Small Intestinal Bacterial Overgrowth in Functional Dyspepsia: A Systematic Review and Meta-Analysis

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INTRODUCTION: **This systematic review and meta-analysis aimed to determine the role of small intestinal bacterial overgrowth (SIBO) in patients with functional dyspepsia (FD).**

METHODS: **Electronic databases were searched until July 2020 for studies reporting prevalence of SIBO in FD. The prevalence rates, odds ratio, and 95% confidence intervals (CIs) of SIBO in FD and controls were calculated.**

RESULTS: **Seven studies with 263 patients with FD and 84 controls were identified. The odds for SIBO in patients with FD were significantly higher as compared to that in controls (odds ratio = 4.3, 95% CI, 1.1–17.5, 4 studies, 234 participants); however, there was moderate heterogeneity in this analysis. Including high-quality, case-control studies (all using glucose breath tests [GBTs]), the risk of SIBO in patients with FD as compared to controls was 2.8 higher (95% CI 0.8–10.0, 3 studies, 200 participants) with minimal heterogeneity in this analysis. Using the lactulose breath test, SIBO prevalence in FD was significantly higher (53.4%, 95% CI 33.9–71.9, 3 studies, 110 participants) as compared to that with GBT (17.2%, 95% CI 8.6–31.6, 4 studies, 153 participants). Substantial heterogeneity was found in studies using the lactulose breath test but not in studies using GBT. There was no significant difference in SIBO prevalence in patients with FD according to FD subtype.**

DISCUSSION: **This meta-analysis suggests a link between FD and SIBO. The quality of evidence is low and can be largely attributed to the type of breath test for SIBO diagnosis and clinical heterogeneity. More appropriately designed studies are required to confirm the link between SIBO and FD.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B898.

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INTRODUCTION

Functional dyspepsia (FD) is a chronic gastrointestinal disorder characterized by upper abdominal symptoms attributed to altered gastroduodenal function, in the absence of any identifiable structural explanation for the symptoms by traditional diagnostic procedures (1). Two major subgroups of FD are recognized postprandial distress syndrome (PDS), with postprandial fullness or early satiation, and epigastric pain syndrome (EPS), with epigastric pain and/or burning. The pathophysiology of FD is multifactorial, and several factors including gastroduodenal motor and sensory dysfunction, impaired mucosal integrity, low-grade immune activation, gut microbial dysbiosis, and dysregulation of the gut-brain axis have all been implicated (2).

Historically, the duodenum was nominally considered to be sterile, with microbes only present because of cross-contamination or small intestinal bacterial overgrowth (SIBO) (3). However, the evidence now demonstrates that the small intestine is colonized by bacteria in health and disease, and that a dysbiosis (defined as an alterations in the composition, density, and/or function of intestinal microbes) occurs in a variety of chronic conditions including functional gastrointestinal disorders (FGIDs) including irritable bowel syndrome (IBS) and FD (4,5), inflammatory bowel disease (IBD) (6), and chronic liver disease (7).

SIBO is one of the most widely recognized and established forms of microbial dysbiosis. Historically, the presence of $>10^5$ colony-forming units per milliliter (cfu/mL) of colonic-type

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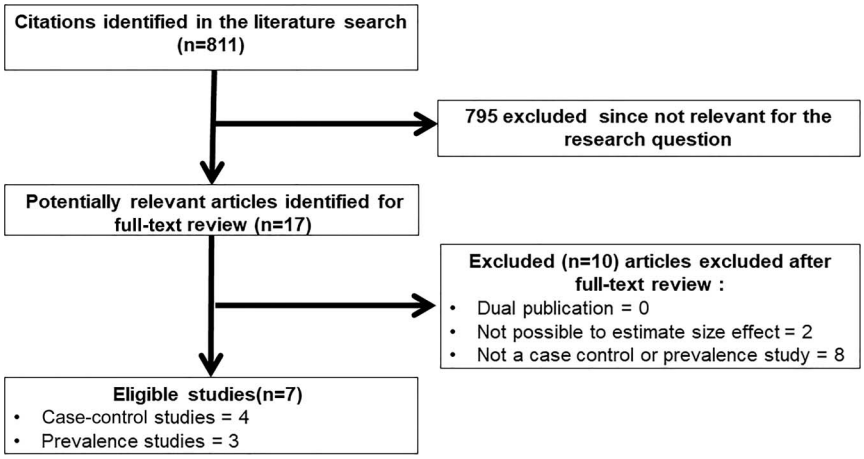

Figure 1. Flow diagram of assessment of studies identified in the systematic review and meta-analysis.

