between genetic and environmental factors.[17] A large number of meta-analyses have identified several risk factors for IBD, mainly including smoking, urban living, appendectomy, tonsillectomy, antibiotic use, oral contraceptive use, consumption of soft drinks, vitamin D deficiency, depression, obesity and psoriasis.[18–22] In addition, several protective factors of IBD were also identified in meta-analyses, such as exercise, tea consumption, high levels of folate and high levels of vitamin D.[20]

Despite the extensive meta-analyses conducted on observational studies to assess a wide range of risk factors associated with IBD in recent years, limitations in research design, variations in exposure factor assessments and inconsistent outcomes pose challenges in reaching definitive conclusions. In 2019, Piovani *et al*[20] published an umbrella review to assess environmental risk factors for IBD. They finally analysed 71 environmental risk factors associated with IBD. However, they mainly focused on the external environmental factors and ignored the influence of internal environmental factors on IBD, such as obesity, depression and psoriasis. To the best of our knowledge, there has been a lack of comprehensive review and evidence assessment regarding all internal and external environmental risk factors associated with IBD. In order to develop effective prevention strategies for IBD, it is imperative to systematically evaluate the methodology quality, potential biases and validity of all available studies on the risk factors for this condition. Henceforth, we intend to conduct an umbrella review of meta-analyses in order to provide a comprehensive overview of the evidence pertaining to IBD risk factors.

OBJECTIVES

The aim of the present study is to conduct a comprehensive review encompassing meta-analyses, with the purpose of systematically evaluating the methodological quality, potential biases and validity of all epidemiological evidence pertaining to risk factors associated with IBD. Additionally, this study aims to provide an overview of the existing evidence regarding IBD risk factors.

METHODS AND ANALYSIS

Design and registration

We will systematically search, extract and analyse the data from reported systematic reviews and meta-analyses which focus on the risk factors of IBD following the Preferred Reporting Items for Overviews of Reviews guidelines,[23] and the checklist has been completed (online supplemental table S1). This umbrella review will be performed following the methodological guideline of the Joanna Briggs Institute Manual for Evidence Synthesis of Umbrella Reviews[24] and the Cochrane handbook for the conduction of systematic reviews.[25] In addition, we have prospectively registered this umbrella review in the International Prospective Register of Systematic Reviews, and registration number is CRD42023417175 (https://www.crd.york.ac.uk/PROSPERO/). The study began in November 2022 and is expected to be completed in December 2024.

Patient and public involvement

The patients or the public have not been involved in developing the present protocol. And they will not be involved in conducting the umbrella review.

Eligibility criteria

Systematic reviews and meta-analyses of non-interventional studies that evaluate the risk factors for IBD (including IBD-U) of any ethnicity or sex in all countries and settings are eligible for inclusion. Data on individual risk factors will be extracted separately if two or more risk factors are reported in a single meta-analysis. The list of index publications included in eligible meta-analyses is reviewed to identify those that are present in two or more reviews. A citation matrix will be generated, presenting all the meta-analyses as columns and the included index publications as rows. The overlap will be estimated by calculating the corrected covered area (CCA) to assess if specific index publications are over-represented. CCA reflects the actual degree of overlap, independent of large reviews. In case a high or very high overlap is detected, defined as CCA equal to or exceeding 10%, we plan to retain the review that is (1) the most recent, (2) contains a greater amount of information and (3) demonstrates higher rigour in terms of methodology, evaluated through AMSTAR-2 and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) scale assessments.[26 27] Besides, if the latest meta-analysis does not perform dose–response analysis, while another meta-analysis does, both studies will be included for data extraction. We will exclude meta-analyses that evaluate the therapeutic effects of a certain treatment on IBD. Non-English studies, animal and cell culture studies will also be excluded. In addition, we excluded studies with very low quality in AMSTAR-2 scores.

Population

This umbrella review focuses on systematic reviews with meta-analyses that assess the risk factors associated with

IBD. The original articles included in these systematic reviews and meta-analyses should specifically examine risk factors that have the potential to either increase or decrease the likelihood of developing IBD. However, studies evaluating the effectiveness of specific treatments for IBD, investigations into the pathogenesis of this condition, as well as research on factors contributing to exacerbation and recurrence of IBD will be excluded from this review.

Exposure

We will include meta-analysis which report at least one risk factor of IBD, including environmental, lifestyle, disease-related, treatment-related, demographic, genetic, social and psychophysiological risk factors. The strength of risk factors should be evaluated by OR, relative risk (RR) or HR with 95% CIs.

