Meta-analysis and systematic review of the association between adverse childhood events and irritable bowel syndrome

Shreeya Joshee, Lauren Lim, Alexis Wybrecht, Riley Berriesford, Mark Riddle

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jim-2021-002109).

University of Nevada Reno School of Medicine, Reno, Nevada, USA

Correspondence to
Shreeya Joshee, University of Nevada Reno School of Medicine, Reno, NV 89557, USA; shreeyaj@med.unr.edu

Accepted 12 January 2022
Published Online First 27 January 2022

ABSTRACT

Irritable bowel syndrome (IBS) is a disorder of gut–brain interaction characterized by abdominal pain, bowel habits alterations, constipation, and/or diarrhea. Adverse childhood experiences (ACEs) are events such as abuse and mental illness causing childhood trauma. Studies report higher prevalence of ACEs in patients with IBS with varied effect consistency and association strength. A systematic review and meta-analysis were conducted to evaluate current literature, assess heterogeneity and research gaps in this relationship. A search across PubMed, Embase, PsycINFO, and Google Scholar with keywords ('childhood adversity' OR 'childhood trauma' OR 'adverse childhood events') AND ('irritable colon' OR 'irritable bowel syndrome') yielded 106 studies. A restricted maximum likelihood model of 15 chosen studies with 272,686 participants found the association between ACEs and IBS to be uncertain given the considerable heterogeneity (I^2=93.58%, p<0.001). Objective reporting methods for ACE and IBS, study size, and study quality explained some heterogeneity. Twelve studies showed publication bias (Egger's test, p<0.001), which further weakened interpretation. Gender-stratified subanalysis of three studies found ACEs associated with IBS in females (pOR=2.20, 95% CI (1.13 to 4.29), I^2=66.90%) with substantial heterogeneity, but no association in males (pOR=1.30, 95% CI (0.62 to 2.78)). This meta-analysis explores the current literature to understand the biopsychosocial perspective of IBS and ACEs' role as risk factors. However, the risk of publication and design/study quality biases substantiates the need for further research. If an association is confirmed, further mechanistic research and development of targeted psychological therapies may be warranted.

To cite: Joshee S, Lim L, Wybrecht A, *et al*. *J Investig Med* 2022;**70**:1342–1351.

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder affecting 11.2% of adults in North America and 7%–18% of the world's population.[1–3] IBS is considered a disorder of gut–brain interaction characterized by abdominal pain, bowel habits alterations, constipation and/or diarrhea.[4] In the USA, this disorder accounts for an estimated $1.07 billion in direct medical costs and an additional estimated $20 billion in indirect costs due to absence from work.[5 6] A positive IBS diagnosis is made with the Rome classification system along with patient history, physical examination, and limited laboratory tests, and colonoscopy/endoscopy when indicated.[7]

Understanding the underlying causes and disease-modifying factors of IBS is an active focus of investigation. Multiple pathogenic pathways including abnormalities of brain–gut interactions, intestinal microbiota alterations, immune dysregulation, and visceral hypersensitivity have been identified; however, a complete understanding remains elusive, and there are likely many different mechanisms that produce the varied symptomatology.[5 8] Triggering events have also been explored, including acute gastrointestinal (GI) infections, antibiotic exposure, and psychological trauma.[9–11] Within the category of trauma, adverse childhood events (ACEs) and the neurocognitive associations with GI abnormalities have been described and provide rationale for possible initiation of disease-modifying effects.[5] ACEs are events such as abuse, mental illness, and domestic violence that cause trauma in childhood. Some studies have reported a higher prevalence of ACEs in patients with IBS when compared with those without IBS, but some studies have not found an association.[5 12–14]

We conducted a systematic review and meta-analysis to describe the population of studies that have sought to explain the association between ACEs and IBS in adult and adult/child populations, explore the strength, consistency, and potential sources of heterogeneity in these studies, and describe the gaps in current epidemiological research. If an association is confirmed, this substantiates the need for further research into the field and the development of interventions to reduce ACE in those vulnerable to developing IBS.

METHODS

A systematic literature review was done in adherence to the Meta-Analyses and Systematic Reviews of Observational Studies (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)) guidelines.[15] A preliminary search was conducted across PubMed, Embase, PsycINFO, and Google Scholar for articles in English with keywords

optimized for each database to yield the highest amount of relevant results.

PubMed

We used the keywords (adverse childhood experiences) OR ((‘Adverse Childhood Experiences’) OR (adverse childhood experiences (Title/Abstract)) OR ((‘childhood adversity’) OR (‘childhood abuse’) OR (‘child of impaired parents’) OR (‘Adult Survivors of Child Adverse Events’)) AND (((irritable bowel syndrome) OR (irritable bowel syndrome (Title/Abstract))) OR (irritable bowel syndrome (MESH Major Topic)). Eligible search dates 1940 to 2020.

Embase

We used the keywords (‘childhood adversity’ OR ‘childhood trauma’ OR ‘adverse childhood events’) AND (‘irritable colon’ OR ‘irritable bowel syndrome’). Eligible search dates 1947 to 2020.

Google Scholar

We used the keywords (‘childhood adversity’ OR ‘childhood trauma’ OR ‘adverse childhood events’) AND (‘irritable colon’ OR ‘irritable bowel syndrome’). Eligible search dates 1990 to 2020.

PsycINFO

We used the key words (‘Adverse Childhood Experiences’) OR (‘childhood abuse’) AND (‘irritable colon’ OR ‘irritable bowel syndrome’). Eligible search dates 1927 to 2020.

Title and abstract screening

Title and abstract screenings were performed independently by two of four researchers (SJ, AW, LL, and RB) to identify articles of interest using the following criteria: (1) original published study, (2) IBS and non-IBS populations evaluated, (3) ACE questions asked. Non-human studies, review articles, and commentaries were excluded. Two researchers independently determined eligibility based on title and abstracts criteria of our primary search. A third researcher adjudicated any disagreements of inclusion.

