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REVIEW

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Factors influencing rectal hypersensitivity in irritable bowel syndrome: A systematic review and meta-analysis

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Abstract

Background: A frequent, although not universal, feature of irritable bowel syndrome (IBS) is heightened sensitivity to mechanical stimulation of the rectum, termed rectal hypersensitivity (RH). Differences in RH-based on sex, IBS subtype, IBS diagnostic criteria and age of population studied are incompletely understood. We aimed to determine whether IBS population had lower pain thresholds than healthy controls.

Methods: We searched MEDLINE and EMBASE databases (1970–2021). Prospective studies that compared pain/discomfort thresholds to mechanical rectal stimuli in IBS and healthy controls were included. Data were pooled for meta-analyses and effect sizes were calculated with 95% confidence interval (CIs).

Results: Our search strategy identified 809 studies of which 32 studies met the inclusion criteria. Reduced rectal pain thresholds was more common in IBS patients compared to healthy controls with an effect size of 1.00 95% CIs (0.77–1.24) ($p < 0.0001$) ($I^2 = 78.6\%$). The pediatric IBS population had lower pain thresholds than adult IBS populations ($p = 0.05$) but no difference based on IBS diagnostic criteria, subtype or sex.

Conclusion & Inferences: The results suggest that reduced rectal pain threshold to experimental stimulation is far more common in IBS patients than healthy controls. Further research is required to understand the pathophysiological and therapeutic implications of rectal sensitivity such as its role in measuring response to treatment and prognosis in IBS.

KEYWORDS
abdominal pain, irritable bowel syndrome, visceral hypersensitivity

1 | INTRODUCTION

Rectal hypersensitivity is defined as increased sensitivity to experimental stimuli applied to the gastrointestinal (GI) tract.[1] It can arise due to a combination of either heightened sensitivity to noxious stimuli (hyperalgesia) and/or non-noxious stimuli (allodynia) due to factors such as peripheral and central sensitisation.[2] Additional mechanisms include alterations in central factors such

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as aberrant brain processing[3] and abnormal descending inhibitory control of pain pathways.[4,5]

Irritable bowel syndrome (IBS) is characterized by visceral pain and altered bowel habits. IBS is thought to be a disorder of a dysfunctional gut-brain axis where symptoms are present in the absence of demonstrable organic disease.[6] IBS is subtyped according to the predominant bowel habit into IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed bowel habit IBS (IBS-M) and IBS unclassified (IBS-U).[7] IBS has a reported prevalence of around 4.5% and is associated with a large reduction in quality of life.[8]

In IBS, the cause of visceral pain is incompletely understood but it is considered that rectal hypersensitivity exerts an important effect.[9,10] Rectal pain thresholds can be evaluated using mechanical (manual or automated using a barostat), nutrient, chemical, thermal or electrical stimuli to discriminate whether pain thresholds are higher or lower in different groups. The intensity of pain when using such techniques is most commonly measured using a self-report visual analogue scale (VAS). In IBS patients' there is a correlation between symptom severity and pain sensitivity to mechanical rectal distension.[11,12] Provocation tests suffer from significant heterogeneity as distension protocols and definitions for a painful stimulus vary from study to study, although recent international efforts have sought to improve standardization.[13] This variation in testing conditions has prevented the development of standardized normal values from which hyper, normo and hyposensate individuals can be identified. Repeated exposure to experimental provocation stimuli can normalize rectal sensation probably due to habituation.[14] However, mechanical stimulation is currently regarded as the most reliable instrument to assess rectal sensitivity.[15] At present rectal provocation testing is rarely used outside of GI physiology units in the clinical setting.[16] Rectal sensation testing can be considered in the evaluation of rectal hyposensitivity when assessing for megarectum and in the consideration of fecal incontinence when anal sphincter function may be impaired.[16] Current standard of practice is for balloon distension either using phasic or ramp distension techniques, barostat is mainly reserved for research environments.