bacteria in culture of jejunal aspirates is the traditionally accepted gold standard for diagnosis of SIBO (8). However, this definition relies on invasive tests (aspiration of small intestinal content) and lacks universal acceptance in terms of the cutoff values for diagnosing SIBO. In clinical practice, culture methods have been largely replaced by breath tests (9), which are simple, noninvasive tests for the diagnosis of SIBO (10). These are based on the measurement of exhaled gases such as hydrogen (H_2) and methane (CH_4) after a carbohydrate challenge (9). However, compared with culture-based methods, breath tests have lower sensitivity and specificity for the diagnosis of SIBO (11). In addition, there are several methodological problems including use of different substrates and different doses of substrates, length of the test, sampling intervals, and definition of a normal and abnormal breath test, which may question their validity as diagnostic tests in clinical practice (12). Thus, one of the major challenges in SIBO diagnosis is the lack of sensitive and specific diagnostic tests (13).

Several studies have reported an increased prevalence of SIBO in patients with FD (14) and identified several risk factors for SIBO in patients with FD. However, the results are conflicting. Patients with FD are frequently treated with proton pump inhibitors (PPIs) which are potentially considered a risk factor for SIBO by impairing the acid barrier of the stomach. Thus, the role of PPI may require special attention when the link between SIBO and FD is analyzed. We performed a systematic review and meta-analysis (i) to determine the prevalence of SIBO diagnosed by clinically validated methods in patients with FD (and FD subtypes) and controls; (ii) explore the link between diagnostic modality and variations in SIBO prevalence; (iii) assess the risk of PPI use for SIBO in patients with FD, and (iv) assess the effect of antibiotic therapy on symptom improvement in FD patients with SIBO.

MATERIALS AND METHODS

Search strategy

Electronic databases, including PubMed, MEDLINE (OvidSP), and EMBASE, were searched from initiation (1966) up to July 2020 for all studies assessing the prevalence of SIBO in patients with FD and/or FGIDs. The detailed literature search strategy is outlined in Figure 1, and this was conducted with the expert assistance of our librarian. The search strategy has been outlined in Figure S3(A) and S3(B), Supplementary Digital Content 1, http://links.lww.com/AJG/B898. The initial search was not limited to specific languages to capture all appropriate studies. "Snowball" methods including pursuing references of references and electronic citation tracking to identify all the relevant articles were used.

Selection of studies

Criteria for study inclusion are provided in Table 1. Two authors (S.R.G and A.S.) independently conducted an initial screen of abstracts and titles. Abstracts were eliminated if the study did not investigate the association between SIBO and FD or FGIDs. Prevalence studies and case-control studies, recruiting unselected subjects meeting diagnostic criteria for FD, that reported the prevalence of SIBO using clinically validated methods in patients with FD, and compared the prevalence of SIBO in FD versus controls and reported efficacy data after antibiotic treatment of SIBO in patients with FD were eligible for inclusion. The diagnosis of FD was based on the clinical assessment, questionnaire data, or specific symptom-based criteria, including the Rome criteria. Studies not reporting original data, manuscripts not published as full articles, those reporting on mixed populations of FGIDs with no separate data on FD, or those who did not use clinically validated methods to diagnose SIBO in FD were excluded (11). Antibiotic and/or PPI data were extracted from the selected studies. We also extracted SIBO prevalence rates in FD patients with concomitant IBS. Disagreements between reviewers were resolved by mutual consensus after reference to the original published article.

Data extraction and quality assessment

All data were extracted independently by 2 authors into a Microsoft Excel spreadsheet (2010 Professional edition; Microsoft Corp, Redmond, Washington). The following information was extracted from each study independently by the 2 reviewers: author, year of publication, journal, study design, country, source of controls, method of diagnosis of SIBO including test duration, quantity of substrate used, and the cutoff criteria for diagnosis of SIBO, mean age, sex, concurrent use of PPI and antibiotics, and any significant comorbidities including previous surgery for patients with FD and the control group. In addition, for all patients with FD, data regarding mode of diagnosis of FD, subtype,

Table 1. Eligibility criteria for the studies included in systematic review and meta-analysis

Eligibility criteria
• Case-control or prevalence studies, published as full articles in peer-reviewed journals.
• Adults with a presumed diagnosis of FD based on questionnaire or meeting specific diagnostic criteria.[a] • Non-FD control group, referred to as "controls" included healthy asymptomatic controls. • Studies reporting on efficacy data after antibiotic treatment of SIBO in patients with FD were also included.
• Clinically validated methods to diagnose SIBO.[b]
• Participants not specially selected.