Full-text screening

Each retrieved article was then evaluated by three researchers for inclusion (RB, AW, LL) using the following criteria: (1) evaluation of ACE through self-reporting, questionnaire or clinical diagnosis; (2) IBS diagnosis by self-reported, clinical diagnosis or medical record coding; (3) description of the criteria used to determine ACE; (4) extractable data for the numerator and denominator estimate of ACE prevalence in adult and children patients with diagnosis of IBS, and in comparative study designs, ACE prevalence in healthy controls. Studies that failed to meet these four criteria were excluded. If data were not extractable, corresponding authors of the retrieved articles were contacted for additional data or clarification. Reference lists of each retrieved article were also reviewed by title and article retrieved as with the primary search methods.

Data extraction

The primary outcome of interest for this review was the prevalence of ACE in individuals diagnosed with IBS compared with the prevalence of ACE in those without an IBS diagnosis. An additional subgroup analysis was performed for gender stratified data in three studies. Data extracted included study design, participants characteristics, mean age, exposure ascertainment methods, outcome ascertainment methods, and numerator and denominator for relevant groups. If numerator denominator data were not available (necessary to calculate and OR), reported ORs and CIs were extracted for purpose of conducting pooled estimate models. After article selection and retrieval were performed, it was discovered that there were three papers that stratified results by gender; therefore, in post hoc analysis we stratified analyses by gender.

Data analysis and evidence synthesis

To assess the relationship between adherence to IBS and ACE, summary estimates of the ORs were calculated using restricted maximum likelihood (REML) model to estimate the heterogeneity of variance.[16] While any model can be biased, the REML has reasonable properties in OR meta-analyses.[17] Heterogeneity among the pooled studies was evaluated with the I^2 statistic and Cochran’s Q test and explored visually and statistically through subgroup-based Forrest plots.[18] I^2 values from 0% to 40% may represent minimal heterogeneity, 40% to 60% may represent moderate heterogeneity, 60% to 90% may represent substantial heterogeneity, and 90% to 100% may represent considerable heterogeneity.[18] Q tests, as represented by p values, were be considered heterogeneous when $p<0.01$.[18] Pooled summary estimates are reported for overall and subanalyses where I^2 values <90%. Publication bias was assessed through funnel plot visualization and Egger’s test.[19]

When evidence of heterogeneity was found, subgroup analyses were performed to explore potential sources of heterogeneity including study size, quality, design, location, and population, and methods of both disease and exposure ascertainment. Pooled estimates for heterogeneity explorations are provided for completeness regardless of I^2 value. When evidence of publication bias was noted, a trim-and-fill analysis was conducted to estimate the impact of this bias on meta-analysis results.[20] All analyses were conducted using the *meta* command suite in Stata V.16 SE (StataCorp, College Station, Texas, USA).

Quality assessment of articles

To assess the quality of the included articles, we used the Down’s and Black Quality Assessment Tool, where two reviewers scored each article for quality domains of study characteristics, external validity, internal validity (bias), and internal validity (confounding) (online supplemental figure 1).[21] The quality of each meta-analysis study was evaluated by two reviewers, and their scores were averaged to obtain the final score of each paper. In post hoc analysis, study quality was also used as a subgroup measure to explore heterogeneity.

RESULTS

The database search yielded 106 results with 24 duplicates published between October 1993 and September 2020. Eighty-two papers were screened with their title and abstracts, and 34 papers were reviewed for full-text

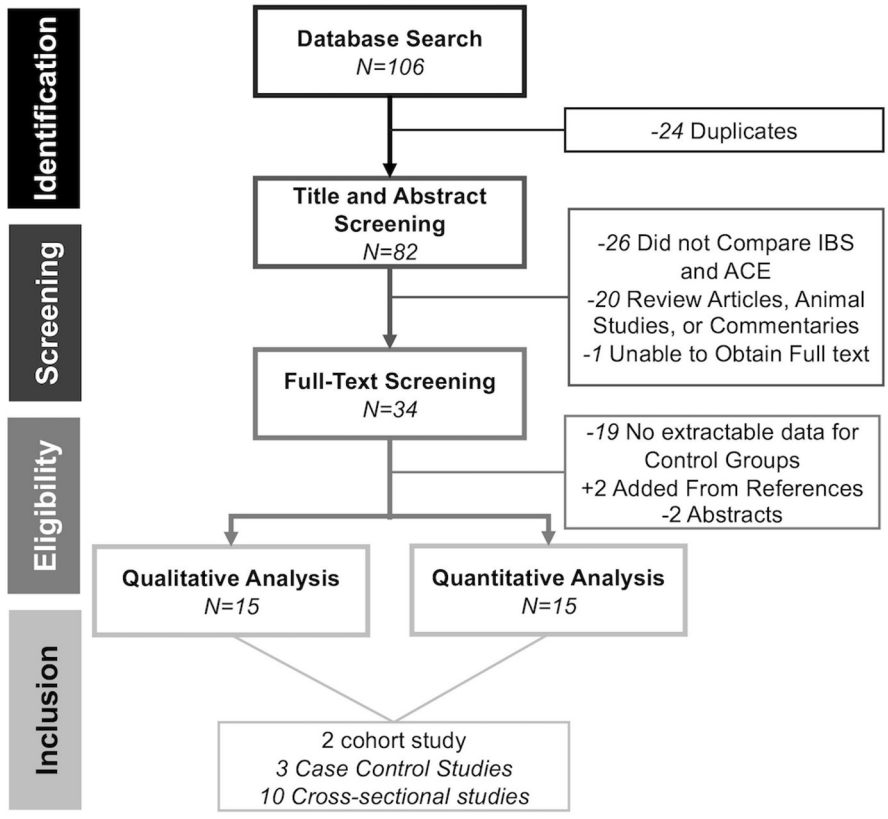

Figure 1 Modified PRISMA flow diagram detailing studies identified during database search and subsequent screenings. ACE, adverse childhood experience; IBS, irritable bowel syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

