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Risk factors for developing irritable bowel syndrome: systematic umbrella review of reviews

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Abstract

Background Irritable bowel syndrome (IBS) is a debilitating disorder affecting 4–9% of the global population. It is a multifaceted disorder with complex and varied causes. This review aims to consolidate the evidence regarding IBS risk factors by examining existing systematic reviews and meta-analyses, covering potential genetic, immunological, psychological, and dietary causes.

Methods Systematic literature searches were conducted in MEDLINE, Embase and Cochrane library databases. Study selection and data extraction were conducted independently by four authors, with discrepancies resolved by consensus with a senior author. Systematic reviews examining risk factors of IBS development were eligible for review. Results were narratively synthesized. Quality of reviews were analysed using AMSTAR 2, and evidence were appraised using GRADE methodology.

Results A total of 69 systematic reviews were included in this study. Most reviews were of "critically low" quality, while the remaining were "low" quality. Common shortcomings included the absence of a list of excluded studies with justifications for their exclusion and inadequate consideration of the risk of bias in individual studies. Eight major categories of risk factors for IBS identified were as follows: dietary, genetic, environmental, psychological, gut microbiome, socio-economic, physiological, and pathological, albeit overlaps exist. The most frequently reported risk factors for IBS development were female gender and anxiety disorders, with overall GRADE evaluation of "low"; depression and gastroenteritis, with overall GRADE evaluation of "moderate".

Conclusions Clinical practice should prioritize recognition of these risk factors. Future reviews should improve their reporting of results based on the PRISMA guidelines, to enhance the quality of research in this field.

Protocol registration PROSPERO CRD42023493739.

Keyword Irritable bowel syndrome, Risk factors, Overview of reviews, Umbrella review, Systematic review

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Background

Irritable bowel syndrome (IBS) is a disorder of the gut-brain axis diagnosed through the symptom cluster outlined in the ROME IV criteria [1, 2]. It is an exceedingly common condition, affecting some 4–9% [3] of the global population, and with significant adverse effects and impediments. Research has consistently shown that IBS reduces the quality of life related to health [4] and contributes to workplace absenteeism at a societal level [5], underlining its economic burden [6]. Additionally, the global trend towards adopting a Western diet and lifestyle [7] is expected to increase the incidence of IBS. Given its rising prevalence [7] and the chronic nature of this condition [8], this necessitates further research into the risk factors for new-onset IBS to develop preventive measures against the onset of the condition.

At present, the causes of IBS are varied, complex, and incompletely understood [9]. Research continues to explore a broad range of risk factors, including genetic [10], immunological [11], psychological [12], and dietary elements [13]. Recent years have seen burgeoning interest in understanding how the gut microbiota [14], the interactions between the gut and the brain [15], and gastrointestinal motility [16] contribute to the development of IBS. Furthermore, the field of exposomics [17, 18], which examines the influence of environmental factors on disease development, is shedding new light on new risk factors for IBS. For instance, air pollution, already linked to various health issues, is now being investigated for its potential role in altering the gut microbiome and increasing the risk of IBS in previously healthy individuals [19, 20]. The expanding body of research underscores the relevance and timeliness of an overview of systematic reviews on these topics, which would help synthesize and critique current knowledge and findings.

Addressing this gap, this study attempts a umbrella review of existing systematic reviews [21], specifically focusing on risk factors associated with the onset of IBS in individuals who were previously healthy. These findings aim to bridge the gap between research on IBS risk factors and their applications in clinical settings, enhance current preventive strategies, and inspire further investigations into this critical area.

Methods

Search strategy

We searched MEDLINE, Embase, and Cochrane library databases from database inception to November 11, 2024. This current systematic review was performed with reference to the latest Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [22], with search terms including but were not limited to "Irritable Bowel Syndrome", "Risk Factors" and "Systematic Review". The search strategy was developed in consultation with an information management specialist, and the full search strategy is available in the Supplementary Material (Table S1). The study protocol was prospectively registered in PROSPERO (registration number CRD42023493739).

Eligibility and selection criteria

All search results were imported into Covidence (Melbourne, Victoria, Australia) for the identification and removal of duplicates. To ensure consistency and rigour, the Covidence software was set to ensure that each article was reviewed independently by two reviewers independently at every stage, including both the title and abstract screening and the full-text review phases. For the title and abstract screening, five reviewers (FS, TOSK, ASPT, JQ, and DTL) were involved to ensure comprehensive coverage of the large number of search results and to identify a wider pool of potentially eligible studies before reaching consensus with a senior reviewer. Discrepancies at both stages were resolved through consensus with a senior author (QXN or KTHS). Only original systematic reviews of observational studies, including cohort, case–control and cross-sectional studies, or interventional studies in English or with an English translation were included. Non-systematic narrative reviews, editorials, opinion pieces and case reports were excluded from the study. Studies which investigated primary risk factors of IBS in previously healthy individuals which may include but were not limited to dietary factors, psychosocial factors, gastrointestinal infections, certain medication uses, lifestyle factors such as physical activity and sleep patterns, genetic predisposition, environmental factors and socioeconomic factors. Studies without a clear diagnosis of IBS, those that examined non-specific exposures, interventions for managing IBS, secondary risk factors (that might affect the course or management of IBS), animal studies, or those involving pediatric populations were excluded.

Data extraction and outcomes

The primary outcomes of interest in this paper include the measure of the strength of association between the defined risk factor(s) and the development of IBS, reported in relative risks (RR), odds ratios (OR), or prevalence/incidence rates in the reviewed studies. Narrative synthesis of collected data was conducted. Study characteristics, populations, risk factors examined, IBS outcome measures and key findings would be extracted from included papers, with similar risk factors being grouped together (e.g. dietary, psychological, early life exposures)

across different studies. We also provided a summary of the evidence supporting each category and evaluated the strength of association with developing IBS.

Quality assessment and risk of bias

The Measurement Tool to Assess Systematic Reviews (AMSTAR2) tool was used for quality assessment and check for robustness of evidence provided in the studies included in this systematic review [23]. The AMSTAR2 tool comprises 16 items that evaluate various aspects of a systematic review's methodology, such as the comprehensiveness of the literature search, the justification of excluded studies, the appropriateness of the methods used to synthesize results, and the assessment of the risk of bias in individual studies. This produces an overall grading of an article: high, moderate, low or critically low. To comprehensively evaluate the level of evidence for frequently mentioned risk factors, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was used [24]. The GRADE framework evaluates evidence in five domains, namely: Risk of bias, inconsistency, indirectness, imprecision and publication bias.

Results

Summary of included studies

The initial search from the Embase, MEDLINE and Cochrane Library databases yielded 4903 articles. References were imported into Covidence, resulting in the automated removal of 1119 duplicates. Further screening resulted in the manual removal of 3784 articles not meeting the including criteria during the title and abstract sieve, with 101 articles remaining for full-text screening. Grey literature was also searched, identifying two articles for review, one of which was not retrievable. Finally, a total of 69 systematic reviews [2, 25–92] published between 2002 and 2024 were included. The process of literature search and article selection is summarized in Fig. 1. A summarized list of studies and their reason(s) for exclusion after full-text review is detailed in the Supplementary Material (Table S2).