Outcomes

The diagnosis of IBD in the original research should refer to the internationally recognised IBD diagnostic guidelines, such as the European Crohn's and Colitis Organisation (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline for Diagnostic Assessment in IBD.[28]

Study designs

Only systematic reviews and meta-analyses of non-interventional studies that evaluate the risk factors for IBD of any ethnicity or sex in all countries and settings are eligible for inclusion. All included systematic reviews and meta-analysis need to focus on the risk factors of IBD and describe the meta-analysis method in detail, including complete search strategy, inclusion and exclusion criteria, literature quality evaluation criteria, result evaluation, analysis methods and procedures, and results interpretation criteria. The original articles in systematic reviews and meta-analysis included prospective or retrospective cohort designs, case-control studies or cross-sectional studies.

Information sources

We will search PubMed, Embase, Web of Science and the Cochrane Database of Systematic Reviews from the initial through April 2023 (last update) for systematic reviews and meta-analyses of non-interventional studies. In addition, the reference lists of all included meta-analyses will also be screened for additional articles.

Search strategy

We will retrieve the databases through a combination of Medical Subject Headings (MeSHs), keywords and text words associated with IBD following the Scottish Intercollegiate Guidelines Network Search Filters (SIGN) guidance of literature searching: (((risk) OR (incidence)) AND ((systematic review) OR (meta-analysis))) AND (((inflammatory bowel diseases) OR (Inflammatory Bowel Disease)) OR (Bowel Diseases, Inflammatory)).[29]

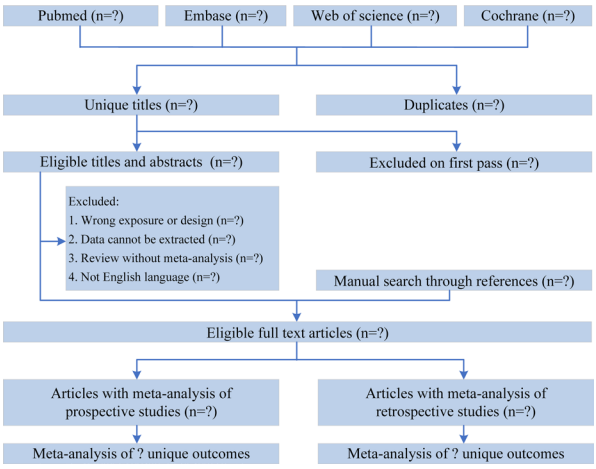

Figure 1 Flow chart of the systematic search and selection process.

A detailed search strategy is provided in online supplemental table S2.

Study selection

All retrieved literature will be screened using Endnote V.X9. After excluding duplicates, two authors will screen the titles and abstracts and identify meta-analyses which meet the inclusion standard through full-text reading independently. All disagreement in the process between the two authors will be resolved by a third author. In addition, we will hand search studies from the reference lists to identify meta-analysis that might have been ignored (figure 1).

Assessment of methodological quality

Two authors will assess the methodological quality of each meta-analysis using AMSTAR-2, a valid, strict and reliable measurement tool in assessing the quality of systematic reviews and meta-analyses.[30] AMSTAR-2 comprises a total of 16 items, with item 2, item 4, item 7, item 9, item 11, item 13 and item 19 being the key components. Based on these items, the report is categorised into four levels: (1) high quality—where either no non-key items or only one non-key item fails to meet the criteria; (2) moderate quality—when more than one non-critical element does not meet the requirements; (3) low quality—if at least one key entry fails to meet the standards along with or without any non-key entries failing to comply; and finally; (4) very low quality—when multiple key entries do not satisfy the specified criteria. Besides, according to the GRADE, evidence of each risk factor will be evaluated and graded as 'high', 'moderate', 'low' or 'very low' quality.[31] In addition, we will classify the epidemiological evidence of each risk factor into four categories using the evidence classification criteria: class I (convincing evidence), class II (highly suggestive evidence), class III (suggestive evidence), class IV (weak evidence) and NS (non-significant) (table 1).[32–34]