review. One paper selected for full-text review could not be obtained in its entirety despite repeated attempts to contact the author.[22] A total of 15 studies were selected for the final meta-analysis (figure 1). Overall, 272,686 participants from five different countries (USA, UK, Canada, Germany, and Australia) were assessed with either a cross-sectional (n=10), retrospective cohort (n=2), or case–control study (n=3) design. Study participants could be categorized into three populations: adult (mixed gender), adult and children (mixed gender), or adult women. IBS diagnostic criteria were determined through ROME criteria, physician report/electronic medical record (EMR), standardized questionnaire, or patient self-report. ACE exposure was identified and categorized via self-report, standardized questionnaire, literature-based structured interview, or physician report/EMR. Table 1 lists the studies included in this meta-analysis along with summary data from each study.

A REML pooled analysis based on 15 studies found that a higher report of ACEs was found among those with IBS compared with non-IBS matched controls, although with considerable heterogeneity (I^2=93.58%, p<0.001) (figure 2A). Efforts to understand heterogeneity among ACE exposure and IBS disease found that reporting methods based on objective assessments explained some heterogeneity. ACE reporting methods that used a structured interview or standard questionnaire (n=12 studies) showed a stronger association between ACE and IBS (pOR=2.04, 95% CI (1.45 to 2.88)) with considerable heterogeneity (I^2=93.15 %, p<0.001), compared with those who used more subjective measures (n=3 studies) such as self-reporting (pOR=1.23, 95% CI (1.03 to 2.45)) with minimal heterogeneity (I^2=8.78 %, p=0.29) (figure 3A). A subanalysis of IBS diagnosis methods revealed a similar trend where objective measures (n=13 studies) showed stronger association between the variables of interest (pOR=1.93, 95% CI (1.39 to 2.69)) with considerable heterogeneity (I^2=93.06 %, p<0.001) when compared with self-reporting (n=2 studies) of IBS diagnosis by patients (pOR=1.29, 95% CI (1.02 to 2.63)) with moderate heterogeneity (I^2=41.11 %, p=0.19) (figure 3B). Analyses based on study design, population, location, tertile of study size, and study quality were also performed. Study design, population, location and quality did not reveal differences in effect estimates among published studies (online supplemental figure 2). Studies in the lowest tertile of study participants (n=76–254) showed minimal heterogeneity (I^2=40.84 %, p=0.11) versus the middle tertile (n=302–279) which showed considerable heterogeneity (I^2=92.99 %, p<0.001) and highest tertile (n=824–241,971) which also showed considerable heterogeneity (I^2=95.47%, p<0.001) of study participants (figure 4A). Studies that were in the highest tertile according to study quality showed no association between IBS and ACE (pOR=1.34, 95% CI (0.74 to 2.45)) with considerable heterogeneity (I^2=91.58%, p<0.001) (figure 4B).

Assessment for publication quality broken down by quality domains is shown in online supplemental figure 1. The average score of all papers was 22.3 with an SD of 4.11. Nine studies were identified to have significant issues with

Table 1 Characteristics of the studies included in the meta-analysis

First author, year	Study design	Location	Participants	Population	Mean age (years)	IBS diagnosis criteria	Prevalence	2*2 table	ACE evaluation criteria	OR (95% CI)
Berens, 2020[26]	Cross-sectional	Germany	381	Adults	36.17 IBS 29.45 control	Rome III	ACE in IBS=63.7% ACE in non-IBS=48%	A=81 B=61 C=46 D=66	ACE criteria (10Q)	1.90 (1.15 to 3.14)
Bradford, 2012[12]	Cross-sectional	USA	729	Adults	23.4 IBS 35.1 control	Rome III with physician evaluation for FGID	ACE in IBS=76.6% ACE in non-IBS=36%	A=225.2 B=156.4 C=68.8 D=278.6	ETI-SR	5.83 (4.18 to 8.14)
Chandan, 2020[41]	Retrospective cohort	UK	241,971	Adults	23.4 all	THIN diagnostic codes	ACE in IBS=33.1% ACE in non-IBS=N/A	A=77 889 B=N/A C=1 57 095 D=N/A	Exposure code from EMR	1.27 (1.19 to 1.35)
Fuller-Thompson, 2011[42]	Cross-sectional	Canada	7342	Adults and children	Not listed	Self-Reported Physician Diagnosis	Not listed	Not listed	Canadian Community Health Survey	1.52 (2.12 to 1.09)*
Goodwin, 2013[35]	Retrospective cohort	UK	17,415	Adults and children	Not listed	Self-reported	Not listed	Not listed	Self-reported, guardian or physician reported	1.18 (0.98 to 1.42)*
Heitkemper, 2001[28]	Case–control	USA	Multiple distinct samples		Multiple distinct samples	BDQ, symptoms and GI diagnostic testing	ACE in IBS=41.3% ACE in non-IBS=31.4%	A=69 B=27 C=98 D=59	Structured interview	Multiple distinct samples
			88	Adult women (1989–1994)	33.5 IBS 32.7 control		ACE in IBS=52.3% ACE in non-IBS=34.1%	A=23 B=15 C=21 D=29		2.12 (0.89 to 5.00)
			165	Adult women (1994–1999)	32.3 IBS 32.1 control		ACE in IBS=37.3% ACE in non-IBS=28.6%	A=46 B=12 C=77 D=30		1.49 (0.69 to 3.20)
Heitkemper, 2011[43]	Case–control	USA	72	Adult women	Not listed	Rome II and currently symptomatic	ACE in IBS=52.5% ACE in non-IBS=3.1%	A=21 B=1 C=19 D=31	Childhood Trauma Questionnaire	34.26 (21.22 to 2.21)
Jones, 2013[34]	Cross-sectional	Australia	307	Adults	46.4 IBS 53.2 control	Rome I	ACE in IBS=50% ACE in non-IBS=50%	A=103.5 B=50 C=103.5 D=50	Self-reported	1.00 (1.81 to 0.62)
Ju, 2020[44]	Case–control	USA	362	Adults	31 IBS 30 control	BSQ	ACE in IBS=70.6% ACE in non-IBS=63%	A=139 B=104 C=58 D=61	CTES	1.36 (1.14 to 1.62)
Park, 2016[14]	Cross-sectional	USA	302	Adults	34.4 IBS 30.4 control	Rome II	ACE in IBS=75% ACE in non-IBS=58%	A=111 B=89.32 C=37 D=64.68	ACE criteria (18Q)	2.05 (1.21 to 3.48)