FD, functional dyspepsia; SIBO, small intestinal bacterial overgrowth.
[a]Rome criteria (1,37–39).
[b]Lactulose or glucose breath tests or jejunal aspirate and culture (or any combination of these) for diagnosing SIBO.

overlap with the other FGIDs, treatment of SIBO in FD patients with antibiotics and objective and subjective response after treatment, and the prevalence of methane-positive SIBO in patients with FD and controls was recorded. This systematic review and meta-analysis is consistent with the proposals for the reporting of meta-analysis of observational studies in epidemiology guidelines (15) and meets the preferred reporting items for systematic reviews and meta-analysis statement requirements (16). The quality of the prevalence studies included was assessed by using the Joanna Briggs Institute (JBI) critical appraisal tools for use in JBI systematic reviews for prevalence studies (17). The risk of bias was ranked as high when the study reached up to 49% of "yes" score, moderate when the study reached from 50% to 69% of "yes" score, and low when the study reached over 70% of "yes" score. In addition, the quality of the case-control included studies was assessed using the Newcastle-Ottawa scale (NOS) which judges the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure of interest, to assign a maximum score of 9 stars (18).

Data analysis

In an initial step, case numbers of patients with FD and controls (using various diagnostic modalities) in the respective cohorts were determined. In a second step, the pooled odds ratio (OR) and 95% confidence intervals (CIs) for the prevalence of SIBO in patients with FD and their respective controls were calculated. Subgroup analysis stratified by diagnostic modalities, FD subtypes, effect of PPI, and methane-positive SIBO in patients with FD were performed. Finally, we compared the proportion of patients responding to antibiotic therapy regarding normalization of breath tests and assessed the symptom response after antibiotic treatment in SIBO-positive FD patients and controls.

Analyses for the association between SIBO and FD and descriptive analysis were performed using the Statistical Package for Social Sciences (SPSS Version 26, Armonk, IBM Corporation, NY) and Comprehensive Meta-analysis Software (CMS) Version 3.3.070. NJ. In the "results" section, we report the observed (unweighted) number of positive cases and total tested in addition to the weighted pooled estimates. OR and pooled prevalence estimates of disease were calculated using a random effects model (19) to appropriately account for between-study variability. The statistical package CMS used logit transformation of proportions and the variance of the logit to estimate pooled event rates within groups and to compare event rates between groups. If one or more cells had a value of 0, then the CMS software automatically adds a fixed value of 0.5 to the respective cell for computation of log OR and variance. Between-study variation was evaluated using Cochrane's studies (20) and was quantified through the I (2) index in which values close to 100 indicate substantial variation between studies while values close to zero indicate minimal between-study variation. Standard approaches (Egger test (21) and inspection of funnel plots) were applied to identify potential publication biases. Furthermore, either χ^2 test $P < 0.10$ or $I^2 >$ 50% indicated substantial heterogeneity.

RESULTS

Search results

The initial literature search revealed 811 publications. Of these, 17 published articles seemed to be relevant for the study question and were retrieved for further evaluation. Ten articles were excluded as ineligible leaving 7 appropriate studies (Figure 1). Three of the 7 studies were prevalence studies (22–24), and the remaining 4 were case-control studies (14,25–27). All case-control studies included healthy volunteers in the non-FD control group. The characteristics of all the studies in the current meta-analysis including the methodology pertaining to diagnosis of SIBO and patient characteristics are outlined in Table 2 and Tables S1 and S2, Supplementary Digital Content 1, http://links.lww.com/AJG/B898.

Prevalence of SIBO in patients with FD

Overall, 7 studies (14,22–27) reported the prevalence of SIBO in patients with FD. Four studies used the glucose breath test (GBT) (14,23,26,27), and 3 used the lactulose breath test (LBT) (22,24,25) for SIBO diagnosis in patients with FD. Using breath tests, the prevalence of SIBO in patients with FD was 32.7% (95% CI 21.6–46.1, see Figure S1, Supplementary Digital Content 1, http://links.lww.com/AJG/B898); however, there was considerable heterogeneity in the studies included in this analysis ($I^2 = 86.26$, $P = 0.0001$).