Table 1 Evidence classification criteria

Evidence class	Description
Class I: convincing evidence	>1000 cases (or >20 000 participants for continuous outcomes), statistical significance at $p<10^{-6}$ (random effects), no evidence of small-study effects and excess significance bias; 95% prediction interval excluded the null, no large heterogeneity (I^2<50%)
Class II: highly suggestive evidence	>1000 cases (or >20 000 participants for continuous outcomes), statistical significance at $p<10^{-6}$ (random effects) and largest study with 95% CI excluding the null value
Class III: suggestive evidence	>1000 cases (or >20 000 participants for continuous outcomes) and statistical significance at p<0.001
Class IV: weak evidence	The remaining significant associations with p<0.05
NS: non-significant	P>0.05

Data extraction

Two authors will independently extract the following data from each eligible study: (1) name of author, (2) publication time, (3) risk factors, (4) type of IBD (CD, UC or IBD-U), (5) number of included studies, (6) number of cases and total participants, (7) study design (cross-sectional, case-control, cohort), (8) length of follow-up and (9) RR, OR or HR estimates with 95% CIs. In addition, we will extract the meta-analytical model used (random or fixed), estimate of heterogeneity (I^2 and Cochran's Q-test) and small-study assessment (Egger's test, Begg's test and funnel plot). When dose–response analysis and subgroup analysis are performed, we will extract the p value for nonlinearity and any reported estimate for subgroup analysis. Any disagreement will be resolved by a third author.

Data summary

We will recalculate the RR, OR or HR with 95% CIs through random or fixed effects models and evaluate the heterogeneity (I^2 and Cochran's Q-test) and small-study effects (Egger or Begg test for each systematic review and meta-analysis with over 10 studies) in each meta-analysis when sufficient data are provided.[35–37] Risk factors will be categorised into the following five aspects according to the health ecological model[38 39]: innate personal trait (including age, gender, race, genetics, birth status, height, weight, body mass index, underlying diseases, previous treatments, etc), behavioural lifestyles (including diet, exercise, smoking, drinking, staying up late, working hours, etc), interpersonal network (including marriage, family relationship, social relationship, etc), socioeconomic status (including occupation, family economic level, debt, etc) and macroenvironments (including urban or rural environment, pets, immigrants, residential environment, etc).

For risk factors identified as class I or II evidence, we will conduct sensitivity analysis when sufficient data are provided to identify the effect of some individual study on total significance of the evidence. Dose–response analysis for any risk factors of IBD will also be extracted from the involved meta-analyses. Furthermore, if the most recent meta-analysis does not include clinical research studies that have been included in other meta-analyses, we will merge the data from these studies and conduct a reanalysis. A p value <0.10 is regarded as statistically significant for heterogeneity tests. For other tests, a p value <0.05 is identified as significant. Evidence synthesis is performed through Review Manager V.5.4 (Cochrane Collaboration, Oxford, UK). Egger and Begg test and sensitivity analysis are conducted via Stata (V.15.1).

Ethics and dissemination

Ethical approval is not required for this umbrella review. We will seek to submit the results for publication in a peer-reviewed journal or present it at conferences.

DISCUSSION

IBD is most common in working adults aged 20–40 years, and the prevalence rate is similar in men and women, which has a great negative impact on the quality of life and work of patients. At present, there is a lack of clear understanding of the specific aetiology and pathogenesis of IBD, and at the same time, it has caused a heavy burden on the global health system due to its characteristics of recurrent symptoms, poor effect of drug treatment and surgical intervention.

Up to now, a large number of researchers around the world have carried out clinical research and evidence-based medical research on the risk factors of IBD. The umbrella evaluation will evaluate the advantages and disadvantages of existing evidence-based evidence from systematic review and meta-analyses on the risk factors of IBD, help to understand the potential risk factors for the occurrence and development of IBD in a more comprehensive way from multiple dimensions, provide a theoretical basis for the development of more clinical effective prevention and control measures for IBD, and provide directions for further clinical research. To our knowledge, this study will be the first umbrella review to cover all potential risk factors for IBD. In order to better present the evidence evaluation results of IBD risk factors,

this study will classify all potential risk factors based on the health ecological model.

Limitations

This study also possesses certain limitations. First, our search will be limited to English databases, potentially introducing bias by excluding studies in other languages. Second, only published data will be considered, disregarding any unpublished or forthcoming evidence-based evidence. Lastly, this study will solely extract and analyse existing data from systematic reviews and meta-analyses, omitting data from original studies not included in these reviews and analyses.

Contributors Conceptualisation, writing – original draft and writing – review and editing: all authors. Methodology: ZO, ZL and RQ. Project administration and supervision: RQ.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

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