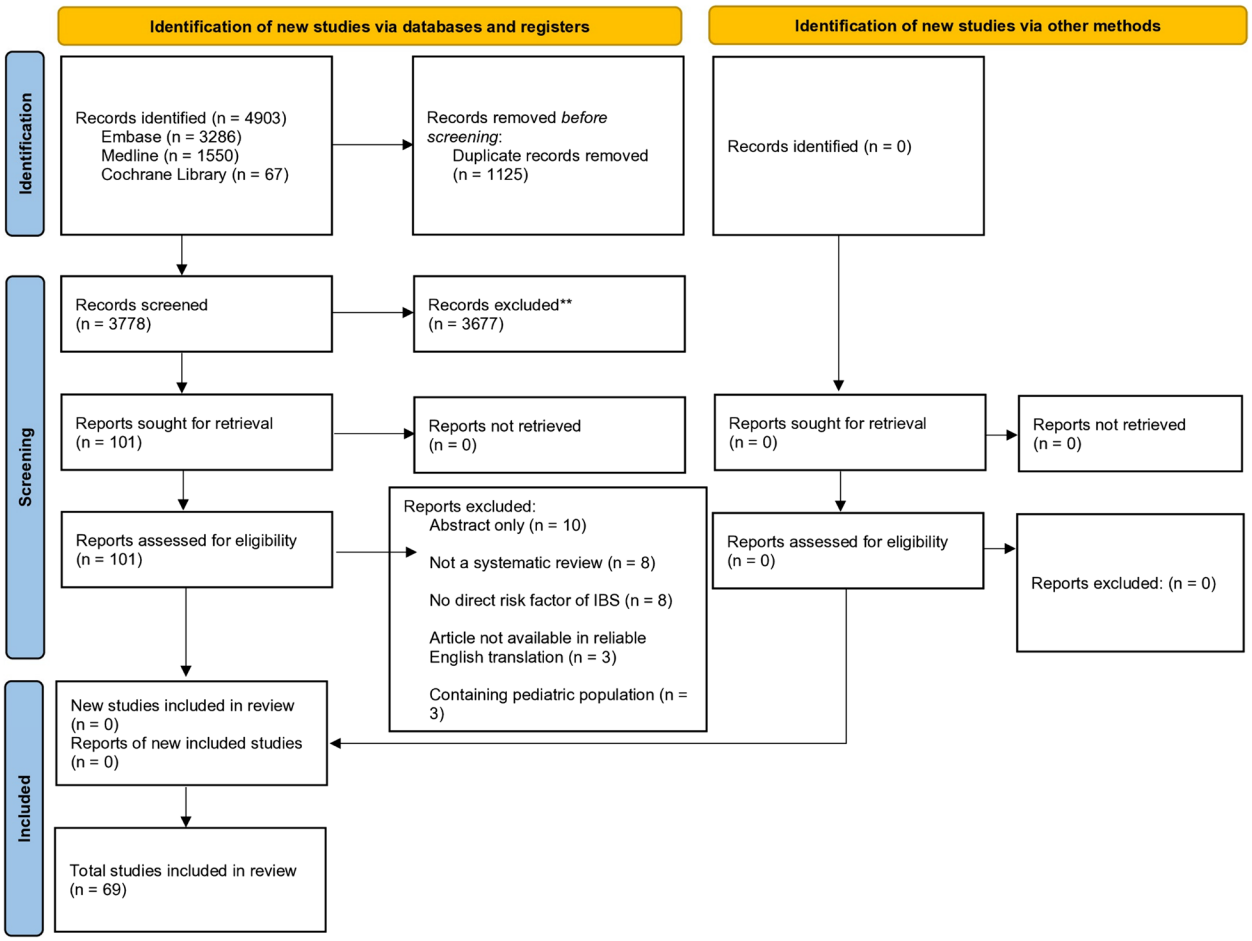

Fig. 1 PRISMA flowchart showing the study search and selection process

Appraisal of quality of reviews

As rated using the AMSTAR2 tool, all studies were categorized as "low" (15 studies, 22%) or "critically low" (53 studies, 77%) or moderate (1 study, 1%). More than half the studies adhered to the population, intervention, comparator group, outcome (PICO) framework for research questions, explained the selection of study designs for inclusion, performed study selection and data extraction in duplicate, report sources of funding, utilize the appropriate statistical combination of results in meta-analysis, provide satisfactory explanation and discussion of heterogeneity, adequately investigate publication bias and report potential conflict of interest, including funding for the study. More than half, at least partially, adhered to having an explicit statement of review methods and reporting deviation from study protocol, have a comprehensive literature search strategy, describe included studies in adequate detail and use a satisfactory technique for assessing risk of bias (ROB) in individual studies. However, the most common critical flaws were not prospectively registering their study protocols, providing a list of excluded studies and justifying the exclusions and providing an account for the ROB in individual studies when interpreting/discussing the results of the review. The details of the AMSTAR2 results of included reviews are explained in Table 1.

Significant factors across reviews

The included reviews have analysed the literature across some 30 databases, with most studies analysing literature from PubMed, MEDLINE, Embase, Cochrane, Web of Science, Scopus and Google Scholar. Collectively, the literature was searched from inception to 2023. Most of the reviews analysed purely observational studies, while three reviews [27, 54, 55] included interventional studies in their analysis. The risk factors identified from the included reviews have been grouped into eight common themes listed below. The summary of findings is shown in Table 2.

Dietary factors

High ultra-processed food consumption [28] and fatty food [40] were reported as significantly associated with IBS development. Alcohol consumption [30, 50, 79] were reported as risk factors of IBS. Food allergy [87] was also reported as a common risk factor.

Genetic factors

Genetic factors are being female [2, 30, 40, 45, 47–49, 51, 79, 81], having a family history of IBS [49, 50, 87] and TNFSF15 polymorphism [82]. Conflicting evidence surrounds 5HTTLPR as most studies [26, 72, 80] did not report it as a risk factor, the SLC6A4 [82] polymorphism is significantly associated with IBS development. GNB3 C825T [41, 59, 82], IL-10 rs1800871 [62, 82], IL-10 rs1800870 [62], IL-10 rs1800872 [62] and TNF-α rs1800629 [82] polymorphisms were found not to be risk factors for IBS. Conversely, COMT rs4680 [82] and IL-10 rs1800896 [82] were found to be significantly associated with decreased IBS development.

Environmental factors

Smoking [87], air pollutants [50, 89], sharing a bedroom up to age 5 years old [89], raising herbivorous pets [50, 89] or history of pet ownership [89], poor sanitation [89] and shorter period of breastfeeding [50] were found to have significant association with IBS development.

Psychological factors

Anxiety disorders [30, 40, 45, 67, 79, 87], depression [30, 40, 45, 58, 67, 79, 87], neuroticism [45], somatization at the time of infectious enteritis [45], stress [30, 40, 87], binge-eating disorder, anorexia nervosa and eating disorders not otherwise specified [38] were found to have significant association with IBS development. Post-traumatic stress disorder (PTSD) [57], history of past trauma [90] and history of childhood sexual abuse [85] were found to be a significant risk factor of IBS.

Gut microbiome

Clostridioides difficile (C. difficile) [64] infection for longer than 7 days was found to be a significant risk factor for IBS. A history of colonic spirochetosis [33], antibiotic exposure [45, 50], infective gastroenteritis [30, 37, 45, 50, 71, 89], *Blastocystis* spp. [63, 73], *C. difficile*, *Salmonella* spp., *Shigella* spp., *Escherichia coli (E. coli)* [70] and *Helicobacter pylori* [88] were found to have significant associations with IBS development. Levels of *Bifidobacterium* spp. [73, 83] were reported to be significantly lower in patients with IBS compared to patients without IBS. *Severe acute respiratory syndrome coronavirus 2* (SARS-COV2) was also associated with a higher incidence of IBS [53]. A significant proportion of the IBS population was also observed to have gut dysbiosis [89].