The primary aims of this study were to assess if pain thresholds to mechanical rectal stimulation were different in the IBS population compared to healthy controls. Secondary aims were to ascertain if there were differences in rectal pain thresholds based on IBS diagnostic criteria used, IBS subtype, sex or age. The reason for this is that there is some evidence that Rome III and IV represent a more severe phenotype of the disease than the earlier Rome iterations as reported prevalence is higher using previous versions of the Rome criteria[8,17] compared to using Rome IV. In addition, there is some evidence that some patients, particularly those with IBS-C may demonstrate hyposensitivity[18,19] but this is not a universal conclusion.[20] Therefore we aimed to see if there were differences in pain thresholds based on IBS subtype.

Despite the large number of published studies on rectal provocation testing in IBS patients, to the best of our knowledge, there has been no meta-analysis on the topic.

Key Points

Background

- Reduced rectal pain thresholds are considered to be a feature of irritable bowel syndrome (IBS) although this epiphenomenon is variably reported.

Findings

- In 32 studies with 1452 individuals with IBS, compared to 567 healthy controls, reduced rectal pain thresholds were more common with a large effect size.
- Pediatric IBS patients demonstrated larger reduction in pain thresholds than adults.
- There were no differences based on diagnostic criteria, subtype, or sex.

What is the impact on clinical practice in the foreseeable future?

- Reduced rectal pain thresholds are frequently seen in patients with IBS and may impact clinical presentation. Therefore this phenomenon requires physician awareness.
- Rectal hypersensitivity should be considered an important mechanism of pain in IBS and future studies should focus on understanding its pathophysiology and importance as a marker of response to treatment.

2 | MATERIALS AND METHODS

2.1 | Study population and study design

The systematic review and meta-analyses were conducted according to the PRISMA recommendations and were registered with PROSPERO (*Reference CRD42018095687*).[21] The search of the literature was performed using MEDLINE and EMBASE (1970–2021). This was carried out using the set search strategies outlined in the Table S1. There were no language restrictions. Eligibility criteria are shown in Box 1. The bibliographies of all relevant studies and available meeting abstracts were screened to identify studies that were missed by the original search criteria. Senior authors were contacted to provide additional information where required. Articles were assessed independently by two reviewers (CR and AA) using the predetermined eligibility criteria. Disagreements were resolved by consensus.

2.2 | Data extraction

The name of the first author, year of publication, location of study, IBS population size, control population size, IBS criteria and primary

BOX 1 Eligibility criteria

Inclusion criteria

- Diagnosis of IBS according to ROME criteria
- Assessing of IBS and a healthy control population
- Measurement of pain/ discomfort thresholds using mechanical rectal distension
- Prospective study.

Exclusion criteria

- If testing pain/discomfort thresholds by means other than mechanical such as electrical.
- Retrospective studies were rejected due to the risk of repeat data.

outcome data which were recorded in means and standard deviations were extracted into an Excel Spreadsheet (Excel 2016, Microsoft).

The primary outcome was to see if there was a difference in pain/discomfort threshold in IBS and control populations. Secondary outcomes were assessed to see if pain thresholds differed between IBS subtype, IBS diagnostic criteria used, sex and age studied. Paedatric populations were defined as being less than 18 years old. To perform secondary analysis, data were pooled from the studies that provided the necessary information to perform the subgroup analyses. Standard deviations were calculated according to the Cochrane Collaboration guidelines.[22]

2.3 | Quality assessment and risk of bias

Two investigators performed a biased assessment independently for all studies included in the meta-analysis. Bias was scored in six areas using a modified checklist for case–control studies.[23] These areas were: (1) blinding of assessors, (2) use of international criteria to diagnose IBS, (3) use of aged-matched controls, (4) use of sex-matched controls, (5) exclusion of other chronic pain disorders and (6) controlling for other known factors that affect pain sensation such as anxiety and depression.

2.4 | Data analysis

Data were pooled for meta-analysis and a random effect model using the Hartung–Knapp–Sidik–Jonkman method was chosen. Heterogeneity was assessed using the I^2 statistical test which gives values between 0% and 100%, with 0% representing no observed heterogeneity. Outcomes were assessed using Hedges' g effect sizes and are reported with 95% confidence intervals (CI). A prespecified secondary analysis was performed to determine if the effect size was modified in various subgroups. Meta-regression was performed to determine if rectal compliance played a role in the development of reduced rectal pain thresholds using studies that provided data on rectal compliance. The statistical criterion was $p < 0.05$. Evidence of publication bias was assessed by using a funnel plot and Egger's Test. Propriety software was used to perform the meta-analysis and generate the plots (Comprehensive Meta-Analysis Version 2, Biostat, Version 2) and (R, R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Search results

The search generated 809 citations of which 81 were classed as relevant and 32 met the inclusion criteria comprising 1452 individuals with IBS and 567 controls, see Figure 1. In total, 49 studies were rejected. The characteristics of the included studies are shown in Table S2.

