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REVIEW ARTICLE

Prevalence and predictors of small intestinal bacterial overgrowth in systemic sclerosis: a systematic review and meta-analysis

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Abstract

The reported prevalence of small intestinal bacterial overgrowth (SIBO) among patients with systemic sclerosis (SSc) is highly variable. We conducted this systematic review and meta-analysis to estimate the prevalence and identify predictors of SIBO in SSc by summarizing all of the available data. A comprehensive literature search of the PubMed, Cochrane Library, and EMBASE databases from inception to July 2020 was conducted for studies correlating SIBO with SSc. Studies were screened, and relevant data were extracted and analyzed. The pooled prevalence of SIBO among SSc patients and the odds ratio (OR) of SIBO among SSc patients compared with healthy controls were calculated. Furthermore, predictors of SIBO in SSc were evaluated. Fourteen studies containing 700 SSc patients and 217 healthy controls met the inclusion criteria. The pooled prevalence of SIBO in SSc was 34% (95% CI 27–42%). The OR of SIBO in SSc patients was 12.51 (95% CI 6.51–24.03) compared with the healthy controls. Subgroup analyses showed that the prevalence of SIBO in SSc was higher in studies using the lactulose hydrogen breath test (LHBT) for diagnosis (56%, 95% CI 46–67%) compared with those that used the glucose hydrogen breath test (GHBT) (27%, 95%CI 20–35%) and a jejunal aspirated culture (JAC) (35%, 95%CI 25–51%). The prevalence of SIBO in SSc was higher in studies conducted in Western countries (38%, 95% CI 31–47%) than those conducted in Asian countries (15%, 95%CI 10–23%), and the prevalence of SIBO in the SSc population defined by ACR-EULAR 2013 (50%, 95% CI 0.21–0.79) was higher than the prevalence defined by ACR 1980 (30%, 95% CI 0.17–0.42) or other criteria (32%, 95% CI 0.16–0.48) Moreover, the risk of diarrhea was higher in SSc patients with SIBO than those without SIBO (OR 8.82, 95% CI 4.09–19, $P < 0.00001$); gender, SSc subset, digital ulcer, and pulmonary fibrosis do not seem to be associated with SIBO in SSc. Antibiotic therapy seems to be effective with SIBO in SSc patients. Approximately one-third of SSc patients tested positive for SIBO with a significantly increased risk over the controls. The prevalence of SIBO in SSc varied according to the SIBO diagnostic test performed, geographic area, and SSc diagnostic criteria. The presence of diarrhea may be a predictor of SIBO in SSc. Antibiotic treatment can lead to eradication of SIBO and gastrointestinal symptomatic improvement in SSc patients.

Key Points

- *SIBO was detected in SSc patients in many studies, with a pooled prevalence of 34%.*
- *The prevalence of SIBO in SSc varied according to the SIBO diagnostic test performed, geographic area, and SSc diagnostic criteria.*
- *The risk of SIBO in SSc was increased by nearly thirteenfold compared to the healthy controls.*
- *Diarrhea, but not gender, SSc subset, digital ulcer and pulmonary fibrosis, was associated with SIBO in SSc patients.*
- *For SSc patients with SIBO, antibiotic treatment can lead to eradication of SIBO and gastrointestinal symptomatic improvement.*

Keywords Small intestinal bacterial overgrowth · Systemic sclerosis · Systematic review · Meta-analysis

Xin Feng and Xiao-Qing Li contributed to the work equally and regarded as co-first authors.

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Introduction

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease characterized by fibrosis of the skin and internal organs, vasculopathy, and the presence of specific autoantibodies [1, 2]. Its prevalence varies from

38 to 341 per million people, and it causes significant disability and mortality [3]. SSc occurs more frequently in women, and it generally has two subsets: limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc). SSc involves multiple organ systems including the dermatologic, gastrointestinal (GI), pulmonary, cardiac, renal, and musculoskeletal systems [1, 3, 4]. It is reported that GI involvement affects up to 90% of SSc patients which is second only to skin in causing clinically discernible fibrosis in SSc [5, 6]. The pathogenesis of intestinal involvement of SSc includes the fibrosis of the enteric connective tissue, vascular damage, smooth muscle cell inflammation and atrophy, and myenteric neural dysfunction due to collagen deposition or autoantibodies [5–8]. Complications of GI involvement in SSc, including gastroesophageal reflux disease, intestinal pseudo-obstruction, malnutrition, diarrhea, constipation, and small intestinal bacterial overgrowth (SIBO), severely impair the SSc patient's quality of life and affects their prognosis [6, 7].

SIBO is defined as an increase in the number ($\geq 10^5$ bacteria) and/or abnormal type of bacteria in the small intestinal tract [9]. The gold standard for diagnosing SIBO remains a microbial investigation of a jejunal aspirated culture (JAC). Non-invasive tests, such as the lactulose hydrogen breath test (LHBT) and the glucose hydrogen breath test (GHBT) are also used for the diagnosis of SIBO, with a sensitivity and specificity of 52.4%/62.5% and 85.7%/81.8% respectively [10]. Interestingly, there seems to be a strong association between SSc and SIBO, and a previous study reported that the prevalence of SIBO in SSc patients ranged from 18 to 55% [11]. Hypomotility of the gastrointestinal tract, likely due to neuronal degradation and collagen deposition, may result in stasis of the small intestine content and allow upstream small intestinal bacterial overgrowth in SSc [5, 6]. Subsequently, SIBO can aggravate SSc patients' GI symptoms, including diarrhea, abdominal pain, flatulence, abdominal distension, and malabsorption of nutrients [5, 11]. Antibiotic treatments, such as ciprofloxacin, rifaximin, norfloxacin, and metronidazole, seem to be effective for SIBO in SSc. Limited data indicate that the eradication rate of SIBO was 100% in SSc patients treated with ciprofloxacin, 73.3% in those receiving rifaximin, 52.4% in those treated with intermittent rotating norfloxacin and metronidazole [12].

The goal of this comprehensive systematic review and meta-analysis was as follows: (a) determine the pooled prevalence rates of SIBO among individuals with SSc, (b) determine the pooled odds ratio (OR) of SIBO among SSc patients compared with the controls, and (c) identify potential correlates of SIBO in SSc patients that might be used to predict the presence of SIBO.

Methods

Search strategy

A standard protocol, based on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations, was conducted for study inclusion, data extraction, and data analysis [13]. A computerized literature search of the PubMed, Cochrane Library, and EMBASE databases was performed from inception to July 2020 for all relevant articles. The search terms were as follows: (scleroderma OR systemic sclerosis) AND (small intestinal bacterial overgrowth OR small intestine bacterial overgrowth OR SIBO OR small bowel bacterial overgrowth OR SBBO OR breath test OR enteric bacterial overgrowth OR lactulose hydrogen OR glucose hydrogen OR jejunal aspirate). There were no language restrictions. A hand search was also performed on the reference lists of selected articles to help identify additional potentially relevant studies.

