1 Effect of Yoga in the therapy of Irritable Bowel Syndrome: A Systematic Review

- 2 Dania Schumann¹, Dennis Anheyer¹, Romy Lauche^{1, 2}, Gustav Dobos¹, Jost Langhorst¹ and
- 3 Holger Cramer^{1, 2}
- ⁴ Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, Faculty of
- 5 Medicine, University of Duisburg-Essen, Essen, Germany
- ² Australian Research Centre in Complementary and Integrative Medicine (ARCCIM),
- 7 University of Technology Sydney, Sydney, Australia

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10 Abbreviations:

- ANS autonomic nervous system; BSI-18 Brief Symptom Inventory 18; CI confidence
- interval; CSI Child Somatization Inventory; ECG Electrocardiography; EGG surface
- electrogastrography; FACIT Functional Assessment of Chronic Illness Therapy Fatigue
- Subscale; FDI Functional Disability Index; GI gastrointestinal; GIS Global Improvement
- Scale; IBS Irritable bowel syndrome; HADS Hospital Anxiety and Depression Scale; IBS-
- 16 D diarrhea predominant IBS; IBS-GAI IBS Global Assessment of Improvement; IBS-
- 17 QOL Irritable Bowel Syndrome Quality of Life questionnaire; IBS-SSS IBS Symptom
- 18 Severity Scale; MBSR mindfulness-based stress reduction; NRS Numeric Rating Scale;
- 19 PANAS-X The positive and negative affect schedule; PHQ-15 The patient health
- 20 questionnaire-15; PNS parasympathetic nervous system; PSQI The Pittsburgh Sleep
- 21 Quality Index; RCT(s) Randomized controlled trial(s); SF-36 Health-Related Quality of
- 22 Life Short Form 36; SMD Standardized mean differences; STAI state and trait anxiety
- inventory; VSI The visceral sensitivity index; WMF Weekly Monitoring Form;

- 26 Correspondence
- 27 M.Sc. Dania Schumann
- 28 Kliniken Essen-Mitte, Klinik für Naturheilkunde und Integrative Medizin, Knappschafts-
- 29 Krankenhaus
- 30 Am Deimelsberg 34a
- 31 45276 Essen
- 32 Germany
- 33 Phone: +49201 174 25015
- 34 Fax: +49201 174 25000
- 35 Email: d.schumann@kliniken-essen-mitte.de
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- 42 Abstract

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- 43 **Background & Aims:** This review aims to systematically survey the effects of yoga on
- symptoms of irritable bowel syndrome (IBS), pain, quality of life, mood, stress and safety in
- 45 IBS patients.
- 47 **Methods:** MEDLINE/Pubmed, Scopus, the Cochrane Library, CAM-QUEST, CAMbase, and
- 48 IndMED were screened through November 2015. Randomized controlled trials (RCTs)
- 49 comparing yoga to usual care, non-pharmacological or pharmacological interventions were
- analyzed for patients with IBS. Primary outcomes included gastrointestinal symptoms, quality

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of life and pain. Anxiety, mood and safety were defined as secondary outcomes. Risk of bias 51

was assessed according to the Cochrane Collaboration recommendations.

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Results: Six RCTs with a total of 273 patients were included in the qualitative analysis. There

was evidence for a beneficial effect of a yogic intervention over conventional treatment in

IBS, with significantly decreased bowel symptoms, IBS severity and anxiety. Further, there

were significant improvements in quality of life, global improvement and physical

functioning after yoga compared to no treatment. Two RCTs reported safety data stating that

no adverse events occurred. Overall, risk of bias of the included studies was unclear.

Conclusions: The findings of this systematic review suggest that Yoga might be a feasible

and safe adjunctive treatment for people with IBS. Nevertheless no recommendation can be

made regarding yoga as a routine intervention for IBS patients due to major flaws in study

methods. More research is needed with respect to a high quality study design and consensus

in clinical outcome measurements in IBS.