3.2 | Rectal hypersensitivity in IBS

Irritable bowel syndrome participants had lower pain thresholds in comparison to healthy controls with a large effect size, 1.00 95% CIs (0.77–1.24) ($p < 0.0001$) ($I^2 = 78.6\%$), see Figure 2.

3.3 | IBS effect size based on IBS subtype, diagnostic criteria, sex and age

Of the 31 studies included in the meta-analysis, nine provided data for the different IBS subtypes. Compared to healthy controls, the effect size was strongly positive for both IBS-C and IBS-D. There was a significant difference between the subgroups ($p = 0.001$), however, when IBS-M subtype along with studies that did not differentiate between subtypes were removed from the analysis there was no significant difference in pain thresholds ($p = 0.40$). The effect size for IBS-C is 0.98 (0.39–1.58) and for IBS-D 1.37 (0.36–2.37). A forest plot is shown in Figure 3 *plot A*.

Of the 31 included studies, nine used Rome I, 18 used Rome II, two used Rome III and two used Rome IV. There was no statistical difference found between the groups ($p = 0.21$). A forest plot is in Figure 3 *plot B*.

Of the 31 studies included eight provided data about sexes covering 242 women and 83 men with IBS. There was no statistical difference identified between the sexes ($p = 0.13$). A forest plot is in Figure 3 *plot C*.

Three studies examined 39 pediatric individuals with IBS. The effect size for adult IBS patients compared to adult controls was 0.94 95% CI (0.70–1.17) whereas, in the pediatric IBS patients compared to pediatric controls was 1.85 95% CI (−0.07–3.77). There was a statistically significant difference between adult and pediatric populations ($p = 0.05$). A forest plot is in Figure 3 *plot D*.