Study selection

Studies were included if they met the following criteria: (a) cohort study or case-control study or cross-sectional study; (b) age > 18 years; (c) studies recruiting subjects meeting the diagnostic criteria for SSc (such as ACR 1980 or ACR-EULAR 2013); (d) valid methods assessing SIBO were any of the following tests or their combinations: GHBT, LHBT, or JAC; (e) studies were in a full-text format. We also excluded the following: (a) case reports, review articles, and letters; (b) animals research; (c) duplicated data. We did not determine the cut-off values for the positive tests as long as the criteria were defined prospectively. When a study used more than one type of test for the diagnosis of SIBO, we extracted the data separately for each of the methods used.

Data extraction and quality assessment

The data were independently extracted by two authors (X Feng and XQ Li) using a structured information collection form. The following data were extracted: first author, year of publication, study design, country of origin, diagnostic tests of SIBO, criteria used to define presence of SIBO, percentage of females, number of patients with dcSSc, and prevalence of SIBO in SSc patients. Any disagreement between the two authors was resolved by a third author (Jiang Z). The quality of a cohort study or case-control study was evaluated by the Newcastle-Ottawa scale in three domains as follows: the selection of subjects, the comparability of the groups, and the determination of the outcome of interest [14]. The quality of a cross-sectional study was assessed by the modified Newcastle-Ottawa scale [15]. Studies with a score ≥ 6 were

considered high quality studies, whereas those with a score < 6 were considered poor quality studies.

Statistical analysis

The pooled prevalence of SIBO in all individuals with SSc was calculated. In addition, for cohort study or case-control studies, data were pooled for both groups, the prevalence of SIBO was compared between the two groups to calculate an odds ratio (OR) and a 95% confidence interval (CI). *P* values less than 0.05 were considered statistically significant. We assessed for heterogeneity using I^2 statistics. Heterogeneity was divided into four categories (very low, low, moderate, and high), with the corresponding I^2 of $I^2 < 25\%$, $25\% < I^2 < 50\%$, $50\% < I^2 < 75\%$, and $I^2 > 75\%$, respectively. The fixed effects model was used in the absence of heterogeneity ($I^2 < 50\%$); otherwise ($I^2 > 50\%$), the random effects model was used. Furthermore, the Egger test was performed to assess any potential publication bias. $P > 0.05$ in the Egger test was considered to indicate no publication bias. Subgroup analysis was performed to analyze the sources of heterogeneity if there was moderate or high heterogeneity. All statistical analyses were performed using R 3.5.3 and RevMan 5.3.

Results

The described search strategy identified 565 potentially relevant studies (313 from PubMed, 233 from EMBASE, and 15 from Cochrane Library). Four references were added after hand searching the reference lists of all of the selected studies. After the exclusion of 109 duplicate articles, the titles and abstracts of 456 unique articles were reviewed. Subsequently, 417 studies were excluded as they did not meet our inclusion criteria. This resulted in 39 studies for a full-text review. Seventeen were excluded after the full-length review since they did not report the outcomes of interest, while seven articles were excluded because they were not in a full-text format. One of the studies copied data from another and was excluded. Finally, 14 studies [16–29] (8 cohort studies and 6 cross-sectional studies) containing 917 subjects (700 SSc patients and 217 controls) remained for qualitative analysis and quantitative synthesis (Fig. 1). Since SIBO was assessed with two different diagnostic tests with different results in two studies [26, 29], we considered these studies as four different studies to calculate the prevalence of SIBO. The characteristics and quality appraisal of the included articles are summarized in Table 1. Twelve of the 14 articles [16–26, 28] were high quality, and two [27, 29] were considered low quality.

Prevalence of SIBO in patients with SSc

All 14 studies [16–29] reported the prevalence of SIBO in patients suffering from SSc. Overall, the prevalence of SIBO in SSc ranged from 13 to 65%, with a pooled prevalence of 34% (95% CI 27–42%) (Fig. 2). We used a random effects model, as the heterogeneity was high ($I^2 = 79\%$). The results of the Egger test indicated that there was publication bias ($P = 0.00056$) (Fig. 3). In order to explore the sources of heterogeneity between the studies, we performed a subgroup analysis based on the SIBO diagnostic tests. The pooled prevalence of SIBO in three studies [16, 21, 25] using LBT was 56% (95% CI 46%–67%, $I^2 = 63\%$) compared with 27% (95% CI 20–35%, $I^2 = 62\%$) in the ten studies [17–20, 22–24, 26, 28, 29] using GBT and 35% (95% CI 25–51%, $I^2 = 0$) in the three studies [26, 27, 29] using JAC (Fig. 4). When subgrouping based on the geographic areas, the prevalence of SIBO was 38% (95% CI 31–47%, $I^2 = 71\%$) among the patients from Western countries [16, 19–29], and 15% (95% CI 10–23%, $I^2 = 0$) among the patients from Asian countries [17, 18] (Fig. 5). Finally, in subgroup analyses by SSc diagnostic criteria, the prevalence of SIBO in the SSc population defined by ACR-EULAR 2013 (50%, 95% CI 0.21–0.79) was higher than the prevalence defined by ACR 1980 (30%, 95% CI 0.17–0.42) other criteria (32%, 95% CI 0.16–0.48) (Fig. 6).

Prevalence of SIBO in SSc patients when compared with controls

Six case-control studies [21, 22, 25–27, 29] reported the prevalence of SIBO in 258 SSc patients compared with 217 healthy controls. The risk of SIBO among individuals with SSc was higher than the healthy controls, with the pooled odds ratio (OR) of 12.51 (95% CI 6.51–24.03, $P < 0.00001$) (Fig. 7). Using the fixed effects model, there was no heterogeneity between the studies ($I^2 = 0$, $P = 0.68$). However, we could not perform an Egger test because relatively few studies were included.

Predictors of SIBO in patients with SSc

Six studies [17, 24–27, 29] including 249 SSc patients examined diarrhea as a predictor of SIBO in SSc. Overall, the SSc patients with SIBO were more likely to suffer from diarrhea than those without SIBO, with the pooled OR of 8.82 (95% CI 4.09–19, $P < 0.00001$) (Fig. 8a). There was very low heterogeneity detected between the studies ($I^2 = 9\%$, $P = 0.36$). Furthermore, three studies [17, 20, 24] assessed the link between females and SIBO in SSc; the pooled OR of females within the SSc individuals with SIBO compared to those without SIBO was 0.96, and the difference did not reach statistical