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Keywords: Irritable Bowel Syndrome, IBS, Yoga, Review

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Introduction

Irritable bowel syndrome (IBS) is a condition characterized by the following symptoms: 70

abdominal pain, often in combination with constipation or diarrhea, bloating and changes in

stool appearance. Aggravation of symptoms is frequently reported after meals, which are not

limited to the lower abdominal tract but can also include nausea, belching and pyrosis ^{1, 2}.

Although pathophysiological diagnostics are lacking for most cases, patients suffer from

abdominal pain and comorbidities that have a strong impact on life quality ^{3, 4}.

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- 76 It is the most common functional gastrointestinal (GI) disorder with worldwide prevalence
- rates ranging from 9–23%, it accounts for up to 12% of total visits to primary care providers
- and with up to 70% it is the most common disorder diagnosed by gastroenterologists ^{4, 5}.
- 79 The current diagnosis of IBS is based on Rome-III criteria ^{1, 2}, which states the following
- 80 criteria, that have to be met: recurrent abdominal pain or discomfort associated with two or
- 81 *more* of the following:

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- a) Improvement of discomfort with defecation
- b) Onset associated with a change in frequency of stool
- c) Onset associated with a change in form (appearance) of stool
- d) Change in passage (sensation of incomplete defecation or need of pushing)
- e) Appearance of mucus in stool, often accompanied by bloating

Symptoms have to be present for the last 3 months on at least 3 days/month with a symptom onset of at least 6 months prior to diagnosis. Furthermore, other diseases that might result in such symptoms must be excluded: Chronic inflammatory diseases, neoplasia or infectious diseases. Such organic diseases are often associated by signs of other diseases than IBS include sudden weight loss, blood in stool and fever.

Yoga is a part of the ancient Indian philosophy which dates more than 5000 years back ⁶. Yoga has evolved with a focus on physical practice with a strong connection to the traditional indian medicine system, called Ayurveda ("the science of life") ⁶. Yoga has been adapted as a method in complementary medicine and is practiced especially in terms of prevention and therapy of diseases ⁷. Yoga traditionally consists of body postures (sanskrit: Asanas), breathing exercises (Pranayama) and meditation (Dyana). The goal of practicing yoga asanas

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focuses on strengthening of muscle tissues and nervous system, while reaching a balance of

body and mind 8 .

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Different theories have been developed to explain the origin of irritable bowel syndrome such

as visceral hypersensitivity and psychosocial factors e.g. disturbed stress regulation ^{3, 9} and

autonomic nervous system (ANS) dysfunction appears to be involved in the pathophysiology

of IBS ¹⁰. Psychiatric comorbidities are common as well and need particular consideration ¹¹.

One explanation, as could be demonstrated by an increasing quantity of preclinical literature,

is the finding of bidirectional signaling between the brain and the gut which has led to the

suggestion that both play an equivalent role in the pathophysiology of psychiatric disorders or

in chronic abdominal pain syndromes, such as IBS ¹²⁻¹⁶. It is hypothesized that Yoga practice

corrects underactivity of the parasympathetic nervous system (PNS) induced by stress ¹⁷ and

it has been proven to be effective in the reduction of stress and psychological disorders in

different patient populations ¹⁸⁻²³. These factors play an important role in the onset and

persistence of IBS, suggesting that Yoga may be efficacious in improving IBS symptoms.

Therefore, the purpose of this review was to examine the efficacy and safety of Yoga as a

treatment for patients with IBS.

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Methods

PRISMA guidelines for systematic reviews ²⁴ and the recommendations of the Cochrane

Collaboration ²⁵ were followed.

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Eligibility criteria

Types of studies

Randomized controlled trials (RCTs) and randomized cross-over studies were eligible, only if

they were published as full paper.