Continued

Table 1 Continued

First author, year	Study design	Location	Participants	Population	Mean age (years)	IBS diagnosis criteria	Prevalence	2*2 table	ACE evaluation criteria	OR (95% CI)
Rahal, 2020[27]	Cross-sectional	Germany	824	Adults	44.59 IBS 30 control	BSQ	ACE in IBS=60.4% ACE in non-IBS=36.3%	A=223 B=165 C=146 D=290	ETI-SR	2.68 (2.02 to 3.56)
Talley, 1993[45]	Cross-sectional	USA	104	Adults	54 IBS 58 control	BDQ with Manning Criteria	ACE in IBS=31.3% ACE in non-IBS=9.7%	A=10 B=7 C=22 D=65	30-minute semistructured interview from DSM III-R	4.22 (1.43 to 12.43)
Talley, 1994[30]	Cross-sectional	USA	919	Adults	39.6 IBS 39.5 control	BSQ with Manning Criteria	ACE in IBS=15.4% ACE in non-IBS=9.5%	A=20 B=75 C=110 D=714	Drossman Sexual *et al* Questionnaire	1.73 (1.01 to 2.95)
Talley, 1998[32]	Cross-sectional	Australia	726	Adults	45 IBS 43 control	BSQ	Not listed	Not listed	Drossman Sexual *et al* Questionnaire	2.02 (1.29 to 2.15)
Videlock, 2009[33]	Cross-sectional	USA	86	Adults	40.4 IBS 37.3 control	Rome II	ACE in IBS=47.7% ACE in non-IBS=46.2%	A=21 B=18 C=23 D=21	Structured Clinical Interview from DSM IV	1.06 (0.45 to 2.53)

*Adjusted ORs.
A, IBS positive and ACE positive ; ACE, Adverse Childhood Events; B, IBS negative and ACE positive; BDQ, Bowel Disease Questionnaire; BSQ, Bowel Symptom Questionnaire; C, IBS positive and ACE negative; CTES, Childhood Trauma Event Scale; D, IBS negative and ACE Negative ; DSM, Diagnostic and Statistical Manual of Mental Disorders; EMR, Emergency Medical Records; ETI-SR, Early-Trauma Inventory Self Report; ETISR-SF, Early-Trauma Inventory Self Report-Short Form; GI, gastrointestinal; IBS, irritable bowel syndrome; THIN, The Health Improvement Network.