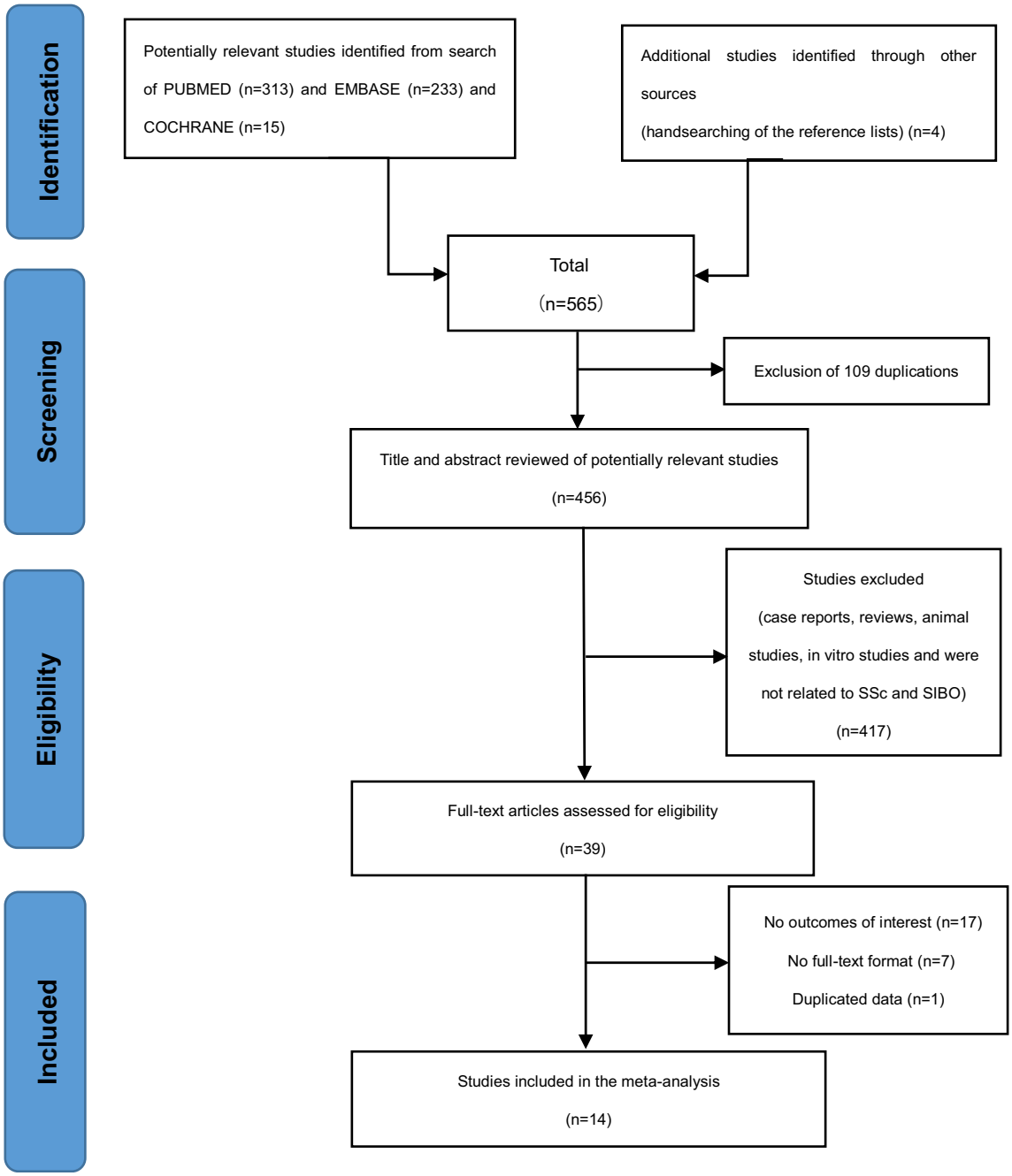


Fig. 1 Flow chart of the selection process of articles

significance (95% CI 0.42–2.17; p = 0.92) (Fig. 8b). Three studies [17, 20, 24] reported the association between the SSc subset and SIBO in SSc. The percentage of dcSSc in SIBO-positive patients was not significantly different than in SIBO-negative patients, with the pooled OR of 0.67 (95% CI 0.33–1.39, p = 0.29) (Fig. 8c). Similarly, there were no significant differences between SSc with and without SIBO in digital ulcer [17, 20, 24] and pulmonary fibrosis [17, 20, 24], with an OR of 1.57 (95% CI 0.54–4.53, p = 0.41) and 0.62 (95% CI 0.30–1.26, p = 0.19), respectively. (Fig. 8d–e)

Discussion

Although this subject has been previously presented in a systematic review by Polkowska-Pruszyńska et al. [11], in this study we performed the first meta-analysis to provide the latest evidence on the association between SIBO and SSc by summarizing data from seven additional studies. The pooled prevalence of SIBO in SSc was 34%. The SIBO prevalence of SSc patients seems to depend on the type of SIBO diagnostic test used, with higher prevalence with LHBT (56%) than GHBT (27%) and JAC (35%), and depends on the geographic

Table 1 Main characteristics of the studies included in this meta-analysis

Study	Country	Study design	SIBO diagnostic test	Prevalence of SIBO in SSc patients	SIBO diagnostic criteria	SSc diagnostic criteria	Percentage of female	Number of patients with dcSSc	Quality assessment
García-Collinot et al [16], 2020	Mexico	Cross-sectional	LBT	48/74 (64.9%)	Hydrogen peak 20 ppm above baseline prior to 90 min, or a double peak was considered positive for bacterial overgrowth in the small bowel	ACR-EULAR 2013 [30]	Overall 70/74 (94.6%)	Overall 32/74 (43.2%)	Selection: 4 Comparability: 2 Outcome: 2
Sawadpanich et al [17], 2019	Thailand	Cross-sectional	GBT	12/89 (13.5%)	At least one of the following criteria: (1) H2 and/or CH4 increase > 20 ppm above baseline; (2) H2 and/or CH4 increase > 10 ppm on 2 consecutive measurements within the first 2 h; (3) H2 and/or CH4 increase > 10 ppm between minimal and maximal values	ACR 1980 [31]	SIBO: 9/12 (75%) Non-SIBO:50/77 (64.9%)	Overall 65/89 (73%) SIBO: 9/12 (75%) Non-SIBO:56/77 (72.7%)	Selection: 4 Comparability: 2 Outcome: 3
Adarsh et al [18], 2017	India	Cross-sectional	GBT	7/37 (18.5%)	A rise ≥ 12 ppm over the fasting value in H2 and/or CH4 concentration in 2 consecutive readings	Literature criteria [32]	Overall 46/50 (91.7%)	Overall 16/50 (32%)	Selection: 4 Comparability: 0 Outcome: 3
Marie et al [19], 2015	France	Cross-sectional	GBT	44/125 (35.2%)	At least one of the following criteria: (1) H2 and/or CH4 increase > 20 ppm above basal value; (2) H2 and/or CH4 increase > 10 ppm on 2 consecutive measurements within the 2 first hours; (3) H2 and/or CH4 increase > 10 ppm between minimal and maximal values	ACR-EULAR 2013 [30]	Overall 99/125 (79.2%)	Overall 43 (34.4%)	Selection: 4 Comparability: 2 Outcome: 3
Tauber et al [20], 2014	France	Cross-sectional	GBT	14/37 (38%)	H2 and/or CH4 increase > 20 ppm in 2 consecutive measurements or H2 and/or CH4 increase > 12 ppm in 3 consecutive measurements	Not stated	Overall 29/37 (78.4%) SIBO: 10/14 (71.4%) Non-SIBO: 19/23 (82.6%)	Overall 14/37 (37.8%). SIBO: 5/14 (35.7%) Non-SIBO: 9/23 (39.1%)	Selection: 4 Comparability: 2 Outcome: 3
Savarino et al [21], 2013	Italy	Cohort study	LBT	Cases: 47/99 (46%) Controls: 3/60 (5%)	H2 and/or CH4 excretion increase > 10 ppm compared with baseline in three consecutive air samples	Literature criteria [32, 33]	Cases: 89/99 (89.9%) Controls: 50/60 (83.3%)	Cases: 31/99 (31.3%) Controls: none	Selection: 3 Comparability: 2 Outcome: 1
Gemignani et al [22], 2013	Italy	Cohort study	GBT	Cases: 9/50 (18%) Controls: 3/60 (5%)	H2 concentration increase at least 12 ppm from the basal value	Literature criteria [34]	Cases: 43/50 (86%) Controls: 48/60 (80%)	Cases: 18/50(36%) Controls: none	Selection: 4 Comparability: 2 Outcome: 3
Fynne et al [23], 2011	Denmark	Cohort study	GBT	Cases: 3/15 (21%) Controls: not stated	A rise of more than 10 ppm above baseline	Literature criteria [35]	Cases:13/15 (86.7%) Controls: 12/17 (70.6%)	Cases: 15/15 (100%) Controls: none	Selection: 3 Comparability: 2 Outcome: 1