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Types of outcome measures

- To be eligible, RCTs had to assess at least one primary outcome:
- 1. Improvement in the severity of symptoms of IBS, measured by patient-rated scales, such as
- the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) ²⁷, or any other validated
- scale.
- 2. Pain or disability measured through means such as a Numeric Rating Scale (NRS).
- 3. Improvement in quality of life or well-being measured by any validated scale such as the
- Health-Related Quality of Life—Short Form-36 (SF-36) ²⁸, the Irritable Bowel Syndrome
- Quality of Life (IBS-QOL) questionnaire ²⁹ or Functional Disability Index (FDI) ³⁰.
- 158 Secondary outcomes included:
- 1. Stress, measured by any validated scale such as the Cohen Perceived Stress Scale (CPSS)
- 160 ³¹.
- 2. Anxiety, Depression or fatigue measured by any validated scale such as hospital anxiety
- and depression scale (HADS) or Fatigue Impact Scale (FIS) ^{32, 33}.
- 3. Safety of the intervention assessed as number of patients with adverse events or side
- 164 effects.

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Search methods

- MEDLINE/Pubmed, Scopus, the Cochrane Library, CAM-QUEST, CAMbase, and IndMED
- were searched from their inception through 2nd November 2015. The literature search was
- 169 constructed around search terms for "yoga", "pranayama", "asana" and search terms for
- 170 "irritable bowel syndrome". For PubMed, the following search strategy was used:
- 171 ("Yoga"Mesh OR "Yoga"Title/Abstract OR "Yogic"Title/Abstract) OR
- 172 "Pranayam*"Title/Abstract) OR "Asana*"Title/Abstract) AND ("irritable bowel
- syndrome"Mesh OR "irritable bowel"Title/Abstract OR "IBS"Title/Abstract). The search
- strategy was adapted for each database as necessary.

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Additionally, reference lists of identified original articles or reviews and the tables of contents of the International Journal of Yoga Therapy, the Journal of Yoga & Physical Therapy, and the International Scientific Yoga Journal SENSE were searched manually. Abstracts identified during literature search were screened by 2 review authors independently. Potentially eligible articles were read in full by 2 review authors to determine whether they met eligibility criteria. Disagreements were discussed with a third review author until consensus was reached. If necessary, additional information was obtained from the study

authors.

Data extraction and management

Data on patients (e.g. age, diagnosis), methods (e.g. randomization, allocation concealment), interventions (e.g. yoga type, frequency, and duration), control interventions (e.g. type, frequency, duration), co-interventions, outcomes (e.g. outcome measures, assessment time points) and results were extracted independently by two authors using an a-priori developed data extraction form. Discrepancies were discussed with a third review author until consensus was reached. If necessary, the study authors were contacted for additional information.

Risk of bias in individual studies

Two authors independently assessed risk of bias using the risk of bias tool proposed by the Cochrane Collaboration ²⁵. This tool assesses risk of bias on the following domains: selection bias, performance bias, attrition bias, reporting bias, detection bias and other bias. Risk of bias was assessed for each criterion as 1) low risk of bias, 2) unclear, 3) high risk of bias. Discrepancies were discussed with a third review author until consensus was reached.

Results

Literature search

The literature search retrieved 93 records, 1 additional record was retrieved through other sources. 63 non-duplicate records were screened and 57 records were excluded because they did not fulfill RCT design and/or yoga was not an intervention. Six full-text articles (RCTs) with a total of 273 patients were included in qualitative analysis 34-39.

Study characteristics

207 Characteristics of the sample, interventions, outcome assessment and results are shown in 208 Table 1.

Setting and participant characteristics

Of the 6 RCTs that were included, 2 originated from India ³⁷, 4 from North America (3 from USA ^{34, 35, 38} and 1 from Canada ³⁶). Patients were recruited from gastroenterology clinics ^{34-36, 38}, psychiatry offices ³⁵ and/or internet announcements, flyers and primary care physicians ^{34, 36, 38}. Patients in 1 RCT were diagnosed with IBS according to Rome-I criteria ³⁶, in 1 RCT according to Rome-II criteria ³⁹, and patients in 3 RCTs were diagnosed according to Rome-III criteria ^{34, 35, 38} while 1 of those RCT further included patients with a diagnosis of having recurrent abdominal pain ³⁴. The remaining RCT relied on clinical and laboratory diagnosis only ³⁷. Symptoms had to be present for more than 3 months in 1 RCT ³⁹ and for more than 6 months in the others. Patients in all RCTs were allowed to continue symptomatic medical treatment. Patients' mean age ranged from 14.2 years to 44.1 years with a median age of 32.5 years. Between 0.0% and 89.0% (median: 71.4%) of patients in each study were female.