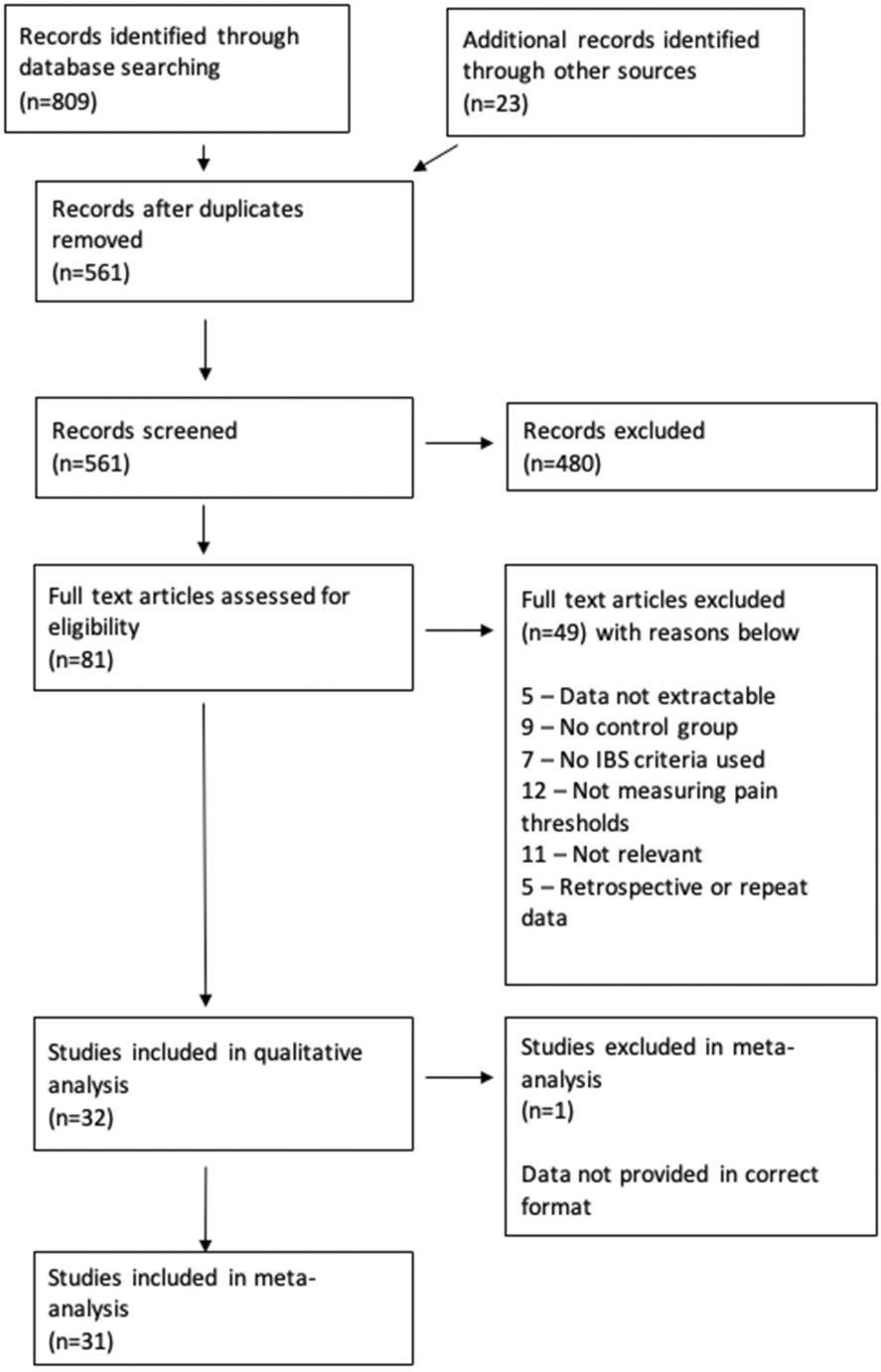

FIGURE 1 Flow diagram of the assessment of studies included in the IBS meta-analysis.

3.4 | Heterogenicity

Heterogenicity was high as shown by $I^2 = 78.6\%$ which is regarded as being a high level of heterogenicity, the reasons for this high level were unclear, a number of statistical tests were used to look for the reasons including detecting outliers, an influence analysis and a Baujat plot which all revealed that the Camilleri et al.[20] and Bouin et al.[24] studies provided a significant amount of the observed heterogenicity. With these studies removed $I^2 = 61\%$ which is regarded as medium heterogenicity and the effect size remained relatively unaffected at 1.07 (0.85–1.28). See Figure S1.

Another cause of possible heterogenicity was the variability in rectal provocation testing using either rectal balloon distension or rectal barostat. Despite this, when we adjusted for the device used heterogenicity remained unchanged at $I^2 = 73\%$. When the different distension protocols using ramp or phasic distension protocols were corrected for, then heterogenicity improved to $I^2 = 65\%$. There was variability in the terms used. When we assessed studies that used pain and discomfort thresholds then heterogenicity did improve to $I^2 = 61\%$. Interestingly, there was no difference in pain threshold effect sizes between studies that use pain or discomfort as their definition ($p = 0.67$).