Table 1 (continued)

Study	Country	Study design	SIBO diagnostic test	Prevalence of SIBO in SSc patients	SIBO diagnostic criteria	SSc diagnostic criteria	Percentage of female	Number of patients with dcSSc	Quality assessment
Marie et al [24], 2009	France	Cross-sectional	GBT	22/51 (43.1%)	At least one of the following criteria: (1) H2 and/or CH4 increase > 20 ppm above basal value; (2) H2 and/or CH4 increase > 10 ppm on 2 consecutive measurements within the first 2 h; (3) H2 and/or CH4 increase > 10 ppm between minimal and maximal values	ACR 1980 [31]	Overall: 41/51 (80.4%) SIBO: 18/22 (81.8%) Non-SIBO: 23/29 (79.3%)	Overall: 25/51 (49%) SIBO: 8/22 (36.4%) Non-SIBO: 17/29 (58.6%)	Selection: 3 Comparability: 2 Outcome: 3
Parodi et al [25], 2008	Italy	Cohort study	LBT	Cases: 30/55 (54.5%) Controls: 4/60(6.7%)	H2/CH4 excretion increase > 10 ppm compared to the basal value in 2 consecutive measurements	Literature criteria [32, 33, 36, 37]	Cases: 50/55 (90.9%) Controls: 48/60 (80%)	Cases: 18/55 (32.7%) Controls: none	Selection: 3 Comparability: 2 Outcome: 1
Kaye et al [26], 1995	UK	Cohort study	JAC and GBT	JAC: cases: 8/24 (33%) Controls: 0 (0%) GBT: cases: 7/21 (33%) Controls: not stated	JAC: (> 10^5 colony forming units per ml (cfu/ml)). Or GBT: (> 20 ppm increase in hydrogen breath from the baseline measurement)	ACR 1980 [31]	Cases: 16/24 (66.7%) Controls: 5/9 (55.6%)	Cases: 6/24 (25%) Controls: none	Selection: 3 Comparability: 2 Outcome: 1
Kaye et al [27], 1994	UK	Cohort study	JAC	Cases: 4/10 (40%) controls: 0 (0%)	> 10^5 colony forming units per ml (cfu/ml)	ACR 1980 [31]	Cases: 8/10 (80%) Controls: 5/10 (50%)	Not stated	Selection: 3 Comparability:1 Outcome: 1
Wegener et al [28], 1994	Germany	Cohort study	GBT	Cases: 3/14 (21.4%) Controls: not stated	A rise of breath H2 concentration > 20 ppm in the first 2 h	ACR 1980 [31]	Cases: 10/14 (71.4%)	Cases: 6/14 (42.9%)	Selection: 3 Comparability:1 Outcome: 2
Cobden et al [29], 1980	UK	Cohort study	JAC or GBT	JAC: cases: 7/20 (35%) Controls: 0 (0%) GBT: cases: 4/20 (20%) Controls: not stated	JAC: (> 10^6 organisms/ml) or GBT: (> 20 ppm increase in hydrogen breath from the baseline measurement)	Not stated	Cases: 18/20 (90%) controls: 9/18 (50%)	Not stated	Selection: 3 Comparability:1 Outcome: 1

LBT, lactulose breath test; *GBT*, glucose breath test; *JAC*, jejunal aspiration culture; *SSc*, systemic sclerosis; *dcSSc*, diffuse systemic sclerosis; *ACR*, American College of Rheumatology; *EULAR*, European League Against Rheumatism

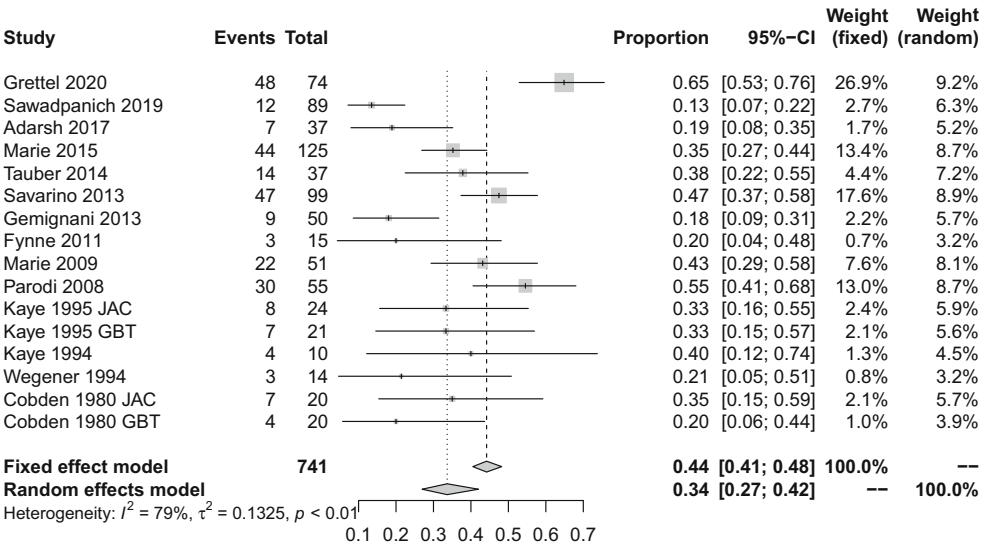


Fig. 2 Forest plot of the pooled prevalence of SIBO in SSc

areas, with higher positivity rates of SIBO in studies from Western countries (38%) than Asian countries (15%). The prevalence of SIBO was higher in studies defined by ACR-EULAR 2013 (50%) compared with ACR 1980 (30%) or other criteria (32%). Furthermore, the risk of SIBO was 12.51-fold higher in SSc patients compared to the healthy controls. The risk of diarrhea was almost nine times higher among SSc patients with SIBO compared to those without SIBO. These observations suggest that SSc could be a predisposing factor for the development of SIBO, especially in those diagnosed by LHBT, defined by ACR-EULAR 2013 or Western populations. Diarrhea may also be a predictor of SIBO in SSc patients.