Intervention characteristics

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Yoga was based on the yoga module developed by research associates of Vivekananda Yoga 224 Research Foundation in 1 RCT ³⁵, on the principles of the Hatha Yoga Pradipika in 1 RCT ³⁷ 225 and 1 RCT did not follow a certain school, but instead selected the yoga exercises based on a 226 review of different yogic literature ³⁹. In 1 RCT Hatha and Iyengar yoga tradition were 227 merged. The remaining 2 RCTs based their yoga intervention on Iyengar yoga ^{34, 38}. All yoga 228 programs included voga postures. Breath control was instructed in 3 RCTs 35, 36, 39, and 229 meditation was an additional part of 1 RCT ³⁵. Program length and intensity varied (Table 1), 230 and asanas were taught by certified yoga teachers in 4 of the studies 34-36, 38, while the other 2 231 gave no further information about the instructors ^{37, 39}. Three RCTs compared yoga to no 232 treatment ³⁴⁻³⁶. 2 of those further divided the yoga intervention group as followed: Kavuri et 233 al. allowed patients in one part of the yoga intervention group to continue with their 234 medication as needed (combined group) and the other group was advised to restrict 235 medication to at most thrice a week (yoga group). Kuttner et al. divided the yoga intervention 236 group according to age specified as adolescents (14-17 years) and young adults (18-26 237 years). One study compared yoga to pharmacological intervention ³⁹. One 3-arm RCT 238 compared yoga to pharmacological care and placebo ³⁷ while one RCT examined yoga versus 239 a walking program ³⁸. The exercise intervention was matched to the yoga intervention in 240 terms of frequency, length, and duration and was led by physical trainers. 241 242 Methods for assessing outcome measures symptoms of IBS are shown in Table 1. For gastrointestinal symptoms a checklist by Blanchard and Scharff ³⁶, Child Somatization 243 Inventory, Global Improvement Scale and Bowel Symptom Score developed by Talley ³⁹, 244 NRS ^{34, 38} Scoring system ³⁷, IBS-SSS ³⁵, and global assessment of improvement (IBS-GAI) ³⁵ 245 were used. Shahabi et al. further checked physical symptoms through the patient health 246 questionaire PHQ-15 ³⁸. Quality of life was assessed in 2 studies using the health related 247 quality of life questionnaire SF-36 ³⁴ and the IBS-QOL-Questionnaire ³⁵. Pain was measured 248

by 3 RCTs using NRS ^{34, 36, 38}. Anxiety was assessed in 5 RCTs using the Revised Child Manifest Anxiety Scale ³⁶, State and Trait Anxiety Inventory STAI ^{38, 39}, or Hospital Anxiety and Depression Scale HADS ³⁵. Depression was assessed through Children's Depression Inventory Short Form ³⁶, positive and negative affect schedule PANAS-X ³⁸ or a subscale of HADS ³⁵. Evans et al. measured depression and stress with the BSI-18, and fatigue through FACIT ³⁴. While all RCTs reported short-term to medium-term effects (up to 6 months post-

intervention), no RCT reported long-term effects.

Risk of bias in individual studies

Risk of bias in individual studies is shown in figure 2. Three studies reported adequate random sequence generation ³⁴⁻³⁶, none of the studies however reported adequate allocation concealment or blinding of participants and personnel. Blinding of outcome assessment was sufficient in one study ³⁵. Four RCTs were free of suspected selective reporting ³⁵⁻³⁹, but one RCT was of high risk ³⁴. High risk had also to be considered concerning performance bias ³⁴, ³⁸, incomplete outcome data ^{34, 38}, and for other bias ^{35, 38} for two studies respectively. Three other RCTs however received low risk rating regarding attrition bias ^{36, 37, 39}.