Socio-economic factors

Child abuse, childhood living density of less than one person per room, parental deprivation, childhood affluence [29, 50], social learning of illness behaviours, parental reinforcement (rejection, hostility, parental punishment, over interference, overprotection), parental coping strategies (family history of mental illness/alcohol, substance use problems), psychological distress during childhood (e.g. parental history of anxiety/ depression/somatization, family stress, childhood, introverted personality) and children with mothers who were young (less than

Table 1 AMSTAR2 quality assessment for reviews included

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall Quality
Abedi et al. 2021 [25]	Yes	No	No	Yes	Yes	Yes	No	Partial yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Afari et al. 2014 [90]	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Areeshi et al. 2013 [26]	Yes	Yes	Yes	Partial yes	No	Yes	No	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Critically low
Almansour et al. 2024 [87]	Yes	No	No	Partial yes	Yes	No	No	Partial yes	No	Yes	-	-	No	No	-	Yes	Critically low
Bernard et al. 2023 [86]	Yes	No	No	Partial yes	Yes	No	No	No	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Chen et al. 2020 [28]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Yes	Yes	Yes	-	-	Yes	Yes	-	Yes	Low
Chitkara et al. 2013 [29]	Yes	No	No	No	No	No	No	Partial yes	No	Yes	-	-	No	Yes	-	Yes	Critically low
Creed et al. 2019 [30]	Yes	No	Yes	Partial yes	No	No	No	Partial yes	Yes	No	-	-	No	No	-	No	Critically low
Czogalla et al 2015 [31]	Yes	Partial yes	Yes	No	Yes	Yes	No	Yes	Partial yes	Yes	Yes	Yes	Yes	No	No	Yes	Critically low
El-Serag et al. 2009 [32]	Yes	No	No	Partial yes	Yes	No	No	Partial yes	No	Yes	-	-	No	No	-	Yes	Critically low
Fan et al. 2022 [33]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Ford et al. 2009 [34]	Yes	No	No	Partial yes	Yes	Yes	No	Partial yes	No	Yes	No	No	No	No	Yes	Yes	Critically low
Gandhi et al 2021 [35]	Yes	Partial yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Guo et al 2021 [36]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Halvorson et al. 2006 [37]	Yes	No	No	Partial yes	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Critically low
Hawkings et al 2023 [39]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	Yes	-	-	Yes	Yes	-	Yes	Low
Hanel et al. 2021 [38]	Yes	Partial yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	-	-	Yes	No	-	Yes	Low
Ibrahim 2016 [40]	Yes	Partial yes	Yes	Partial yes	No	No	No	No	No	No	-	-	No	No	-	Yes	Critically low
Jiang et al. 2017 [41]	Yes	No	No	Partial yes	No	Yes	No	Partial yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Joshee et al. 2022 [42]	Yes	No	Yes	Yes	Yes	No	No	Partial yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Junaid et al. 2023 [85]	Yes	No	No	Partial yes	Yes	Yes	No	Partial yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Critically low
Keithlin et al 2014 [43]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically low
Kerkhoven et al. 2007 [72]	Yes	No	Yes	Partial yes	No	No	No	Partial yes	No	No	No	No	No	No	Yes	Yes	Critically low
Kim et al. 2020 [44]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Klem et al. 2017 [45]	Yes	No	Yes	Yes	Yes	Yes	No	Yes	no	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Leech et al. 2018 [91]	Yes	No	No	Yes	Yes	Yes	No	Yes	Partial yes	No	-	-	Yes	Yes	-	Yes	Critically low
Li et al. 2020 [46]	Yes	No	No	Partial yes	Yes	Yes	No	Partial yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Critically low
Liu et al. 2022 [47]	Yes	Yes	no	Partial yes	No	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Lovell et al. 2012a [49]	Yes	No	Yes	Yes	No	Yes	No	Partial yes	No	No	No	No	No	No	Yes	Yes	Critically low
Lovell et al. 2012b [48]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Low et al. 2020 [50]	Yes	No	Yes	Partial yes	Yes	No	No	Partial yes	-	No	-	-	Yes	No	-	Yes	Critically low
Manzoli et al. 2017 [51]	Yes	No	Yes	Partial yes	Yes	No	No	Partial yes	No	No	No	No	No	No	No	Yes	Critically low
Marasaco et al. 2023 [52]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Partial yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

Table 1 (continued)

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall Quality
Mathur et al. 2024 [53]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Critically low
Motawea et al. 2023 [54]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Partial yes	Partial yes	No	Yes	No	No	Yes	No	Yes	Critically low
Nastaskin et al. 2006 [55]	Yes	Partial yes	Yes	Yes	Yes	Yes	No	No	Yes	No	-	-	Yes	Yes	-	Yes	Critically low
Ng et al. 2018 [57]	Yes	Partial yes	Yes	Yes	Yes	Yes	No	Yes	Partial yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Ng et al. 2019 [56]	Yes	Yes	Yes	Yes	Yes	No	No	Partial yes	No	No	No	No	Yes	Yes	Yes	Yes	Critically low
Ng et al. 2024 [89]	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	-	Yes	Moderate
Nikolova et al. 2022 [58]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	No	Yes	Critically low
Pan et al. 2014 [59]	Yes	No	Yes	Partial yes	Yes	Yes	No	Partial yes	No	No	Yes	No	No	Yes	Yes	No	Critically low
Park et al. 2005 [60]	Yes	No	No	No	No	No	No	No	Partial yes	Yes	-	-	No	No	-	No	Critically low
Pickett-Blakely et al. 2014 [61]	Yes	No	Yes	Partial yes	No	No	No	Partial yes	Yes	No	-	-	No	Yes	-	No	Critically low
Qin et al. 2013 [62]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	No	Critically low
Rostami et al. 2017 [63]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Saha et al. 2022 [64]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Critically low
Saidi et al. 2020 [65]	Yes	Yes	Yes	Yes	Yes	Yes	No	Partial yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Critically low
Schwille-Kiuntke et al. 2015 [66]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Sibelli et al. 2016 [67]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Critically low
Sirri et al. 2017 [68]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	Yes	-	-	No	Yes	-	Yes	Critically low
Silva et al. 2023 [84]	Yes	No	No	No	No	No	No	Partial yes	No	No	-	-	No	No	-	Yes	Critically low
Stanculete et al. 2021 [69]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	No	Yes	-	-	No	No	-	Yes	Critically low
Svendsen et al. 2019 [70]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	No	No	No	Yes	No	Critically low
Tak et al. 2011 [92]	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Thabane et al. 2007 [71]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Low
Valencia et al. 2022 [2]	Yes	Partial yes	Yes	Partial yes	No	Yes	No	No	Yes	Yes	-	-	No	No	-	Yes	Critically low
Wang et al. 2019 [73]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Wang et al. 2022a [74]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Critically low
Wang et al. 2022b [75]	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Partial yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Wang et al. 2023 [76]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Wang et al. 2023 [88]	Yes	Yes	No	Yes	No	No	No	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Whitehead et al. 2002 [77]	Yes	Partial yes	Yes	No	Yes	No	No	No	No	No	-	-	No	No	-	Yes	Critically low
Wongtrakul et al. 2022 [78]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Yang et al. 2022a [79]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Yang et al. 2022b [27]	Yes	partial yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	No	yes	No	Yes	Yes	Low

Table 1 (continued)

Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall Quality
Zhang et al. 2014 [80]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Partial yes	Partial yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zhu et al. 2014 [81]	Yes	No	Yes	Partial yes	Yes	No	No	Partial yes	No	No	No	No	No	No	No	Yes	Critically low
Zhu et al. 2019 [82]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Partial yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zhuang et al. 2017 [83]	Yes	Partial yes	Yes	Partial yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Critically low

Legend:

Q1: Did the research questions and inclusion criteria for the review include the components of PICO (population, intervention, comparator group and outcome)?

Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

Q3: Did the review authors explain their selection of the study designs for inclusion in the review?

Q4: Did the review authors use a comprehensive literature search strategy?

Q5: Did the review authors perform study selection in duplicate?

Q6: Did the review authors perform data extraction in duplicate?

Q7: Did the review authors provide a list of excluded studies and justify the exclusions?

Q8: Did the review authors describe the included studies in adequate detail?

Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

Q10: Did the review authors report on the sources of funding for the studies included in the review?

Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis

Q13: Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table 2 Summary of included reviews and their findings

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Abedi et al., 2021 [25]	- Microbiology/Gut-microbiome	PubMed, EMBASE, Web of Science, Scopus, Google Scholar, Open Grey, ProQuest	Inception to 2021	Case–control, Cross-sectional, Cohort	32	- *Blastocystis* sp. infection	Critically low
Afari et al. 2014 [90]	- Psychological	Pubmed/MEDLINE, PsyINFO and Google Scholar	1948 to 2012	Case control. cohort	71	- Past history of reported trauma	Critically low
Almansour et al. 2024 [87]	- Diet - Genetics - Environment - Pathology	PubMed, Web of Science, CINAHL Ultimate, Scopus	2019 to 2024	Cross-sectional	52	- Food allergy - Family history - Smoking - Anxiety and depression - Low income - Workload - Occupation - Age - Stress - GERD - Diabetes Mellitus - Chronic disease - Abdominal pain	Critically low
Areeshi et al., 2013 [26]	- Genetic Factors	Medline, Embase	Inception to 2013	Case–control	12	-	Critically low
Bernard et al. 2023 [86]	- Pathological	Pubmed, Cochrane, Embase	Inception to 2023	Cohort, Case–control, Cross-sectional	10	- Spondyloarthropathy	Critically low
Chen et al., 2020 [28]	- Dietary Factors	PubMed, EMBASE, Web of Science	Inception to 2019	Cross-sectional, Cohort	20	- High consumption of UPFs	Low
Chitkara et al., 2013 [29]	- Socio-economic Factor - Physiology	Medline, EMBASE	1966 to 2007	Observational	25	- Childhood living density of < 1 person per room - Childhood affluence (Hygiene hypothesis) - Birthweight < 1500 g during infancy - childhood sexual, physical, verbal and emotional abuse - Parental deprivation - social learning of illness behaviour	Critically low
Creed et al., 2019 [30]	- Dietary Factors - Genetic Factors - Environmental Factors - Psychological Factors - Microbiology/Gut-microbiome - Socio-economic Factor - Physiology - Pathology	Medline, Cochrane, Web of Science,	1998 to 2019	Cohort studies	38	- Female gender - Younger age - Psychological stressors, anxiety and depression - Gastrointestinal disorders (e.g. gastroenteritis) - Frequent use of healthcare - Pain disorders (including fibromyalgia and TMJ disorder) - sleep disorders - asthma - diabetes - migraine - chronic liver disease	Critically low

Table 2 (continued)

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Czogalla et al., 2015 [31]	- Genetic Factors	PubMed	Not Stated to Not Stated	Case–control	12 previously published + 2 self-performed case controls	- TNFSF15 rs4263839	Critically low
El-Serag et al., 2009 [32]	- Pathology	Pubmed, Embase	Inception to 2007	Cohort, Nested case–control	17	- GERD	Critically low
Fan et al., 2022 [33]	- Microbiology/Gut-microbiome	Medline, EMBASE, Web of Science, CINAHL	1967 to 2021	Case–control, Case Series	75	- Colonic *Spirochaetosis* spp.	Critically low
Ford et al., 2009 [34]	- Microbiology/Gut-microbiome	Medline, EMBASE	1950 to 2008	Case series, case–control	12	- Positive test for SIBO	Critically low
Gandhi et al., 2021 [35]	- Microbiology/Gut-microbiome	Medline, EMBASE	1966 to 2021	Case control, Cohort, Cross-sectional	IBS: 15 IBS + IBD: 2	-Methane-positive SIBO (specifically IBS-C, not IBS-D)	Low
Guo et al., 2021 [36]	- Pathology	PubMed, EMBASE, Cochrane, Web of Science, Google Scholar, CINAHL	Inception to 2020	Cross-sectional, Cohort, Case–control	6	- Restless legs syndrome	Low
Halvorson et al., 2006 [37]	- Microbiology/Gut-microbiome	Medline, Old Medline, Embase, Cochrane	1950 to 2005	Cohort	8	- Antecedent infectious gastroenteritis (IGE)	Critically low
Hawkings et al., 2023 [39]	- Microbiology/Gut-microbiome	PubMed, Medline, Scopus	2019 to 2023	Cross-sectional, Cohort, Case–control	45	- Previous SARS-CoV-2 infection	Low
Ibrahim, 2016 [40]	- Dietary Factors - Genetic Factors - Environmental Factors - Psychological Factors - Microbiology/Gut-microbiome - Socio-economic Factor - Physiology - Pathology	PubMed, Medline, Embase, Cochrane, Web of Science, Ovid, Google Scholar	1990 to 2015	Cross-sectional, Case–control	16	- Food hypersensitivity - Consumption of fatty food, obesity - Female medical students, - Family history of IBS, - Stress, anxiety, depression, sleep disorders	Critically low
Jiang et al., 2017 [41]	- Genetic Factors	PubMed, Embase, Science Direct, Chinese National Knowledge Infrastructure, Wanfang	Inception to 2017	Case–control	11	Negative association: - C allele of GNβ3 C825T and IBS-C (C vs. T) Positive association: - IBS-D and CC genotype and IBS-D (CC vs. CT + TT)	Critically low
Joshee et al., 2022 [42]	- Socio-economic Factor	PubMed, EMBASE, Google Scholar, PsycINFO	1927 to 2020	Case–control, Cohort, Cross-sectional	15	- Adverse childhood experience in females with IBS	Critically low
Junaid et al. 2023 [85]	- Psychological	Medline, Embase, Web of science, Google scholar, Scopus	2001 to 2021	Case–control, Cross-sectional	7	- Childhood sexual abuse	Critically low
Keithlin et al., 2014 [43]	- Microbiology/Gut-microbiome	PubMed, Agricola, CabDirect, Food Safety and Technology Abstracts	Inception to 2011	Observational	31 (of which 9 pertaining to IBS)	-	Critically low
Kerkhoven et al., 2007 [72]	- Genetic Factors	Pubmed, Medline, Web of Science	Inception to 2007	Case–control	8	-	Critically low
Kim et al., 2020 [44]	- Microbiology/Gut-microbiome	PubMed, Cochrane, Scopus, CINAHL	Inception to 2019	Cross-sectional, Case–control	10	-	Critically low

Table 2 (continued)