The etiology of SIBO is usually complex. There are several important endogenous defense mechanisms against bacterial overgrowth such as gastric acid secretion, intestinal motility, intact ileo-caecal valve, immunoglobulins within intestinal secretion, and bacteriostatic properties of pancreatic and biliary secretion [9, 38]. When these protective mechanisms fail, SIBO can manifest. SSc-associated gastrointestinal hypomotility can lead to small bowel stasis, thereby increasing the likelihood of SIBO [5, 6]. In the study by Adarsh et al.

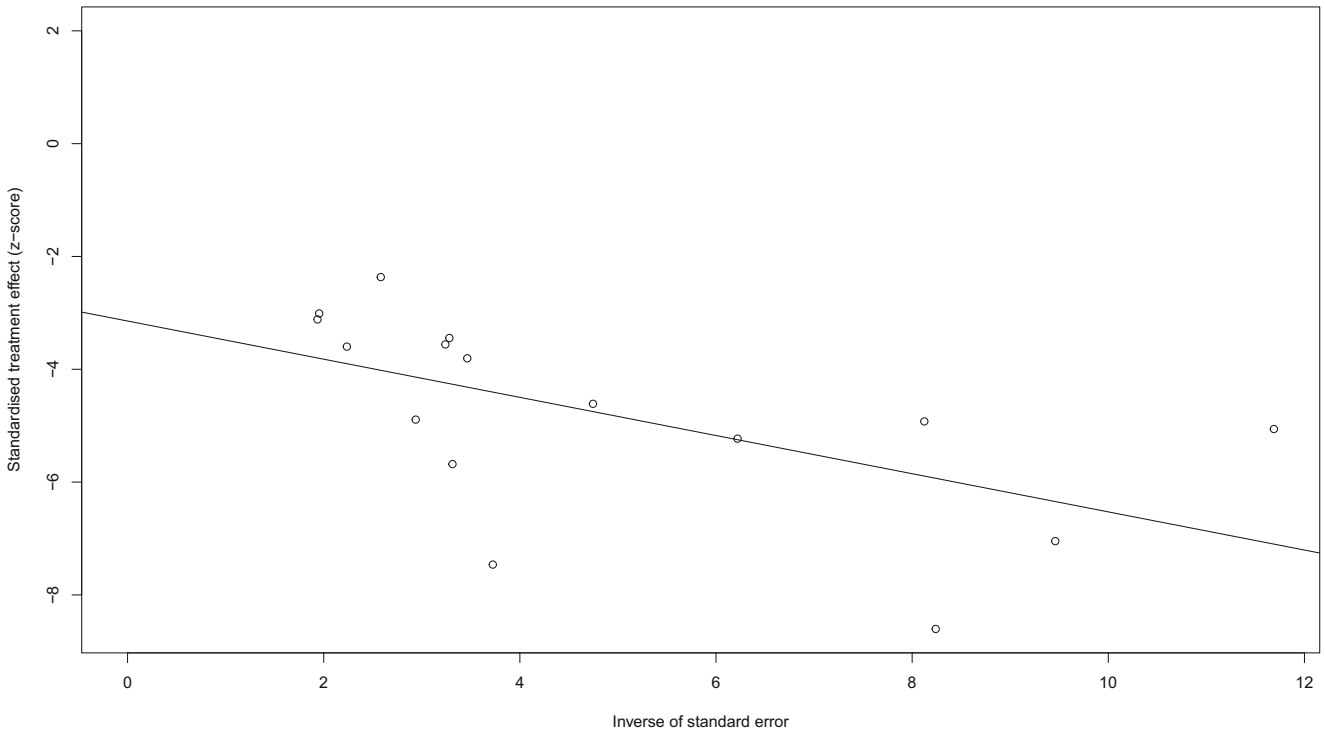


Fig. 3 Egger test showing the publication bias of the meta-analysis (p = 0.00056)

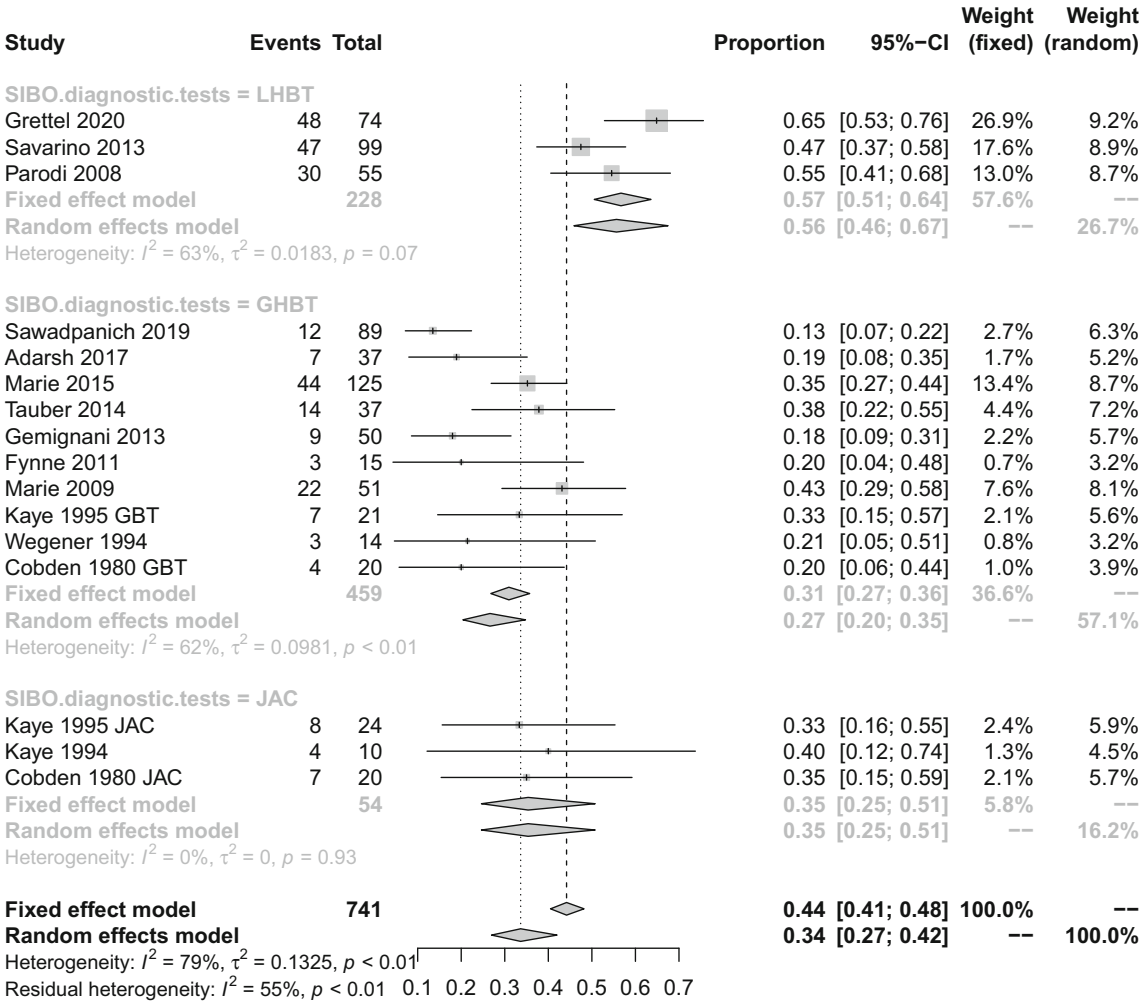


Fig. 4 Forest plot of the prevalence of SIBO in SSc based on the SIBO diagnostic test