Outcomes

Yoga vs. no treatment

Kavuri et al. reported significant improvements in IBS symptom severity and IBS-related quality of life in Yoga and Combination groups when compared to Wait-list Control group. Further, improvement in anxiety and depression scores, IBS Global Assessment of Improvement and autonomic functions were observed which correlated with a reduction in the amount of medicine and supplement use (psyllium, fiber drinks, herbal teas and probiotics) in the Yoga and Combination groups.

According to Kuttner et al. adolescents who received the yoga intervention tended to report lower levels of functional disability and anxiety than adolescents in the control group ³⁶. There were no group differences in depression or overall gastrointestinal symptoms. Pain was assessed but post-intervention results were not displayed due to group differences in baseline levels between control and yoga. Evans et al. reported adolescents assigned to yoga to state significantly improved physical functioning relative to controls, whereas young adults assigned to yoga reported significantly improved IBS symptoms, global improvement, disability, psychological distress, sleep quality, and fatigue ³⁴. For young adults, global improvement, worst pain, constipation, and nausea were significantly improved post yoga, but only global improvement, worst pain, and nausea maintained at the 2-month follow-up. According to IMMPACT guidelines, approximately one-third of participants in the yoga group reported clinically significant improvement in IBS symptoms. Evans et al. found no significant group differences in pain on the NRS. They reported that 44% of adolescents experienced a reduction of at least 1 point on the NRS, and 46% of young adults experienced a reduction of at least 1.74 points on the NRS for abdominal pain, which is a minimally clinically significant difference (MCSD), but no group differences were calculated for MCSD. No evidence was found for short-term effects of yoga compared to no treatment on anxiety. Evans et al. also found no significant evidence for short-term effects on fatigue ³⁴.

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Yoga vs. exercise

Shahabi et al. compared a walking program to a yoga intervention ³⁸. There were no significant group differences between yoga and walking groups. Exploratory analysis of within group treatment effects showed significant differences in abdominal pain, overall GI symptoms, visceral sensitivity and severity of somatic symptoms for yoga. Significant differences in overall GI symptoms, negative affect and state anxiety were observed in the

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walking group. When comparing yoga to exercise, there was a significant group by time interaction for intermediate-term effects. Specifically, mean of overall GI symptoms for yoga

rose from post-treatment to 6-month follow-up, whereas for walking, mean of overall GI

symptoms continued to drop from post-treatment to 6 months.

Yoga vs. medication

Two RCTs compared Yoga to pharmacological intervention ^{37, 39}. Overall, Taneja et al. found no significant difference between control group (loperamide 2-6 mg/day) and yoga group with respect to bowel symptom scores, state anxiety scores and gastric motility. Similarly, no group differences emerged for other measures of autonomic reactivity ³⁹. In a 3-arm study Madhu et al. also found no difference between groups comparing yoga versus medical treatment including 2-3 tablespoons psyllium husk, 1 tablet propantheline (15 mg) thrice a day and 1 tablet diazepam (5 mg) twice a day. After 3 months of treatment 3 of 5 patients on medical therapy, 3 of 5 on yoga showed >50% improvement in their symptoms ³⁷.

Yoga vs. placebo

Madhu et al. also compared yoga versus placebo treatment, but found no differences in between groups, as 3 of 5 on yoga and 4 of 5 on placebo showed >50% improvement in their symptoms ³⁷.

Safety. Two studies reported adverse events ^{34, 35}. Evans et al. reported a participant slipping while in headstand and hitting his knee, but the event was self-limited and did not stop the participant from practicing yoga ³⁴. Kavuri et al. recorded three patients in the yoga group with temporarily aggravated lower back pain ³⁵. A further incident of a cardiac arrest resulted

in death of one participant in the control group. Apparently other self-limited adverse events were mentioned, however group allocation was not mentioned for these participants ³⁵.