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Klem et al., 2017 [45]	- Genetic Factors - Environmental Factors - Psychological Factors - Microbiology/Gut-microbiome - Physiology - Pathology	Embase, Cochrane, Web of Science, Ovid	2006 to 2015	Cohort	45	- Female sex - Exposure to infectious enteritis - Depression - Somatisation at the time of infectious enteritis - Neuroticism - Abdominal pain - Diarrhoea for more than 7 days - Bloody stool - Antibiotic exposure at the time of PI-IBS - Paediatrics - Adults - Exposure to infectious enteritis, - Depression, somatisation at the time of infectious enteritis, neuroticism, - Abdominal pain, diarrhoea for more than 7 days, bloody stool, antibiotic exposure at the time of PI-IBS-	Critically low
Leech et al. 2018 [91]	- Physiology	Medline, Pubmed, Embase, AMED	Inception to 2018	Case-contro, Cohort Cross-sectional	48	- Increased intestinal permeability	Critically low
Li et al., 2020 [46]	- Microbiology/Gut-microbiome	Pubmed, Medline, Embase, Cochrane	Inception to 2019	Case–control	8	-	Critically low
Liu et al., 2022 [47]	- Genetic Factors - Socio-economic Factors	PubMed, Old Medline, Cochrane, Web of Science	Inception to 2021	Cross-sectional surveys	11	- Female medical staff - Medical shift workers - Medical staff with poor sleep quality	Low
Lovell et al., 2012a [49]	- Genetic Factors	Medline, Embase, Embase Classical	EMBASE Classic and EMBASE: 1947; MEDLINE: 1948 to 2011	Cross-sectional	55	- Female	Critically low
Lovell et al. 2012b [48]	- Genetic Factors - Socio-economic Factor - Physiology	Medline, Embase, Embase Classical	1947 to 2011	Cross-sectional surveys	81	- Female - Younger age below 50	Critically low

Table 2 (continued)

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Low et al., 2020 [50]	- Dietary Factors - Genetic Factors - Environmental Factors - Microbiology/Gut-microbiome - Socio-economic Factor - Physiology - Pathology	Pubmed, Embase, Cochrane, Web of Science	1966 to 2018	Case–control, Cohort	27	- Food habits such as excessive intake of pepper - Alcoholism - Smoking - Shorter period of breast feeding - Parental reinforcement e.g. rejection, hostility, parental punishment, over interference, overprotection - Parental coping strategies e.g. family history of mental illness/alcohol - Substance use problems - Adults who have grown up with a father working in manual labour or in a home with living density of > 1 person per room - Child abuse (sexual, emotion, physical or psychological) - Adverse exposures e.g. history of dysentery, abdominal operation, overuse of antibiotics, exposure to coldness, fatigue - Raising herbivorous pets - Air pollution - Psychological distress during childhood e.g. parental history of anxiety/depression/somatisation - Family stress - Childhood parental deprivation - Introverted personality - Parental modelling of IBS symptoms e.g. history of IBS - Childhood gastrointestinal infections - Acute bacterial gastroenteritis - Children with mothers who were young (< 20), divorced or widowed, and with an education of 10–14 years - Children raised in affluent environment - Low birth weight - Preschoolers with a history of allergic disease	Critically low
Manzoli et al., 2017 [51]	- Genetic Factors	Medline, Scopus	Inception to 2017	Cross-sectional	5	-	Critically low

Table 2 (continued)

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Marasaco et al., 2023 [52]	- Microbiology/Gut-microbiome	Medline, EMBASE, Scopus	Inception to 2022	Case–control	10	-	Low
Mathur et al., 2024 [53]	- Genetic Factors - Environmental Factors - Microbiology/Gut-microbiome	Medline, Cochrane, Web of Science, Scopus, Google Scholar	2019 to 2023	Case–control, Cohort	13	- Use of Rome III criteria compared to Rome IV criteria	Critically low
Motawea et al., 2023 [54]	- Pathology	PubMed, Web of Science, Scopus, Ovid	Not stated to Not stated	RCT, Cohort, Case–control, Cross-sectional	8 (of which 4 were included in meta-analysis)	- IgM antibodies against GnRH and GnRH receptor	Critically low
Nastaskin et al., 2006 [55]	- Pathology	Medline, EMBASE, Cochrane, CINAHL, HEALTHSTAR, Evidence Based Medicine, Medscape	EMBASE: 1980 Medline: 1966 HEALTHSTAR: 1975 CINAHL: 1982 Evidence-Based Medicine: 1991 Medscape: 1998 to EMBASE: 2006 Medline: 2006 HEALTHSTAR: 2004 CINAHL: 2006 Evidence-Based Medicine: 2004 Medscape: 2006 Cochrane Library: 2004 only	RCT, Cross-sectional, Case–control	15	-	Critically low
Ng et al., 2018 [57]	- Psychological Factors	PubMed, Medline, EMBASE, Science Direct, Web of Science, Google Scholar, PsycINFO	1988 to 2018	Cohort, Case–control, Cross-sectional	8	- Post-traumatic stress disorder (PTSD)	Critically low
Ng et al., 2019 [56]	- Microbiology/Gut-microbiome	Pubmed, Medline, Embase, Wanfang, Cochrane, Web of Science, Google Scholar	1960 to 2018	Case–control, Cross-sectional	13	- *Helicobacter pylori* (*H. pylori*) infections in paediatric patients, - CagA-positive *H. pylori*	Critically low
Ng et al. 2024 [89]	- Microbiology/Gut-microbiome - Environmental	Medline, EMBASE, Scopus, Cochrane databases	Inception to 2023	Case–control Cross-sectional, Ecological	7	- Air pollutants - Sharing a bedroom up to age 5 years old - Pet ownership; Owning a herbivorous pet - Gastroenteritis - Poor sanitation and hygiene - Gut dysbiosis	Moderate
Nikolova et al., 2022 [58]	- Psychological Factors	Medline, EMBASE, Google Scholar	Inception to 2020	Cohort, Cross-sectional, Case–control	20 (of which 12 were used for quantitative analysis)	- Depression	Critically low
Pan et al., 2014 [59]	- Genetic Factors	PubMed, EMBASE, Chinese National Knowledge Infrastructure, Cochrane, Ovid, Google Scholar	Inception to 2013	Case–control	7	-	Critically low

Table 2 (continued)

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Park et al., 2005 [60]	- Pathology	Medline	1966 to 2005	Experimental studies	12	- Food allergy caused by IgG4 and IgE-mediated hypersensitivity	Critically low
Pickett-Blakely, 2014 [61]	- Physiology	Medline, EMBASE	1980 to 2012	Cross-sectional, Case control, Case series	11	-	Critically low
Qin et al., 2013 [62]	- Genetic Factors	PubMed, EMBASE, Cochrane	Inception to 2013	Case–control	8	Negative association: - IL-10 rs1800870 polymorphism (specifically Caucasian subgroup) Positive association: - IL-10 rs1800872 polymorphism (specifically Asian subgroup)	Critically low
Rostami et al., 2017 [63]	- Microbiology/Gut-microbiome	PubMed, ScienceDirect, Cochrane, Web of Science, Scopus	Inception to 2017	Case–control	*Blastocystis*: 17 *D. fragilis*: 4	- *Blastocystis* spp.. infections - Subtypes 1 and 3 of Blastocystis sp.	Low
Saha et al., 2022 [64]	- Psychological Factors - Microbiology/Gut-microbiome - Physiology - Pathology	Medline, Embase, Cochrane, Web of Science	Inception to 2020	Cohort	13	- Higher BMI, - IBD - Infectious gastroenteritis, - Higher anxiety score and - *C. difficile* infection (CDI) symptom duration > 7 days	Critically low
Saidi et al. 2020 [65]	- Pathology	Pubmed, Embase, Web of Science	Inception to 2019	Cohort, Case–control, Case cohort	13	- Endometriosis	Critically low
Schwille-Kiuntke et al., 2015 [66]	- Pathology	PubMed, Medline, Cochrane, Scopus, PsycINFO	Not stated to Not stated	Case–control, cohort study	6	- Traveller's diarrhoea	Critically Low
Sibelli et al., 2016 [67]	- Psychological Factors	Medline, EMBASE, Web of Science, PsycINFO	Inception to 2015	Cohort, Case–control	11	- Anxiety - Depression	Critically low
Sirri et al., 2017 [68]	- Environmental Factors	PubMed, Web of Science, Scopus	Inception to 2016	Cross-sectional, Cohort, Case–control	42	-	Critically low
Silva et al. 2023 [84]	- Microbiology/Gut-microbiome	Pubmed,	2022 to 2023	Case–control, Cohort	8	- Covid 19	Critically low
Stanculete et al., 2021 [69]	- Psychological Factors	PubMed, Embase, Cochrane, Wiley	Not stated to Not stated	Cross-sectional, Cohort, Case–control	29 (4 of which pertain to IBS)	-	Critically low
Svendsen et al., 2019 [70]	- Microbiology/Gut-microbiome	Medline, Embase	1966 (Medline) 1974 (Embase) to 2019	Cohort	34	- *Campylobacter* spp., - *C. difficile*, - *Salmonella* spp. - *Shigella* spp. - *E. coli*	Critically low
Tak et al. 2011 [92]	- Physiology	Medline, Embase, PsycINFO	1960 to 2009	Case–control	82	-	
Thabane et al., 2007 [71]	- Microbiology/Gut-microbiome - Physiology	Medline, EMBASE	Medline: 1966 Embase: 1980 to 2007	Cohort, Case–Control	18	- Presence of intestinal infections - Shorter durations post-intestinal infection - Younger age	Low