[18], gastric emptying was delayed in 10/36 SSc patients, and oro-caecal transit time (OCTT) was prolonged in 23/37, whereas SIBO was noted in 7/37. This observation suggests that GI motility abnormalities make patients prone to SIBO. Savarino et al. [21] and Gemignani et al. [22] made similar conclusions that OCTT was significantly delayed in SSc compared with the controls, which may be associated with the increased prevalence of SIBO in SSc. In addition, in gastroesophageal reflux therapy in SSc patients, the use of proton pump inhibitors may disrupt the defense mechanisms preventing excessive bacterial colonization of the small bowel [9, 39, 40].

The use of different SIBO diagnostic methods appears to account for the variance in reported SIBO prevalence rates in SSc. The JAC has long been the gold standard for SIBO diagnosis [41, 42]. It was used in two studies [26, 29] in our review, with a SIBO prevalence of 35%. However, it also has limitations including invasiveness, cost, inaccessibility to the distal small bowel, potential for contamination from oral flora, and false negatives for obligate anaerobes [42, 43]. In contrast to a JAC, breath tests are non-invasive, inexpensive methods to evaluate SIBO, but the diagnostic reliability are influenced by the substrate used and the variable criteria used to define a positive test. The pooled prevalence of SIBO diagnosed by LBT in our study was higher than GBT (56% vs. 27%). This might be a result of rapid intestinal transit delivering lactulose to colonic bacteria earlier than expected, which produces excess hydrogen gas and causes higher false-positive results [44–46]. In contrast, glucose is rapidly absorbable in the proximal small bowel and has a low sensitivity for diagnosing SIBO [46, 47]. In addition, the different geographic areas explained the variance of SIBO prevalence in SSc. Our study found that the SIBO prevalence in SSc was higher in Western countries than Asian countries (38% vs. 15%). The first possible explanation for this observation is the different diets of the countries. Diet has a known impact on the microbiome; high fat and carbohydrate foods in the Western diet can decrease beneficial gut microbes and increase total anaerobic microflora and counts of Bacteroides and Enterobacteriales [48]. The second explanation is the inherently different metabolism and physiology among different ethnic groups. Finally, the

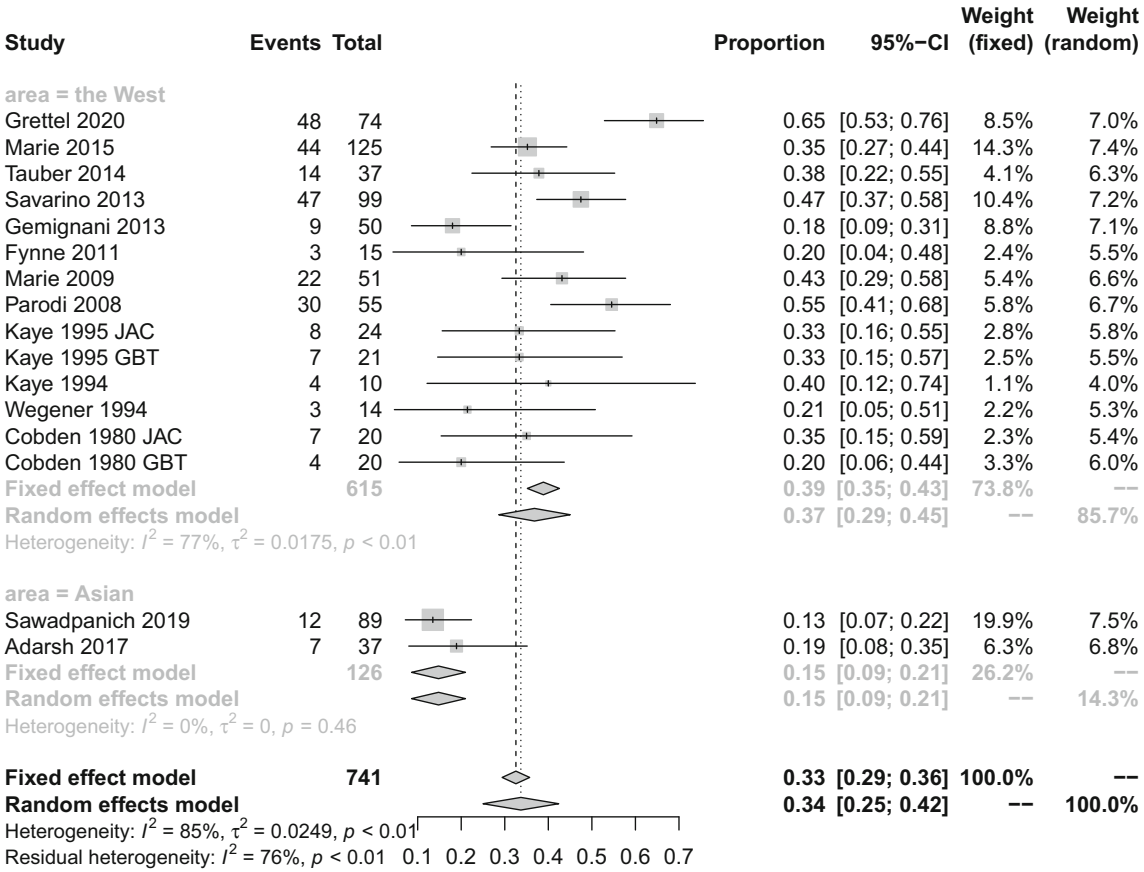


Fig. 5 Forest plot of the prevalence of SIBO in SSc based on the area of included studies

prevalence of SIBO also varies according to the different criteria used to define SSc. In our study, the prevalence of SIBO among patients meeting ACR-EULAR 2013 was higher than in patients meeting ACR 1980 or other criteria (50% vs. 30% and 32%). The differences in the subjects using different SSc diagnostic criteria may explain the high prevalence of SIBO among patients with SSc defined by ACR-EULAR 2013 criteria.

We found SSc patients with SIBO had more diarrhea than their SIBO-negative counterparts, suggesting diarrhea might be a reliable clinical predictor of SIBO in SSc, whereas, gender, SSc subset, digital ulcer, and pulmonary fibrosis were not associated with SIBO in SSc in our study. Furthermore, SIBO was considered to result in malnutrition in SSc patients. Sawadpanich et al. [16] and Parodi et al. [25] found SSc that patients with SIBO had lower levels of serum albumin and vitamin B12, although the difference did not reach statistical significance. Sawadpanich et al. [17] and Cobden et al. [29] reported that patients with SSc complicated by SIBO had less weight than those without SIBO. These results suggest SIBO might play a considerable role in malnutrition in SSc patients.