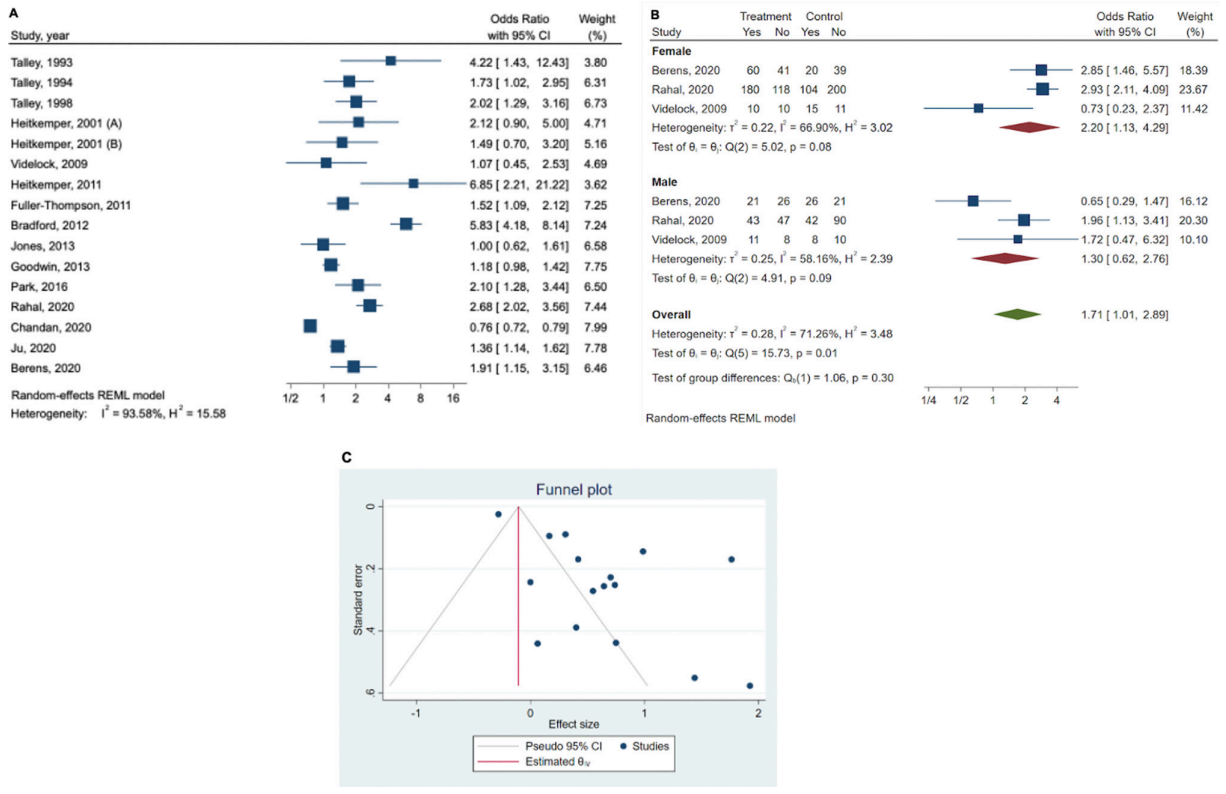

Figure 2 Forest plot with ORs reported by selected studies of adverse childhood events (ACEs) and irritable bowel syndrome (IBS). (A) All studies, n=15 studies. (B) Separated by gender, n=3 studies. (C) Funnel plot (with pseudo 95% CIs) to assess publication bias; Egger's test for publication bias, p<0.001. Twelve studies show risk of significant bias.

internal validity (confounding), seven studies in reporting quality, five studies for internal validity (bias), and three studies for external validity (online supplemental figure 1). In addition to the methodological issues of the population of studies, we also assessed for and observed evidence of publication bias (figure 1C, Egger's test, p<0.001). Given the evidence for publication bias, we performed a trim-and-fill analysis to estimate the numbers of studies missing and estimate the influence on our estimated pooled effect estimate using the methods of Duval and Tweedie.[20] The

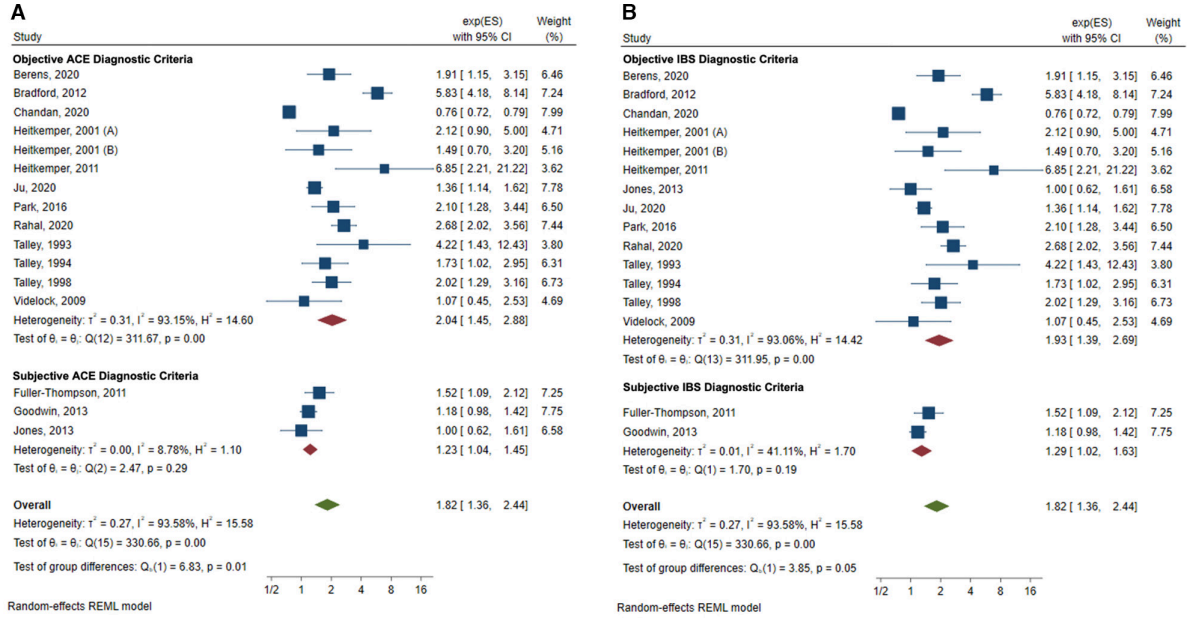

Figure 3 Forest plot with ORs reported by selected studies of adverse childhood events (ACEs) and irritable bowel syndrome (IBS) separated by (A) ACE diagnostic criteria, n=15 studies; (B) IBS diagnostic criteria, n=15 studies.