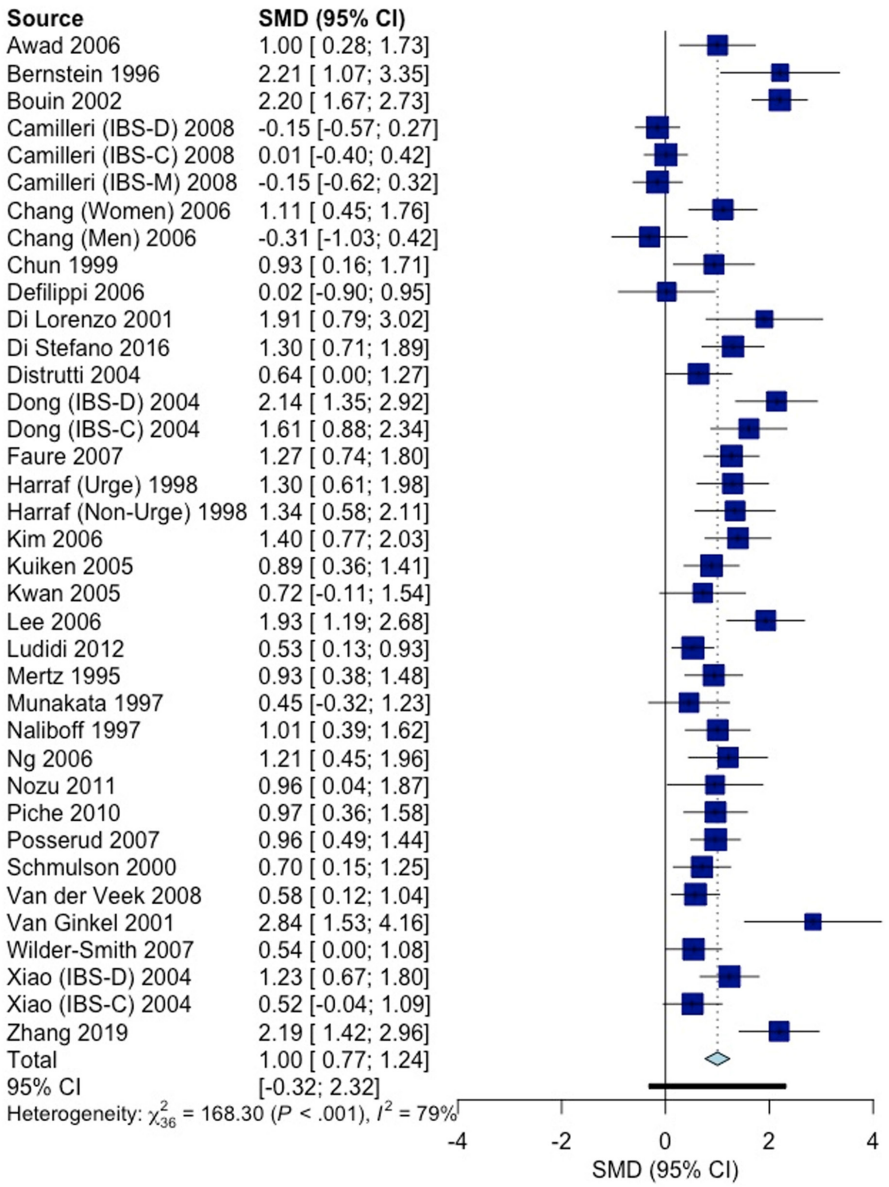

FIGURE 2 A forest plot of the effect sizes for pain thresholds in an IBS vs a control population. The pooled effect size is 0.97 95% CI (0.77–1.17) ($p < 0.0001$).

3.5 | Meta-regression

Results on rectal compliance were provided in seven studies covering 413 individuals with IBS and 160 healthy controls. Lower levels of rectal compliance were found to be associated with a lower rectal pain threshold ($p = 0.006$).

3.6 | IBS study quality assessment

The quality of the studies included in the meta-analysis is summarized in Table S3. All the papers were scored out of 12 with zero indicating the least risk of bias. In most studies, the assessors were not blinded and hence most scored two points for this section although the majority did use a single-blind protocol. A funnel plot was performed to assess for the presence of publication bias which is included in the Figure S2 and an Egger's test was carried out which showed the presence of publication bias. When the publication bias was corrected the resulting effect size remained highly positive at 0.66 95% CI (0.38–0.93) $p < 0.0001$.

4 | DISCUSSION

This meta-analysis demonstrates average rectal pain thresholds were lower in IBS patients in comparison to healthy controls. This observation is common to IBS subtypes and is not modified by the diagnostic criteria or sex. However, pain thresholds were lower in pediatric IBS populations compared to adults.