Table 2 (continued)

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Valencia et al., 2022 [2]	- Genetic Factors - Physiology - Pathology	PubMed, PMC, Medline, Cochrane	2017 to 2022	Case control, Narrative reviews, Systematic reviews, Cross-sectional, Cohort	23	- Female gender - Fibromyalgia - Increased expression of IL-1, IL-2, and TNF-a - Visceral hypersensitivity	Critically low
Vivien et al., 2021 [38]	- Genetic Factors - Psychological Factors - Physiology - Pathology	Pubmed, Medline, Embase, Web of Science	Inception to 2021	Cohort, Cross-sectional, Case–control, Case Report, Interventional	36	- Obesity - Binge-eating disorder; eating disorder symptoms - Anorexia Nervosa, bulimia nervosa, EDNOS - Visceral hypersensitivity	Low
Wang et al., 2019 [73]	- Microbiology/Gut-microbiome	Medline, EMBASE, Cochrane, Web of Science, ClinicalTrials.gov	Inception to 2018	Case–control	23	lower levels of: - *Lactobacillus* spp. - *Bifidobacterium* spp. Higher levels of: - *E. coli* - *Enterobacteriaceae*	Low
Wang et al. 2022a [74]	- Microbiology/Gut-microbiome	Pubmed, Embase, Cochrane	Inception to 2019	Case–control	13	- *H. pylori* infection (in particular for IBS-D)	Critically low
Wang et al. 2022b [75]	- Socio-economic Factor	Medline, EMBASE	Inception to 2021	Case–control, Cohort, Cross-sectional	8	- Shift work schedule	Critically low
Wang et al. 2023 [76]	- Microbiology/Gut-microbiome	Pubmed, Embase, Cochrane, Web of Science, Scopus	Inception to 2022	Cross-sectional, Longitudinal	12	-	Critically low
Wang et al. 2023 [88]	- Microbiology/Gut-microbiome	PubMed, EMBASE, Cochane library, Chinese National Knowledge 72023Infrastructure (CNKI), China Science and Technology Journal (VIP), Wanfang	Inception to 2021	Case–control, Cross-sectional	31	- *H. pylori*	Low
Whitehead et al. 2002 [77]	- Pathology - Psychological Factors	Medline	1966 to 2002	Observational	Not stated	Comorbid somatic conditions: - fibromyalgia - chronic fatigue syndrome - chronic pelvic pain - TMJ disorder - interstitial cystitis - self-reported back pain - premenstrual syndrome - dysmenorrhea - dyspareunia - non-menstrual bleeding Comorbid psychiatric disorders: - major depressive disorder - anxiety - somatoform disorders	Critically low

Table 2 (continued)

Author, year	Factor(s) studied	Search database(s)	Search dates	Type(s) of studies included	Number of studies of included	Significant risk factors[a]	Overall quality
Wongtrakul et al. 2022 [78]	- Pathology	Medline, EMBASE, Google Scholar	Inception to 2020	Observational	11	- Development of migraine is associated with development of IBS	Low
Yang et al., 2022a [79]	- Dietary Factors - Genetic Factors - Psychological Factors - Socio-economic Factor	PubMed, Medline, EMBASE, Chinese, National Knowledge Infrastructure, CINAHL, Weipu, WANFANG	Inception to 2021	Cross-sectional, Cohort	22	- Female gender - Post-graduate students - Medical majors - Smoking - Comorbidities: Anxiety, depression	Critically low
Yang et al., 2022b [27]	- Pathology	Medline, Chinese National Knowledge Infrastructure, Cochrane, Web of Science, Clinical Trial	Inception to 2021	RCTs	12	- Vitamin D deficiency	Low
Zhang et al. 2014 [80]	- Genetic Factors	PubMed, EMBASE, Chinese National Knowledge Infrastructure, Web of Science	Inception to 2013	Case–control	25	-	Low
Zhu et al. 2014 [81]	- Genetic Factors - Socio-economic Factor - Physiology	Medline, Embase, Embase Classical	EMBASE Classic and EMBASE: 1947; MEDLINE: 1948 to 2013	Cross-sectional surveys	79	IBS prevalence - Females significantly more likely than males to develop IBS Developed vs. underdeveloped countries - Ratio of female to male prevalence of IBS significantly more in developed vs. underdeveloped countries	Critically low
Zhu et al. 2019 [82]	- Genetic Factors	PubMed, EMBASE, Cochrane, Web of Science, Clinical Trial	2000 to 2018	Case–control	28	Positive associations - SLC6A4 5-HTTLPR - TNFSF15 rs4263839 - TNFSF15 rs6478108 Negative associations: - COMT rs4680 - IL10 rs1800896	Low
Zhuang et al. 2017 [83]	- Microbiology/Gut-microbiome	Pubmed, Chinese National Knowledge Infrastructure, Wanfang, Cochrane, Scopus, SinoMed, VIP Information	Inception to 2015	Case–control	17	Chinese IBS patients - *Bifidobacteria* spp. - *Lactobacillus* spp. - *E. coli* - *Enterobacteriaceae* spp. Other regions comparison - *Bifidobacteria* spp. - *Bacteroides* spp.	Critically low

Legend: *CFU* Colony-forming units, *IBS* Irritable bowel syndrome, *UPFs* Ultra-processed foods, *SIBO* Small intestine bowel overgrowth, *ACE* Adverse childhood experience, *PI-IBS* Post-infectious irritable bowel syndrome, *IBS-D* Irritable bowel syndrome with diarrhoea, *IBS-C* Irritable bowel syndrome with constipation, *IBS-M* Irritable bowel syndrome with mixed bowel habits, *TMJ* temporomandibular joint, *SMDs* Standardized mean difference, *GnRH* Gonadotropin hormone-releasing hormone, *GERD* Gastroesophageal reflux disease, *PTSD* Post-traumatic stress disorder, *SNPs* Single-nucleotide polymorphisms, *COMT* Catechol-o-methyltransferase, *CDI Clostridioides difficile* infection, *Spp.*, Species, *IGE* Infectious gastroenteritis, *HDI* Health, Education and Income Indexes, *ED* Eating disorder, *EDNOS* Eating disorders not otherwise specified, *BMI* Body mass index

[a] Unless otherwise specified, factors refer to risk factors for IBS

20 years old), divorced or widowed, and with an education of 10 to 14 years [50] were reported as risk factors of IBS. Shift work [47, 74], students in medical majors [40, 79], postgraduate students [79], poor sleep quality [47] and frequent use of healthcare [30] had significant associations with IBS development. High workload, low income and occupation types were commonly reported features of IBS populations [87].