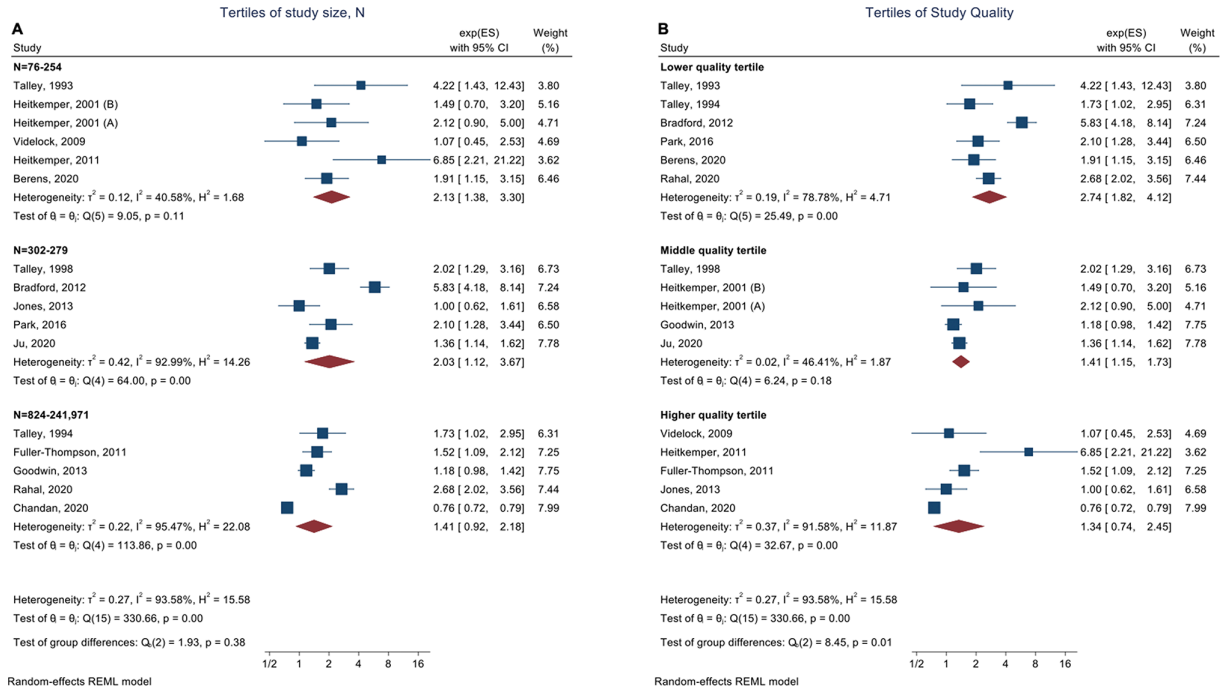

Figure 4 Forest plot with ORs reported by selected studies of adverse childhood events (ACEs) and irritable bowel syndrome (IBS) separated by (A) tertiles of study size, n=15 studies; (B) tertiles of study quality, n=15 studies.

mean effect size of the 16 observed studies is 1.82 (95% CI 1.36 to 2.44). Two hypothetical studies were estimated to be missing and are imputed. If these two studies were included in the meta-analysis, the funnel plot (not shown) would be more symmetrical. After including the imputed studies, we obtain an updated estimate (based on the 18 studies, observed plus imputed) of an OR of 1.58 (95% CI 1.13 to 2.2).

In the post hoc subanalysis focused on gender-stratified data, ACE was a risk factor for developing IBS in females (pOR=2.20, 95% CI (1.13 to 4.29)), but was not a risk factor in males (pOR=1.30, 95% CI (0.62 to 2.78), with substantial heterogeneity in females and considerable heterogeneity in males (female I^2=66.90%, p=0.08; male I^2=93.58%, p=0.09) (figure 2B).

DISCUSSION

This is the first meta-analysis that looked specifically at ACEs and IBS where an association was found between history of ACE and IBS in mixed adult and child populations. However, a significant risk of bias was identified among included studies and evidence for publication bias, which brings caution in interpreting the results. In looking at a similar phenomenon, previous meta-analyses have found associations between trauma (childhood and adulthood), post traumatic stress disorder (PTSD), child abuse, and functional somatic syndromes (including IBS) which may add some coherence to the results.[23–25] For example, Ng *et al*, in 2019, concluded that PTSD is associated with IBS which supports a biopsychosocial view of IBS, and recommended supporting a holistic approach toward its management.[23] A 2014 meta-analysis by Afari *et al* calculated the ORs of functional somatic syndromes and emotional, physical, and sexual abuse to be 2.11, 1.89, and 2.01, respectively.[24] In 2015, Sansone *et al* qualitatively described the current state of the field and explored investigations into the relationship between childhood sexual, emotional, physical abuse and IBS.[25] These corollary observations of associations between psychological trauma and functional somatic complaints provide some coherence to the observed association between ACE and IBS which we found among current published studies.

Aside from the evidence (or lack thereof) from strength and consistency of association, there is reasonable biological plausibility on how ACEs might result in IBS development. For example, it is known that exposure to ACE affects the hypothalamic–pituitary–adrenal (HPA) axis directly or through the accumulation of epigenetic markers.[26–28] In animal studies, ACE-mediated methylation of glucocorticoid receptor promoters leads to HPA axis dysregulation (prolonged elevation of corticosteroids) and the development of visceral hyperalgesia, reduced somatic analgesia, and increased colonic motility, that is, the principal features of IBS.[29] These epigenetic changes may be passed onto any future offspring of affected individual translating the effect of ACEs into permanent genetic predispositions.

In addition to HPA dysregulation through epigenetic mechanisms, ACEs may also affect changes in the brain–gut axis through alternative mechanisms. Study participants with IBS and a history of abuse show a decrease in bowel and peripheral pain thresholds.[30] ACEs may contribute to this pain threshold reduction via impairments in cortical modulation of emotional arousal.[27] This decreases an individual's ability to detect, process, and modulate sensory information in the gut, thus leading to an inappropriate autonomic response.[27] Cheng *et al*, in a study of 67 study participants, found that participants with IBS have significantly

less cardiomyopathic and cardiovagal responses leading up to (p=0.003, p=0.005) and after (p=0.001, p=0.001) flexible sigmoidoscopy.[31] This established that autonomic nervous system dysregulation is correlated to IBS, but further research is necessary to confirm the underlying mechanism behind this connection.

Psychological factors such as neuroticism or mood disorders in those with ACE exposure could affect the manifestation and maintenance of IBS symptoms, further complicating the association between these two variables.[32–35] The abuse, neuroticism, IBS triangle is a self-sustaining mechanism by which individuals may be predisposed to the development and maintenance of IBS.[32] Initially, ACE sets up a lifetime of negative appraisal events via elevated levels of neuroticism and permanently alter the nervous, endocrine, or immune systems.[34 36] In individuals that are biologically predisposed to HPA axis abnormalities, these changes kick-start IBS symptoms.[34] Furthermore, neuroticism increases mood disorders such as anxiety and depression, further increasing GI disturbance.[34] This occurs because of the overlap between neural pathways for hypersensitivity and emotions in the limbic system.[35] Emotional distress and depression also increase sensitivity to bodily sensations and amplify normal somatic systems.[35] Ultimately, the ongoing interactions between neuroticism, mood disorders, and the gut maintain gut disruption leading to the development and perpetuation of IBS through this closed-loop process.