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Discussion

Summary of evidence and implications for clinical practice

In this systematic review of six randomized trials on yoga for irritable bowel syndrome, evidence for beneficial effects of yoga on gastrointestinal symptoms, quality of life and anxiety was found when compared to no treatment. Individual studies reported considerable effects on IBS related symptoms in favor of yoga compared to control group; and yoga also seems to be equally effective as a walking program in improving patient-reported outcomes. Nevertheless some limitations need to be taken into account. Applicability seems to be an important factor concerning regular home practice. In the case of Iyengar yoga, the help of props is often required and the emphasis lies on correct alignment which usually requires supervision. Further less focus is put on relaxation during classes. In contrast to yoga, mean of overall GI symptoms in the walking group continued to drop from post-treatment to 6 months, which can be related to the fact that the percentage of participants who reported regular home practice at 6 months was significantly greater for those in walking (75%) than in yoga (25%). It should be considered that yoga has occasionally been associated with serious adverse events in case studies ⁴⁰. However, no serious adverse events were observed during yoga practice in this review which is in line with previous cross-sectional studies 20, 41 and systematic reviews of yoga interventions in other patient populations that found no evidence for serious yoga-associated adverse events ^{18, 19, 21}. Thus, yoga seems to be a promising and safe treatment for people with IBS supporting recent evidence in multiple studies, suggesting that exercise has a positive effect on IBS associated symptoms ^{42, 43}. Nevertheless, no

recommendations can be made to practice yoga for the relief of IBS symptoms based on this review due to the wide methodological heterogeneity of the studies and mostly unclear risk of bias of the included studies but its practice needs not to be discouraged in this patient population, especially when they feel that it benefits their health, quality of life or IBS-related comorbidities.

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Agreements with prior systematic reviews

To best of our knowledge this is the first systematic review specifically investigating yoga practice in IBS. One descriptive review on yoga for IBS was available which concluded that the essential components of a yoga module for IBS should include postures, breathing, and meditation and should be designed to be easily practiced by most patients, with least complications ⁴⁴. This review included 2 RCTs that were also included in our review ^{36, 39} and a trial which observed that any moderate physical activity three times a week ranging from 20 to 60 minutes, improved symptom severity of IBS when compared to non-active controls ⁴³. A long term follow-up also showed improvement in disease specific quality of life, fatigue, depression and anxiety 42. Another systematic review reviewing eight studies on the effectiveness of yoga for the treatment of anxiety and anxiety disorders reported positive results ⁴⁵. Nevertheless, due to the many methodological inadequacies, diversity of conditions treated and poor quality of most of the studies, no conclusion could be drawn for yoga to be effective in treating anxiety or anxiety disorders in general ⁴⁵. One multimodality approach that also comprises of yoga elements, meditation techniques and breathing exercises is mindfulness-based stress reduction (MBSR). A systematic review investigating whether MBSR is effective in improving physical health outcomes for long-term physical conditions included fifteen studies, finding some preliminary evidence that MBSR might be effective in improving IBS ²⁶. Similar, a systematic review on relaxation therapy for IBS patients showed

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that IBS symptoms decreased significantly, while symptom severity and anxiety decreased due to relaxation therapies without being statistically significant. However, these results need to be interpreted with caution due to the small number of studies examined and associated methodological problems ⁴¹.

External and internal validity

Mainly patients from Asia and people of mixed ethnicities from North America were included. Given that there is no convincing evidence of a difference between western and developing countries in the etiology of IBS ⁴⁶, these findings might not be limited to geographical regions. Since female patients represented the majority of participants, the results might not be fully applicable to male patients. It has to be added though, that eastern and western countries show a female predominance or no gender difference in the prevalence of IBS ⁴⁶. Two studies did not or only partially use Rome criteria as a standard for eligibility ^{34,37}. This further limits the applicability of the results.