Chronic visceral pain is a central defining factor in IBS and contributes to healthcare seeking and reduces the quality of life.[25,26] The absolute cause of chronic visceral pain in IBS is incompletely understood but visceral hypersensitivity remains the germane hypothesis.[27] Although rectal provocation testing is not considered to

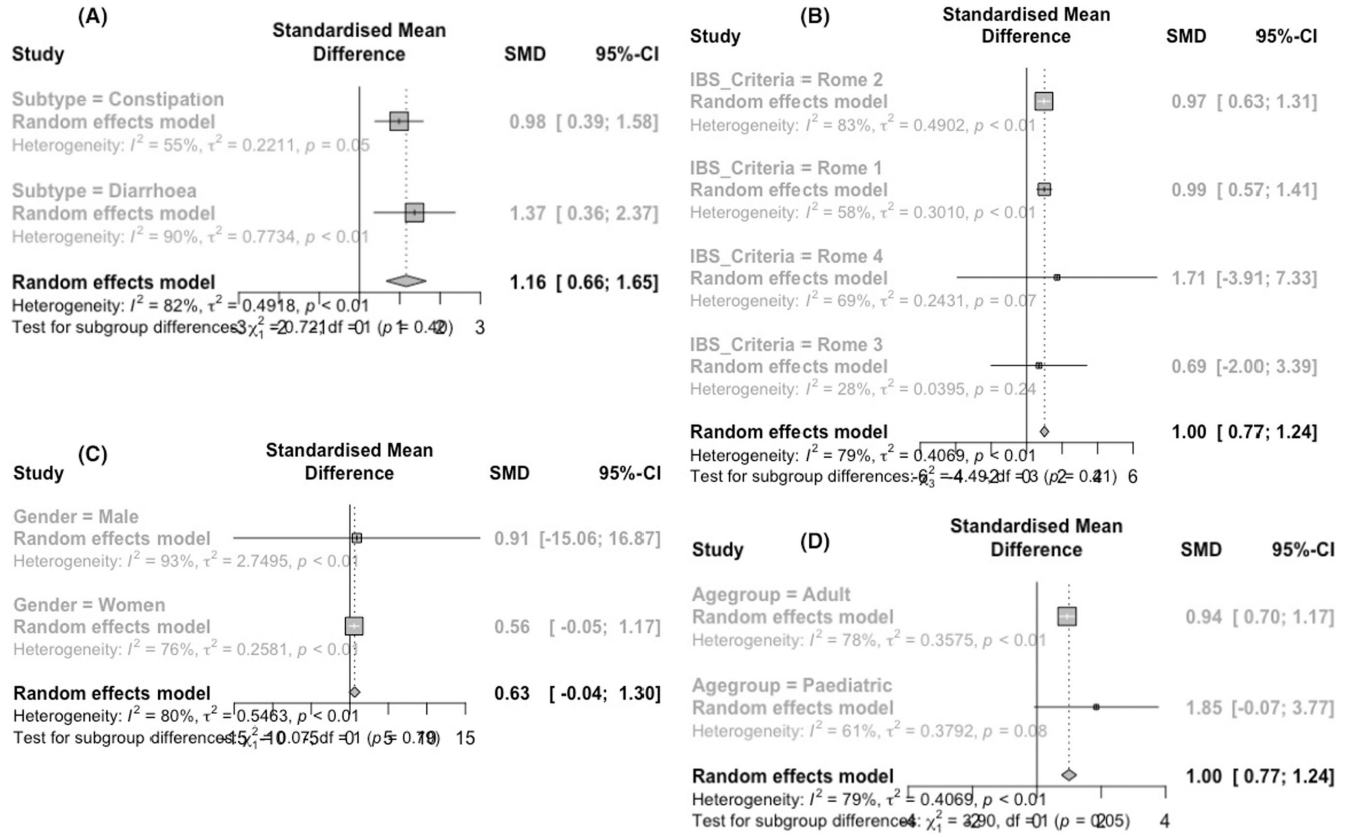

FIGURE 3 Forest Plots showing effect size in different subgroups. Each subgroup is present with the *p* value for the difference between all subgroups. (A) IBS subtype – IBS-D and IBS-C ($p = 0.4$), (B) Rome criteria used to diagnose IBS ($p = 0.21$), (C) Sex ($p = 0.13$) and (D) Age group studied ($p = 0.05$).

display the prerequisite receiver operator characteristics for diagnosis of IBS, provocation testing can be used in the clinical setting in the assessment of evacuation disorders or when a megarectum may be suspected.[16] Our results demonstrate, at least in the participants included in the meta-analysis, that reduced pain thresholds are a defining feature in people with IBS compared to healthy controls.