Lastly, preliminary studies on gene polymorphisms in the serotonin, adrenergic, opioid, and other immunomodulatory systems have shown correlation between specific gene alterations and the symptom prevalence in different subtypes of IBS.[37] In summary, there is evidence to support that childhood trauma modulates HPA, brain–gut, and other neurotransmitter/immune axes that eventually lead to functional and structural changes in physiology, gene expression, and neurobiology. These changes eventually dysregulate GI processes and may predispose an individual to develop IBS.

Of particular interest from this study was the identification of gender differences in the OR of those with IBS and exposure to ACEs where a differential effect in women was found compared with men. There are at least three potential explanations that could independently or jointly account for these differences. The first explanation is the differences in health-seeking behavior of women which may account for the increased diagnosis of IBS in women compared with men who have had a history of ACEs.[28] We are not aware of why a female with an ACE history compared with a male with an ACE history would be more likely to seek care for their IBS, but this possibility cannot be ruled out. Second, studies in which men with IBS are included show that a history of abuse is less reported among males than females.[30] However, it is difficult to accurately judge whether gender differences are because men experience less physically/sexually abusive circumstances or if this connection is difficult to make due to the small relative sample size.[28] As a result, this under-reporting of abuse (and therefore ACE) in males may result in studies that look at ACE/IBS relations to prematurely conclude that exposure to ACE only increases the OR of IBS in females but not males without taking into consideration the aforementioned confounding variables. Lastly, biological responses to HPA disruptions could also explain the gender differences in IBS in those exposed to ACE. It has been well documented in previous studies that an exaggerated HPA response (high salivary cortisol) is associated with IBS symptoms.[38] Although there is no difference in salivary cortisol levels between men and women with IBS, HPA reactivity is increased in IBS males resulting in a faster return to baseline cortisol.[33 38] Slower cortisol returns to baseline have been correlated with greater IBS symptom severity and lower IBS-related quality of life.[33] Overall, more studies need to be conducted to discern whether sex differences in IBS are related to social issues, biological phenomenon, or, more likely, a combination of the two.

This review provides caution in the interpretation of the population of literature currently addressing this topic. Current studies describing the association between ACEs and IBS are affected by many significant biases, including recall bias, inter-study variability, study size, quality and few studies available for analysis. These studies included in this meta-analysis were observational; therefore, this may partially explain the high instance of confounding bias. Most ACE evaluations were completed independently by patients opening it to subjective judgment of both categorization and severity of ACEs. IBS diagnosis also varied by study leading to potential issues with outcome misclassification. Objective ACE and IBS reporting methods showed a stronger association between the two variables which is reasonable since improved assessments may report ACE exposure and IBS diagnosis better than patient self-report. Significant publication bias was also seen; therefore, more studies need to be conducted to fully ascertain whether this publication bias is due to discrepancies in publication success or if ACE truly is an underlying cause of IBS. Given these concerns, the observed associations from the study are likely to change as more studies are conducted and published which describe a full range of effect sizes and directions not currently observed as would be anticipated. If the association between ACEs and IBS can be found in further studies and the mechanisms are better understood, this may lead to better therapy. The explanations for IBS and ACE discussed in this meta-analysis thus far increasingly support viewing IBS from a biopsychosocial perspective given what is emerging from our study of ACEs and other chronic health problems.[39 40] Holistic development of therapeutics and patient management techniques will be warranted once research substantiates the need for such interventions.

CONCLUSION

This meta-analysis explores the current literature which aims to understand the biopsychosocial perspective of IBS and the role of ACEs as potential risk factors. The current population of studies suffers from publication and design biases risks but substantiates that further research is needed to definitively understand the risk and features of the potential link between ACEs and IBS (and other disorders of gut–brain interaction). If an association is confirmed, further mechanistic research and targeted psychological therapies development are warranted. This can include structured pathopsychological interviews that determine ACEs in the patient's history and develops appropriate psychological therapy recommendations along with pharmaceutical

interventions. The mechanism behind the development of IBS in those with ACE is still unclear. Explanations focus on the dysregulation of the HPA axis or the presence of confounding variables such as neuroticism and mood disorders. Differences between females and males have biological and social components that need to be explored in further studies. Other avenues for further research should look into the severity of IBS and ACE scores and also give more attention to creating a singular multimodal explanation for the pathogenesis of IBS in those exposed to ACE. Overall, these data support the importance of a growing number of adverse health outcomes associated with ACEs and substantiate community-based and societal-based interventions to reduce them.

Acknowledgements We thank Alexander Lyubechansky and Terry Henner for their invaluable assistance in obtaining full texts of the articles included in this meta-analysis.

Contributors SJ led the research team and drafted the manuscript with the assistance of RB. LL assisted in compiling the final submission package and assisted in conducting the meta-analysis. AW and RB assisted in conducting the meta-analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Shreeya Joshee http://orcid.org/0000-0002-8173-8984