Physiological factors

Low birth weight [29, 50] and increased intestinal permeability [91] were found to have significant positive association with IBS. There is inconclusive evidence of increasing age [2, 30, 45, 48, 71, 81, 87] as a risk factor for IBS.

Pathological factors

Gastroesophageal reflux disease (GERD) [32, 55, 87], migraine [30, 78], vitamin D deficiency [79], the presence of IgM antibodies against gonadotropin hormone-releasing hormone (GnRH) and GnRH receptor [54], preschoolers with a history of atopy/allergy [50], women with endometriosis [65], asthma [30], diabetes [30, 87], previous abdominal operation and exposure to coldness and fatigue [50] were found to be significant risk factors for IBS development. Temporomandibular joint (TMJ) disorder [30, 77], fibromyalgia syndrome [2, 30, 77], visceral hypersensitivity [2, 38], food hypersensitivity [40, 60], sleep disorders [30, 40], spondyloarthropathy [86], chronic liver disease [30], a history of dysentery [45], restless leg syndrome [36], having diarrhoea for more than 7 days [45] and abdominal pain [45, 87] had a significant association with IBS development. A history of chronic disease was also reported as a common risk factor for IBS development [87].

Empirical evidence and GRADE evaluation

Amongst the risk factors mentioned, female gender, anxiety disorder, depression and gastroenteritis were the most frequently mentioned across reviews. Depression and gastroenteritis were supported with relatively higher evidence, with a "moderate score" when assessed using GRADE. Depression had an association magnitude ranging from RR 1.90 to RR 5.57 and OR 1.49 to OR 2.15, while gastroenteritis had an association with magnitude of RR 3.8 and OR 5.86 to OR 7.3 reported. Female gender and anxiety disorder were supported by relatively lower levels of evidence when assessed by grade, with a "low" score attributed to both. Across reviews, female gender had an association of magnitude OR 1.36 to OR 2.29 while anxiety disorder has an association magnitude of RR 2.38 and OR 1.97 to 2.35. The results of GRADE evaluation for the aforementioned factors are summarized in Table 3.

Discussion

This review of reviews provides an overview of the current evidence regarding the risk factors for the IBS development. Eight overarching categories of risk factors were identified across the 69 included systematic reviews in this study, as illustrated in Fig. 2. Amongst the various risk factors mentioned, four were frequently identified across the included reviews, supported by robust evidence for its position as a risk factor of IBS development: female gender, anxiety disorder, depression and gastroenteritis.

IBS has long been associated with female gender, with an estimated 2–2.5:1 male-to-female ratio for IBS development [93]. While the exact pathophysiology has not been ascertained, a common mechanistic pathway emphasized across literature are the hormonal differences between both genders [94]. In addition to the modulatory effect of progesterone on the 5-hydroxytrptamine (5-HT) system that controls peristalsis [95], estrogen and progesterone have an inhibitory effect on smooth muscle contraction [94]. Consequently, IBS, especially the constipation variant (IBS-C), has a higher incidence in women compared to men [96]. While the interplay between gender and IBS development highlights the importance of this risk factor, the association with worse outcomes further compels further effort in preventing IBS development within this patient group. Fan et al. reports higher IBS symptoms score and lower IBS-quality of life (IBS-QOL) scores experienced in female patients [97]. Cain et al. also reports more somatic symptoms experienced by women afflicted with IBS, including joint and muscle pain [98]. However, despite worse outcomes in female populations, abdominal concerns are more likely to be minimized by healthcare professionals [99]. Windrim et al. reports the internalization of normative views regarding women's pain of lower concern as a possible explanation. Given its significance as a risk factor and outcome modulator, further emphasis on this risk factor is necessitated in clinical guidelines aimed at prevention of IBS development.

A bi-directional association has been established between both mental conditions and IBS development [45, 100]. Mechanistically, two pathways have been described. The increased release of corticotropin-releasing hormone (CRH) in response to stress [12] in anxiety and depression causes hyperactivation of the hypothalamic–pituitary–adrenal axis and autonomic nervous system, consequently altering gut motility and increasing visceral sensitivity [101]. Stress-induced microbiota dysbiosis also causes gut barrier dysfunction and immune

Table 3 Summary of the main findings as per GRADE

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Absolute effect	Overall certainty (GRADE)
Female Gender	High—Many reviews are of "low" or "critically low" quality (AMSTAR2 assessment)	Moderate—Some variability in reported associations	Low—Directly addresses IBS development in relevant populations	Moderate—Some studies have wide confidence intervals, but the overall association remains significant	Not assessed	Female gender shows a higher likelihood of IBS	Low ⊕⊕◯◯
Anxiety Disorder	High—Many reviews are of "low" or "critically low" quality (AMSTAR2 assessment)	Moderate—Some variability in reported associations	Low—Directly addresses IBS development in relevant populations	Moderate—Some studies have wide confidence intervals, but the overall association remains significant	Not assessed	Anxiety disorder is associated with an increased risk of IBS	Low ⊕⊕◯◯
Depression	High—Many reviews are of "low" or "critically low" quality (AMSTAR2 assessment)	Moderate—Some variability in reported associations	Low—Directly addresses IBS development in relevant populations	Moderate—Some studies have wide confidence intervals, but the overall association remains significant	Not assessed	Depression is associated with an increased risk of IBS	Moderate ⊕⊕⊕◯
Gastroenteritis	High—Many reviews are of "low" or "critically low" quality (AMSTAR2 assessment)	Low—Consistent association across studies for post-infectious IBS	Low—Directly addresses IBS development in relevant populations	Moderate—Some studies have wide confidence intervals, but the overall association remains significant	Not assessed	Gastroenteritis is associated with PI-IBS with approximately 10% prevalence in affected patients	Moderate ⊕⊕⊕◯