Antibiotic therapy has been reported to be effective for SIBO in a previous meta-analysis [49]. As for SSc, current recommendations do endorse intermittent or rotating antibiotics to treat SIBO in SSc [50]. Tauber [20] treated 14 SSc patients diagnosed with SIBO with the following rotating antibiotic therapy: amoxicillin 500 mg three times a day (t.i.d.) during the first month, followed by ciprofloxacin 500 mg twice daily (b.i.d.) during the second month and metronidazole 500 mg t.i.d. during the third month. After antibiotics, six of the 14 had a negative breath test. Gemignani [22] conducted a prospective, nonrandomized study, in which nine SSc patients and three healthy volunteers had SIBO diagnosed by GBT. They underwent antibiotic therapy with 1200 mg rifaximin daily plus 5 g partially hydrolysed guar gum daily for 10 days, then SIBO was successfully eradicated in all of the individuals. Similarly, Marie [24] treated 21 SSc patients with norfloxacin 400 mg b.i.d. plus metronidazole 250 mg t.i.d. for 7 days per month. After 6 months, SIBO was eradicated in 11 patients with a significant improvement of intestinal symptoms. In the study by Parodi [25], 30 SSc subjects with SIBO received rifaximin 400 mg t.i.d. for 10 days. SIBO was eradicated in 22 patients as well as significantly improved diarrhea, abdominal pain, bloating, and abdominal tenderness. These studies demonstrate that antibiotic treatment for SSc patients can lead to gastrointestinal symptomatic improvement and eradication of SIBO. In addition to treatment with antibiotics alone, a combination of antibiotics and probiotics

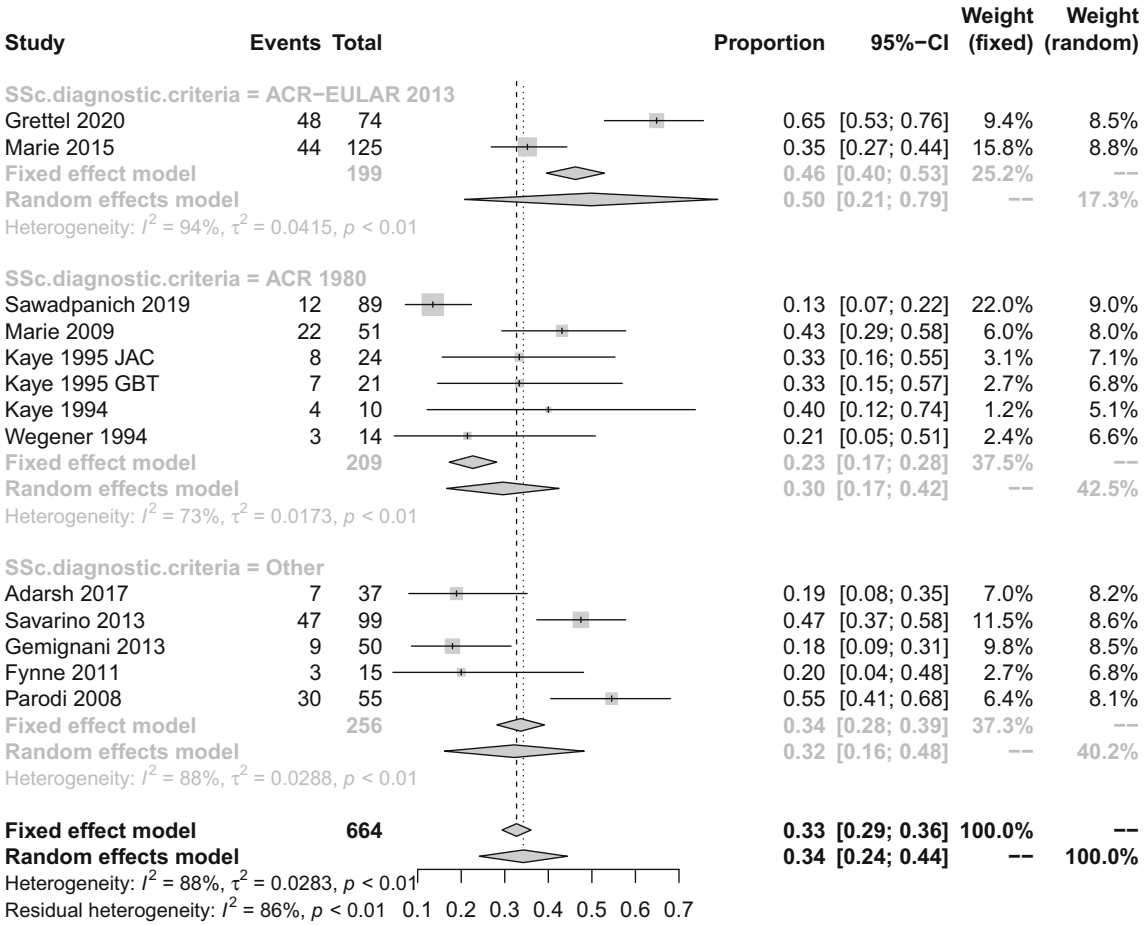


Fig. 6 Forest plot of the prevalence of SIBO in SSc based on the SSc diagnostic criteria

may result in greater improvements in SIBO in SSc patients compared to antibiotics alone. García-Collinot [16] divided 40 SSc patients with SIBO into three groups, including the M group (metronidazole 500 mg b.i.d. for 7 days per month), SB group (S. boulardii 200 mg b.i.d. for 7 days per month), and M + SB group (metronidazole 500 mg plus S. boulardii 200 mg b.i.d. for 7 days, then S. boulardii for 7 more days per month). After 2 months of treatment, SIBO was eradicated in 25% of the M group, 33% of the SB group, and 55% of the M + SB group. The SB and M + SB groups had decreased diarrhea, abdominal pain, and flatulence, but M remained unchanged. At present, it is still difficult to determine the most effective strategy for treating SIBO in patients with SSc. Additional studies are needed to determine the most effective way to treat SSc patients with SIBO.

There are several limitations to our meta-analysis, including (1) a relatively small sample size due to the limited number of patients in each of the included studie; (2) the results of the Egger test calculating the prevalence of SIBO in SSc suggested the possibility of publication bias