REFERENCES

1 Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015;313:949–58.
2 Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:712–21.
3 Klem F, Wadhwa A, Prokop LJ, *et al*. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. *Gastroenterology* 2017;152:1042–54.
4 Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol* 2014;6:71–80.
5 Chitkara DK, van Tilburg MAL, Blois-Martin N, *et al*. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. *Am J Gastroenterol* 2008;103:765–74.
6 Peery AF, Dellon ES, Lund J, *et al*. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012;143:1179–87.
7 Lacy BE, Mearin F, Chang L, *et al*. Bowel disorders. *Gastroenterology* 2016;150:1393–407.
8 Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol* 2014;20:6759–73.
9 Thabane M, Marshall JK. Post-Infectious irritable bowel syndrome. *World J Gastroenterol* 2009;15:3591–6.
10 Maxwell PR, Rink E, Kumar D, *et al*. Antibiotics increase functional abdominal symptoms. *Am J Gastroenterol* 2002;97:104–8.
11 Singh P, Agnihotri A, Pathak MK, *et al*. Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. *J Neurogastroenterol Motil* 2012;18:324–31.
12 Bradford K, Shih W, Videlock EJ, *et al*. Association between early adverse life events and irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2012;10:385–90.
13 Halland M, Almazar A, Lee R, *et al*. A case-control study of childhood trauma in the development of irritable bowel syndrome. *Neurogastroenterol Motil* 2014;26:990–8.
14 Park SH, Videlock EJ, Shih W, *et al*. Adverse childhood experiences are associated with irritable bowel syndrome and gastrointestinal symptom severity. *Neurogastroenterol Motil* 2016;28:1252–60.
15 Page MJ, McKenzie JE, Bossuyt PM. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2020;372:n71.
16 Harville DA. Maximum likelihood approaches to variance component estimation and to related problems. *J Am Stat Assoc* 1977;72:320–38.
17 Langan D, Higgins JPT, Jackson D, *et al*. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods* 2019;10:83–98.
18 Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for systematic reviews of interventions*. Chichester, UK: John Wiley & Sons, 2019: 241–84.
19 Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000;53:1119–29.
20 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
21 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377–84.
22 Alciati A, Mellado C. Do early adverse experiences have a pathogenetic role in the development of functional syndromes? *J Funct Syndr* 2002;2:127–34.
23 Ng QX, Soh AYS, Loke W, QX N, Sen SAY, *et al*. Systematic review with meta-analysis: the association between post-traumatic stress disorder and irritable bowel syndrome. *J Gastroenterol Hepatol* 2019;34:68–73.
24 Afari N, Ahumada SM, Wright LJ, *et al*. Psychological trauma and functional somatic syndromes: a systematic review and meta-analysis. *Psychosom Med* 2014;76:2–11.
25 Sansone RA, Sansone LA. Irritable bowel syndrome: relationships with abuse in childhood. *Innov Clin Neurosci* 2015;12:34–7.
26 Berens S, Banzhaf P, Baumeister D, *et al*. Relationship between adverse childhood experiences and illness anxiety in irritable bowel syndrome - The impact of gender. *J Psychosom Res* 2020;128:109846.
27 Rahal H, Videlock EJ, Icenhour A, *et al*. Importance of trauma-related fear in patients with irritable bowel syndrome and early adverse life events. *Neurogastroenterol Motil* 2020;32:e13896.
28 Heitkemper M, Jarrett M, Taylor P, *et al*. Effect of sexual and physical abuse on symptom experiences in women with irritable bowel syndrome. *Nurs Res* 2001;50:15–23.
29 Coutinho SV, Plotsky PM, Sablad M, *et al*. Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. *Am J Physiol Gastrointest Liver Physiol* 2002;282:G307–16.
30 Talley NJ, Fett SL, Zinsmeister AR, *et al*. Gastrointestinal tract symptoms and self-reported abuse: a population-based study. *Gastroenterology* 1994;107:1040–9. —.
31 Cheng P, Shih W, Alberto M, *et al*. Autonomic response to a visceral stressor is dysregulated in irritable bowel syndrome and correlates with duration of disease. *Neurogastroenterol Motil* 2013;25:n/a–9.
32 Talley NJ, Boyce PM, Jones M. Is the association between irritable bowel syndrome and abuse explained by neuroticism? a population based study. *Gut* 1998;42:47–53.
33 Videlock EJ, Adeyemo M, Licudine A, *et al*. Childhood trauma is associated with hypothalamic-pituitary-adrenal axis responsiveness in irritable bowel syndrome. *Gastroenterology* 2009;137:1954–62.
34 Jones MP, Van Oudenhove L, Koloski N, *et al*. Early life factors initiate a 'vicious circle' of affective and gastrointestinal symptoms: A longitudinal study. *United European Gastroenterol J* 2013;1:394–402.
35 Goodwin L, White PD, Hotopf M, *et al*. Life course study of the etiology of self-reported irritable bowel syndrome in the 1958 British birth cohort. *Psychosom Med* 2013;75:202–10.
36 Danese A, J Lewis S. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? *Neuropsychopharmacology* 2017;42:99–114.
37 Vaiopoulou A, Karamanolis G, Psaltopoulou T, *et al*. Molecular basis of the irritable bowel syndrome. *World J Gastroenterol* 2014;20:376–83.

38 Patacchioli FR, Angelucci L, Dellerba G, *et al*. Actual stress, psychopathology and salivary cortisol levels in the irritable bowel syndrome (IBS). *J Endocrinol Invest* 2001;24:173–7.
39 Lin L, Wang HH, Lu C, *et al*. Adverse childhood experiences and subsequent chronic diseases among middle-aged or older adults in China and associations with demographic and socioeconomic characteristics. *JAMA Netw Open* 2021;4:e2130143.
40 Waehrer GM, Miller TR, Silverio Marques SC, *et al*. Disease burden of adverse childhood experiences across 14 states. *PLoS One* 2020;15:e0226134.
41 Chandan JS, Keerthy D, Zemedikun DT, *et al*. The association between exposure to childhood maltreatment and the subsequent development of functional somatic and visceral pain syndromes. *EClinicalMedicine* 2020;23:100392.
42 Fuller-Thomson E, Sulman J, Brennenstuhl S, *et al*. Functional somatic syndromes and childhood physical abuse in women: data from a representative community-based sample. *J Aggress Maltreat Trauma* 2011;20:445–69.
43 Heitkemper MM, Cain KC, Burr RL, *et al*. Is childhood abuse or neglect associated with symptom reports and physiological measures in women with irritable bowel syndrome? *Biol Res Nurs* 2011;13:399–408.
44 Ju T, Naliboff BD, Shih W, *et al*. Risk and protective factors related to early adverse life events in irritable bowel syndrome. *J Clin Gastroenterol* 2020;54:63–9.
45 Talley NJ, Kramlinger KG, Burton MC, Caroline Burton M, *et al*. Psychiatric disorders and childhood abuse in the irritable bowel syndrome. *Eur J Gastroenterol Hepatol* 1993;5:647–54.