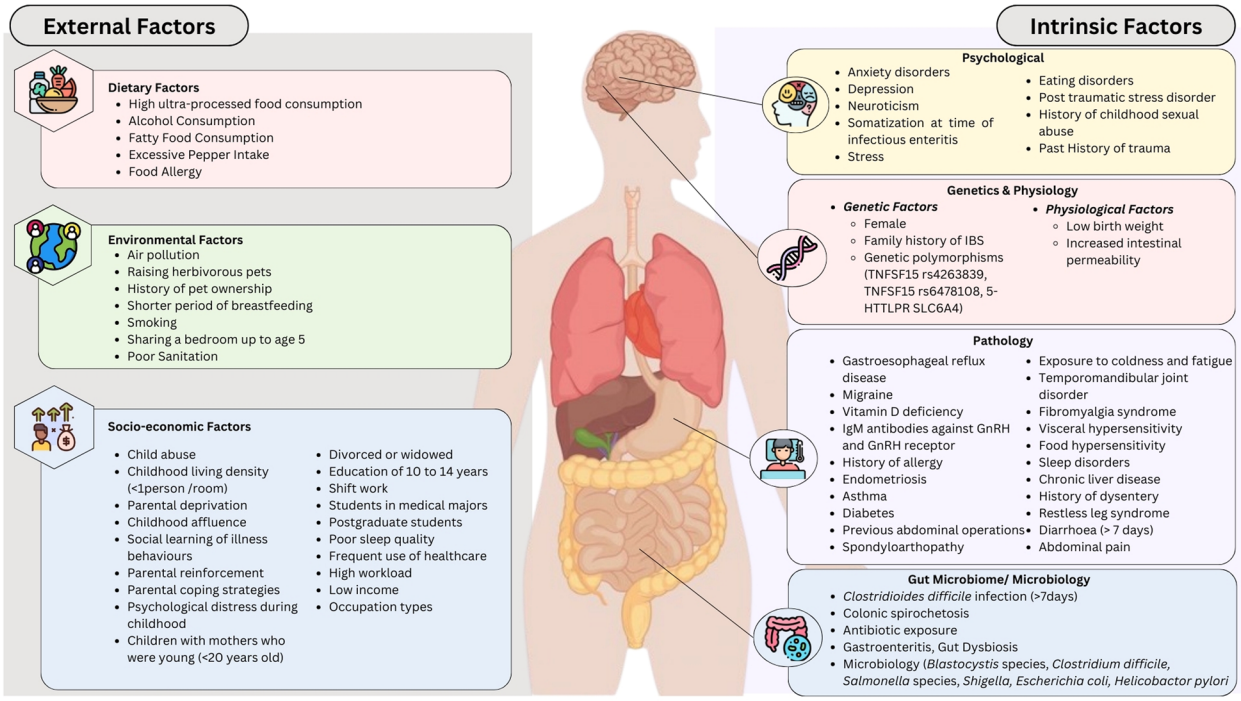

Fig. 2 Overview of risk factors for IBS development based on existing systematic reviews

activation, further contributing to gut motility abnormalities [102]. The impact of IBS onset on individuals with anxiety and depression is extensive, as they are more likely to experience reduced quality of life from the symptoms of IBS and exhibit reduced treatment adherence compared to those without anxiety or depression [100, 103]. However, patients with undiagnosed anxiety and depression who display symptoms of IBS are only offered central neuromodulators and psychological therapies when they fail to respond to pharmacotherapy for symptomatic management of IBS [104]. The resultant delay in resolution of IBS symptoms may cause patient dissatisfaction and inadvertently lead patients to seek alternative therapies which lack robust evidence, thereby increasing the risk of harm [102]. This underscores the need for more stringent screening of comorbid anxiety and depression disorders in the diagnosis of IBS to allow for accurate choice of pharmacotherapies and early referral for psychotherapies where required [105, 106].

In agreement with literature, acute gastroenteritis is a common risk factor amongst various systematic reviews, with reports approximating 10% pooled prevalence [107] of post-infectious IBS (PI-IBS) in acute gastroenteritis patients. Although the exact mechanism is poorly understood, common pathophysiological hypotheses include prolonged imbalance of host immune cells and mediators that affect inflammatory homeostasis, disruption to the intestinal mucosal barrier and intestinal dysbiosis [108]. While any pathogens may potentiate PI-IBS, notable pathogens strongly associated with PI-IBS include as follows: *Norovirus* [109] and *Rotavirus* [110], *E. coli* [111], *Salmonella* spp. [112], *Campylobacter* spp. and *Giardia duodenalis* (*G. duodenalis)* [113]. Despite being a common risk factor, gastroenteritis is however, an easily treatable cause of IBS development. Epidemiological data would prove crucial in capitalizing on this information for effective prevention and treatment considering inter-region difference in infective gastroenteritis pathogen. In addition to gastroenteritis, a patient's gut microbiota also plays a role in IBS development. Specifically, changes in prevalence of indigenous species such as *Faecalibacterium* spp., *Lactobacillus* spp. and *Bifidobacteria* spp. have been linked to IBS development [73, 114]. As probiotics can modulate the composition of gut microbiota, this has resulted in the recent interest for probiotic trials of IBS relief observed in literature [115, 116].

Based on the findings of this study, the authors of this study suggest that future systematic reviews on this topic strongly adhere to the tenets of systematic reviews as outlined by PRISMA-P guidelines. In particular, item 16b and accounting for the biases in the discussion (part of 23b) are requirements that current reviews tend not to fulfill. Furthermore, other requirements, such as 14, 18 and 24a-c, were only partially met. This may be attributed to the multi-faceted nature of the requirement. Future studies should take more care in adequately addressing these criteria. To ensure quality of published literature, it

is advised that journals actively require a protocol checklist, ideally the PRISMA-P checklist, to be submitted for peer review. In agreement with the current stance on study quality [117], adherence to such reporting standards should also have more weightage in a journal's consideration for publication of the report.

To the author's best knowledge, this study presents the first review of reviews to investigate the current evidence of risk factors for IBS development. The findings from this study were reported according to replicable methodology, which adhered to the PRISMA guidelines for systematic reviews [22], recent recommendations by Gates et al. [118] and published literature. The authors of this study also acknowledge the current limitations of this review. Review of reviews focus on published systematic reviews and meta-analyses; thus, more recent studies not identified in original reviews may not have been included in this umbrella review. Secondly, a loss of granularity is apparent in some of the findings listed above, for example the lack of clarity regarding the dose response of specific risk factors including air pollution. Lastly, the evaluation of article quality reveals low adherence to professionally accepted guidelines in several of the systematic reviews and meta-analyses reviewed. When evaluated holistically using the GRADE evaluation model, the evidence ranged between low to moderate for the major risk factors identified in this review. In view of the current limitations, the authors of this review urge the readers to interpret the presented findings with caution.

Conclusions

This umbrella review identified eight overarching categories of risk factors for IBS, of which female gender, anxiety, depression and gastroenteritis were supported by comparatively more robust evidence. While this review attempts to further the understanding regarding the significant risk factors for the development of IBS and the current evidence landscape, the multi-factorial nature of IBS demands continued research. Given that several reviews did not satisfy the good practices and recommendations for methodology as outlined by the PRISMA guidelines [22], there is also a need for caution when interpreting the data contained within the current reviews. The findings of this study also urge stronger adherence to established guidelines for the methodology of future research conducted in this area.

Abbreviations

5-HT	5-Hydroxytrptamine
CRH	Corticotropin-releasing hormone
GERD	Gastroesophageal reflux disease
GnRH	Gonadotropin hormone-releasing hormone
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome-constipation variant
IBS-QOL	Irritable bowel syndrome-quality of life
OR	Odds ratio
PICO	Population, Intervention, Comparator Group, Outcome
PI-IBS	Post-infectious irritable bowel syndrome
PTSD	Post-traumatic stress disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RR	Relative risk
ROB	Risk of bias
TMJ	Temporomandibular joint

Supplementary Information

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Supplementary Material 1.

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None.

Authors' contributions

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures and tables has not been previously published, and the manuscript is not under consideration elsewhere. All authors read and approved the final manuscript. Conceptualization and Design: KTHS, QXN. Acquisition of Data: FS, TSKO, ASPT, JQ, RMP, DTL, KTHS, QXN. Analysis and Interpretation of Data: FS, TSKO, ASPT, JQ, RMP, DTL, KTHS, QXN. Writing – original draft: FS, TSKO, ASPT, JQ, RMP, DTL, KTHS, QXN. Writing – review & editing: FS, TSKO, ASPT, JQ, RMP, DTL, KTHS, QXN. Supervision: KTHS, QXN. All authors reviewed the manuscript.

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Data availability

This study is a systematic review and no original data were generated. All data analyzed in this study were obtained from publicly available sources, specifically MEDLINE, Embase, and the Cochrane Library. These databases are accessible through institutional or individual subscriptions.

Declarations

Ethics approval and consent to participate

Not applicable. The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from institutional review board (IRB) review as this is a systematic review of published papers. No patients or human participants were directly involved.

Consent for publication

Not applicable. This manuscript does not contain data from any individual person.

Competing interests

The authors declare that they have no competing interests.

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