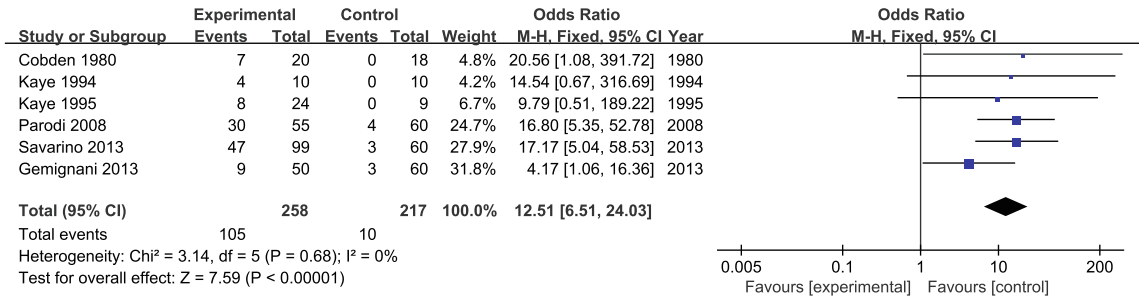
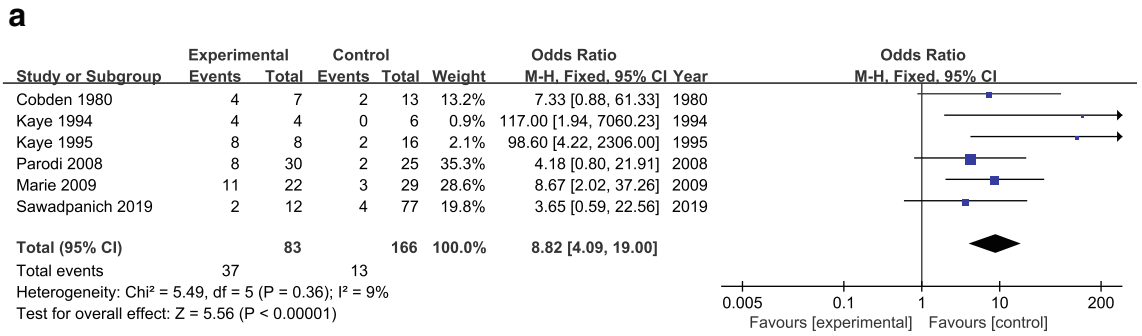
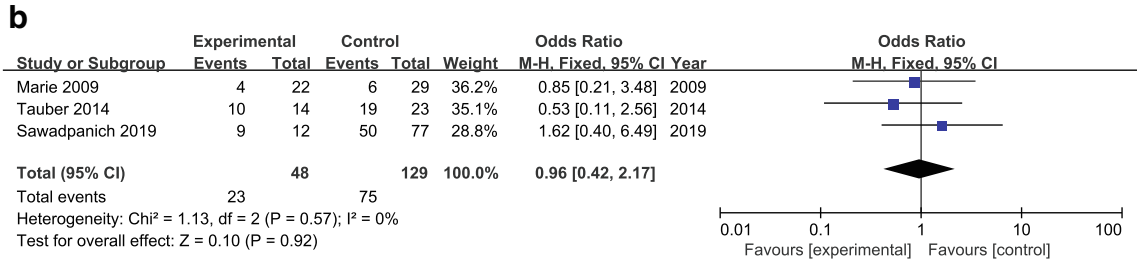
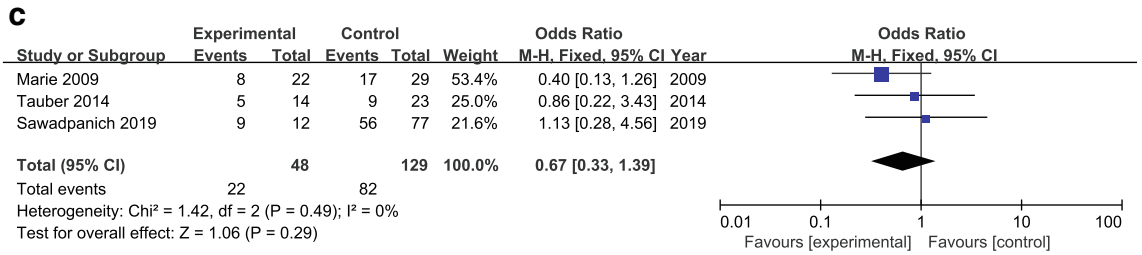
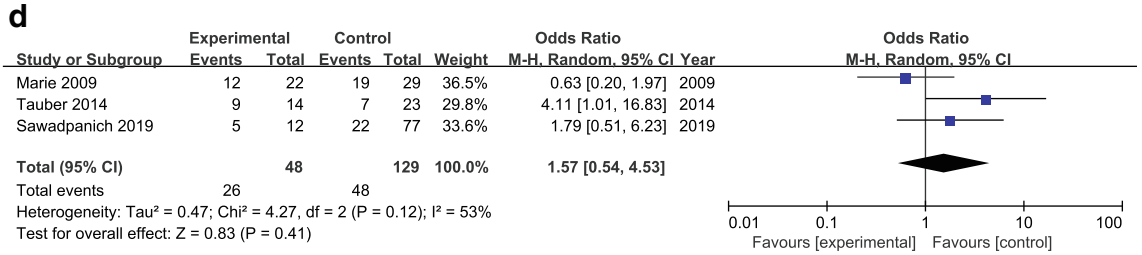


Fig. 7 Forest plot of odds ratios of SIBO in SSc patients compared with healthy controls









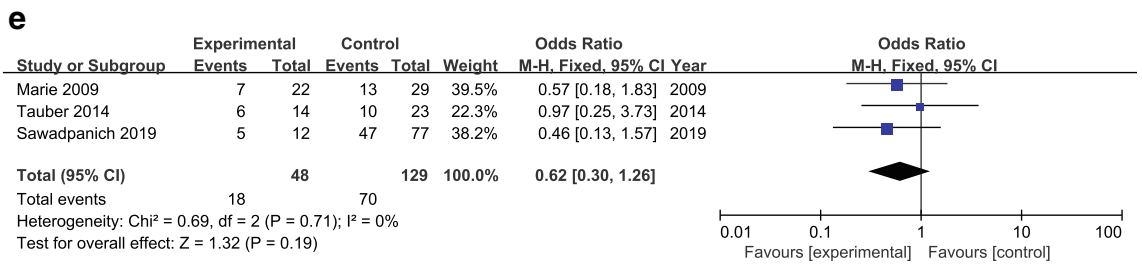


Fig.8 **a** Forest plot of odds ratio for diarrhea in SSc patients with SIBO compared to those without SIBO. **b** Forest plot of odds ratio for female in SSc patients with SIBO compared to those without SIBO. **c** Forest plot of odds ratio for dcSSc in SSc patients with SIBO compared to those without SIBO. **d** Forest plot of odds ratio for digital ulcer in SSc patients with SIBO compared to those without SIBO. **e** Forest plot of odds ratio for pulmonary fibrosis in SSc patients with SIBO compared to those without SIBO

in a number of the studies; (3) different diagnostic tests, different geographic areas of included individuals, and different SSc diagnostic criteria may have introduced heterogeneity. These limitations have likely affected the reliability of the results, suggesting that new research must take these factors into consideration.

In summary, around one-third of SSc patients tested positive for SIBO with a significantly increased risk over the controls. The prevalence of SIBO in SSc varied according to the SIBO diagnostic test performed, geographic area, and SSc diagnostic criteria. The presence of diarrhea may be a predictor of SIBO in SSc. Antibiotic treatment may lead to eradication of SIBO and gastrointestinal symptomatic improvement in SSc patients. Finally, we recommend that SSc patients with gastrointestinal symptoms, such as diarrhea or malnutrition, receive a SIBO diagnostic test in usual clinical practice. The SSc patients who test positive for SIBO should be treated with antibiotics as early as possible.

Authors' contributions All authors had access to the data and a role in writing the manuscript.

Compliance with ethical standards

Disclosures None.

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