Overall, risk of bias of the included studies was unclear. Only one study reported adequate blinding of outcome assessment ³⁵. High risk was found in one study for performance bias ³⁸ and for reporting bias ³⁴, in two studies for attrition bias ^{34,38} and other bias ^{35,38}, respectively. It is noted that the blinding of participants and personnel form an inevitable issue in RCTs investigating yoga interventions. Nevertheless, the observed studies lacked sufficient description of methods such as adequate random sequence generation and allocation concealment. Moreover selective reporting and high drop-out rates represented an issue.

Strengths and weaknesses

Strengths of this review include the comprehensive literature search and the assessment of applicability of the results ⁴⁷. The primary limitation of this review is the deficiency of

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eligible studies, resulting in a relatively limited overall sample size. The applicability of the findings was limited. As only one study reported longer-term effects ³⁸, no conclusions can be drawn on the long-term effects. Publication bias could not be assessed due to the low number of included studies. No unpublished studies or studies published in 'grey literature' were included since the usefulness of including unpublished trials is still under debate as unpublished studies tend to lack peer-review; also investigators are often unwilling to provide unfavorable results ²⁵.

Modes of action

Psychological factors seem to play an important role in the etiology of IBS, as a strong association of psychiatric disorders in 94% of IBS patients can be found ⁴⁸. Headache, fibromyalgia, fatigue and depression were commonly found in individuals with IBS ⁴⁹. Evidence supports the role of stress in IBS patients, particularly in altering brain-gut interactions ⁵⁰. It was hypothesized that yoga addresses the brain-gut axis in the management of IBS with fewer side effects than conventional treatment ⁴⁴.

Implications for further research

Given that the main drawbacks of the included studies concern study methodology and authors of prospect research should not only ensure rigorous methodology but also improve the reporting of yoga trials and follow commonly accepted reporting guidelines (e.g. CONSORT) ^{51, 52}. The choice of outcome measures, future studies should be planned according to methodological recommendations for high quality clinical trials for IBS based on consensus. The Adequate Relief question should be a measure of choice when assessing global symptomatology as an outcome in IBS studies ⁵³. For a more detailed IBS symptom assessment, the IBS Severity Scoring System is preferable and the IBS Quality of Life

measurement scale can be used to establish changes in health-related quality of life 53. Abdominal pain was believed to be the hallmark feature of IBS though newer research suggests that bloating is the predominant complaint of patients ^{54, 55}. Among the pain dimensions, intensity, frequency, constancy and predictability were strongly and independently associated with illness severity while duration, speed of onset and relationship to bowel movements had weaker associations. Thus IBS trials should measure pain dimensions, including intensity, constancy, frequency and predictability to improve upon the customary use of measuring pain as a unidimensional symptom in IBS. Further considerations implied the use of the IBS global assessment of improvement scale (IBS-GAI) and gastrointestinal symptom rating scale ⁵⁴. Further, insufficient power of studies has to be regarded as a limiting factor, comprising of small sample sizes, different patient populations and limited external validity. Most importantly, safety of the intervention was insufficiently reported. Specifically, only two studies explicitly assessed adverse events, although one of them described so-called side effects, i.e. those events with a plausible causality to the intervention, and labelled them adverse events. Future studies should ensure rigorous reporting of adverse events, and the correct use of terminology. Since stress and IBS symptoms seem to be improved by meditation, breathing exercises and yoga 56-58, a holistic approach including breathing practices, relaxation modules and meditation should be considered in designing further studies for patients suffering from an increased gastrointestinal response to stress. At this point, more research is needed to draw definite conclusions. So far, the recent global guidelines of the World Gastroenterology Organization on IBS consider sufficient physical activity and relaxation techniques to be appropriate non-pharmacological approaches ⁵⁹.

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Figure Legends

- 450 Figure 1: Flowchart of the results obtained from literature search
- 451 Figure 2: Risk of bias for each criterion for each included study (top) and risk of bias for each
- criterion presented as percentages across all included studies (bottom)

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Table Legends

455 Table 1: Characteristics of the included studies

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