All included studies used the four different versions of the Rome criteria and although there have been changes to the diagnostic criteria for IBS, our findings indicate that this does not impact the degree of rectal hypersensitivity. In some way, this is surprising as the Rome IV classification of IBS requires the presence of weekly pain and prevalence of IBS drops between the different Rome versions.[9,17] It is difficult to make firm conclusions here as there were only four studies that looked at either Rome III or IV and so further studies are required to confirm whether rectal hypertensives is more common in the newer iterations of Rome. There was a trend towards Rome IV having a greater reduction in pain thresholds than individuals who were identified by other Rome criteria but this did not reach statistical significance. This suggests that reduced rectal pain thresholds may be more common in individuals who have been diagnosed using Rome IV compared to the earlier versions of the criteria. If reduced rectal pain thresholds were more common in the Rome IV population this would indicate that the amount of reduction of rectal pain thresholds may co-relate with disease severity, this does conform with previous work.[11] However further work is required to confirm this hypothesis.

Interestingly, no difference in rectal pain thresholds was observed between IBS-C and IBS-D. Previous studies have suggested there may be a proportion of patients particularly those with IBS-C who may be hyposensate due to alterations in rectal sensorimotor function and compliance.[18,20] Conversely, in IBS-D, sensory defecatory urge threshold and rectal compliance are diminished in comparison to IBS-C and healthy controls.[28] Given the lack of overall effect between subtypes, our data suggest that whilst there are differences in individual studies, an overall effect is not present and reduced rectal pain thresholds are common to all IBS subtypes. From our data, it is far more likely for IBS patients to demonstrate reduced rectal pain thresholds but in many of our studies there were subgroups of IBS patients who had higher pain rectal pain thresholds than controls. These individuals may be hyposensate.

Pediatric IBS patients were more likely to have lower rectal pain thresholds than adult IBS patients. The reason for this difference is unclear and it could be reasoned that pediatric IBS may represent a more severe phenotype. However, other reasons may also explain this difference. For instance, even though both pediatric[29] and adult[30,31] IBS populations often demonstrate hypervigilance as a significant number reported pain before any stimulus was applied. It is plausible that this hypervigilance is more common in the pediatric

IBS cohort. To date, there has been no comparison in the prevalence of hypervigilance between adult and pediatric populations. Similarly, anxiety, stress and hormonal factors may also play a role in the differences observed between adult and pediatric cohorts. Further research is required to understand the reasons for the difference in rectal sensitivity between adult and pediatric patients. Greater anxiety before the procedure may play a role in explaining the difference in rectal pain thresholds between pediatric and adult patients. This could explain the significantly increased levels of hypervigilance in the pediatric populations. Unfortunately, in the studies that assessed anxiety this was in the form of generalized anxiety rather than anxiety towards the distension procedure itself.

The results of the meta-regression show that reduced rectal compliance plays a key role in the lower pain thresholds seen in patients with IBS compared to healthy controls; however, these results do not fully explain the lower pain thresholds seen in IBS patients compared to controls. Reduced rectal compliance is linked with reduced pain thresholds in provocation testing as the rectum is less able to expand as distension increases and therefore a pain stimulus is likely to occur at a lower threshold.[32]

The cause of reduced pain thresholds and likely rectal hypersensitivity is unclear, there is a significant thought that subtle levels of inflammation and immune activation seen in IBS may play a key role.[33,34] In vitro testing shows that high burdens of inflammation may lead to the sensitizing effect of inflammation on afferent neurons.[34] In this regard, some neurotrophic factors, such as nerve growth factor, and heightened expression of the transient receptor potential cation channel subfamily V member 1 (TRPV1) and the purinergic P2X3 receptor measured in the mucosa have been implicated.[35–37] TRPV1 channels are further shown to play a key role in rectal hypersensitivity as the reversal of their activation in a mouse model was able to normalize pain response to rectal distension.[38]

However, in some patient's inflammation may be required as a triggering event such as in post-infectious IBS. In post-infectious IBS occurs in around 10% of episodes of acute gastroenteritis (AG).[39] In AG there is a burden of inflammation which should then improve. The cause of why these symptoms persist is unclear but some genetic and environmental factors have been identified relating to both the episode of AG itself and some prior risk factors such as female, younger age and previous anxiety/depression.[40,41] Interestingly these risk factors are also risk factors for IBS in non-AG patients.[17] A similar phenomenon is seen in patients with quiescent IBD where most patients do not experience long-term abdominal patients, but a subset does which is regarded as being IBD-IBS crossover. The risk factors for development of IBS-IBD crossover seem to be similar to those of IBS and post-infectious IBS further confirming that coexisting psychological comorbidities appear to play a key role in the development of IBS.

Another major factor that has been implicated in the development of IBS is hypervigilance.

Hypervigilance is already known to play a key role in rectal hypersensitivity as experimental stimulation is likely to represent a 'threat' to the patient with repeated exposure reducing this 'threat' through habituation. Habituation has been demonstrated to normalize perceptual ratings to rectal stimulation in IBS patients and this is associated with decreased activity in brain regions and networks associated with pain processing.[15] This indicates that psychological factors play a role in pain processing. In IBS, abdominal pain-related fear learning and memory processes are altered, which may contribute to central pain amplification and hypervigilance which may be enhanced in those with comorbid anxiety and depression.[41,42] Experimentally induced negative emotions during painful rectal distension even in healthy volunteers can lead to increased brain activity in the left thalamus and right dorsal posterior cingulate gyrus.[43] Besides, alterations in descending pain modulatory pathways also contribute to rectal hypersensitivity in IBS.[44] Indeed, altered brain processing to rectal stimulation is seen in IBS patients compared to healthy controls in areas involved in descending pain modulation.[3,5,45] The above mechanisms are likely to be more prominent in IBS than the inflammation solely. In post-infectious IBS the symptoms persist well after the inflammation improves and is thought to be due to central sensitisation.[46]

This study is subject to several limitations. There was significant heterogenicity in the study although this was improved after outliers were removed. There was though still some heterogenicity that persisted. This is likely because of the differences in the site of experimental stimulation and methods used for determining pain given that it is a subjective experience with marked intra-and inter-individual variability.[47] There was an attempt to correct the difference in study methodology by only evaluation studies that assessed rectal as opposed to colonic sensation. All the studies included took place in tertiary care settings so may represent a more severe phenotype than what is seen in other settings.

There is an established link between the presence of depression and anxiety reporting pain at lower pain intensities, so it was surprising that studies did not try and correct for these confounding factors.[48,49] The fact that only some did will have likely increased the observed heterogeneity and unfortunately, a meta-regression was not possible given the lack of data. However, how important such factors are in IBS is unclear as van der Veek et al.[12] did not demonstrate differential rectal sensitivity when IBS participants were stratified according to levels of anxiety, depression or somatization.[12]

Suggestions for further research include using a standardized rectal provocation testing[13] in healthy individuals to identify accurate normal values, which would allow for identification of hyper, hypo and normosensate individuals with IBS. Clinical trials could then be designed focusing on these groups to determine what treatments would be the most efficacious within the different populations.

This meta-analysis indicates that reduced pain thresholds are an epiphenomenon strongly associated with both adult and pediatric IBS populations in comparison to healthy controls. The mechanism causing reduced pain thresholds is not fully understood but is likely due to a combination of peripheral and central factors and is likely to vary in different populations and diseases. Standardized rectal provocation testing, given that it is cheap and widely available, may facilitate the identification of hypersensate individuals

who may benefit from personalisation of treatment strategies that aim to reduce hypersensitivity such as in the use of pain modulators and/ or psychological therapies. However further work is required to suggest that serial testing could be used as a biomarker for success in the treatment of IBS and as a prognostic indicator of long-term outcomes. Rectal barostat could be used in the clinical setting to identify possible responses to pharmalogical[50,51] and psychogical[52] treatments.

AUTHOR CONTRIBUTIONS

Christopher Roberts & Ahmed Albusoda: Designed search protocol; performed data collection; manuscript preparation; statistical analysis; critical revision of the manuscript for important intellectual content. Joint first authors. Adam D Farmer & Qasim Aziz: Pioneered study concept and design, technical support; critical revision of the manuscript for important intellectual content, project supervision. Joint senior authors.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

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SUPPORTING INFORMATION

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