Influence of diagnostic modality on SIBO prevalence in patients with FD

Using LBT as compared to GBT, SIBO prevalence in patients with FD was higher (53.4% (95% CI 33.9–71.9) vs 17.2% (95% CI 8.6–31.6), see Figure S1, Supplementary Digital Content 1, http://links.lww.com/AJG/B898). Moreover, there was no heterogeneity in the studies using GBT ($I^2 = 0$, $P = 0.656$) as compared to statistically significant heterogeneity in those using LBT for SIBO diagnosis in patients with FD ($I^2 = 85.35$, $P = 0.001$),

Table 2. Characteristics of studies showing mode of diagnosis and prevalence of SIBO in FD

No	Author	Study year	Region	Patients with FD, n	Patients with FD subtype, n			Criteria for FD	Controls, n	Type of controls	Mode of diagnosis of SIBO	SIBO in patients with FD, n (%)	SIBO in FD subtype, n (%)			SIBO in controls, n (%)
					EPS	PDS	EPS/PDS						EPS	PDS	EPS/PDS	
1	Shimura et al. (14)	2016	Japan	28[a]	24	4	0	Rome III	35	Healthy controls	GBT	2 (7.1%)	0	2	0	0
2	Costa et al. (25)	2012	Brazil	23	4	10	9	Rome III	11	Healthy controls	LBT	13 (56.5%)	3	5	5	0
3	Ramanathan et al. (26),[b]	2017	India	50	18	23	9	Rome III	50	Healthy controls	GBT	6 (12%)	2	3	1	2 (4%)
4	Adriana et al. (24)[b]	2019	Guatemala	47	NA	NA	NA	Rome IV	NA	NA	LBT	15 (31.9%)	NA	NA	NA	NA
5	Petzold et al. (23)	2019	Germany	82	NA	NA	NA	Rome III	NA	NA	GBT	17 (20.7%)	NA	NA	NA	NA
6	Tuteja et al. (22)	2018	United States	40	NA	NA	NA	Rome III	NA	NA	LBT	29 (72.5%)	NA	NA	NA	NA
7	Shah et al. (27)	2020	Australia	10	1	2	7	Rome IV	44	Healthy controls	GBT	2 (20%)	1	1	0	8 (18.2%)

EPS, epigastric pain syndrome; FBT, fructose breath test; FD, functional dyspepsia; GBT, glucose breath test; LBT, lactulose breath test; NA, not available; PDS, postprandial distress syndrome; SIBO, small intestinal bacterial overgrowth.
[a]11/28 were FD only.
[b]Studies not listed in PubMed.

contributing substantially to the heterogeneity seen in the overall analysis (Table 3).

Differentiating SIBO prevalence between patients with FD and healthy controls is affected by the bias associated with study design

Studies including healthy controls. All 4 case-control studies (14,25–27) included healthy subjects in the control group. The 4 case-control studies included 94 patients with FD and 140 healthy controls. Overall, SIBO prevalence in patients with FD was 24.5% (95% CI 16.2–34.4) compared with 7.2% (95% CI 3.9–12.7) in controls (Table 3). The pooled OR for prevalence of SIBO in patients with FD as compared to healthy controls was 4.3 (95% CI 1.1–17.5, Figure 2), and there was moderate heterogeneity in the studies included in the analysis ($I^2 = 33.33$, $P = 0.188$).

High-quality studies with low risk of bias. JBI critical appraisal tool was used to assess the quality of studies reporting SIBO prevalence in patients with FD. The quality of the 3 prevalence studies and the case group (only patients with FD) of the case-control studies as assessed by the JBI critical appraisal tool is shown in Table S3(B), Supplementary Digital Content 1, http://links.lww.com/AJG/B898. The Newcastle-Ottawa scale (NOS)

Table 3. Summary of studies using different diagnostic modalities to diagnosis SIBO in FD

Mode of diagnosis of SIBO in FD	No of studies	Patients with FD, n	Controls, n	SIBO in Patients with FD, n	SIBO in controls, n	Prevalence rates of SIBO in patients with FD, % (95% CI)	Prevalence rates of SIBO in controls, % (95% CI)	Prevalence of SIBO in FD, OR (95% CI)	Assessment of heterogeneity between studies
All studies, using breath tests	7	263	NA	84	NA	32.7 (21.6–46.1)	NA	NA	$I^2 = 86.26$, $P = 0.0001$
LBT	3	110	NA	57	NA	53.4 (33.9–71.9)	NA	NA	$I^2 = 85.35$, $P = 0.001$
GBT	4	153	NA	27	NA	17.2 (8.6–31.6)	NA	NA	$I^2 = 0$, $P = 0.651$
Prevalence studies ONLY	3	169	NA	61	NA	40.3 (15.5–71.4)	NA	NA	$I^2 = 92.67$, $P = 0.0001$
Case-control studies ONLY	4	94	140	23	10	24.7 (8.7–53.1)	7.2 (3.9–12.7)	4.3 (1.1–17.5)	$I^2 = 37.33$, $P = 0.188$

CI, confidence interval; EPS, epigastric pain syndrome; FBT, fructose breath test; FD, functional dyspepsia; GBT, glucose breath test; LBT, lactulose breath test; NA, not available; OR, odds ratio; PDS, postprandial distress syndrome; SIBO, small intestinal bacterial overgrowth.

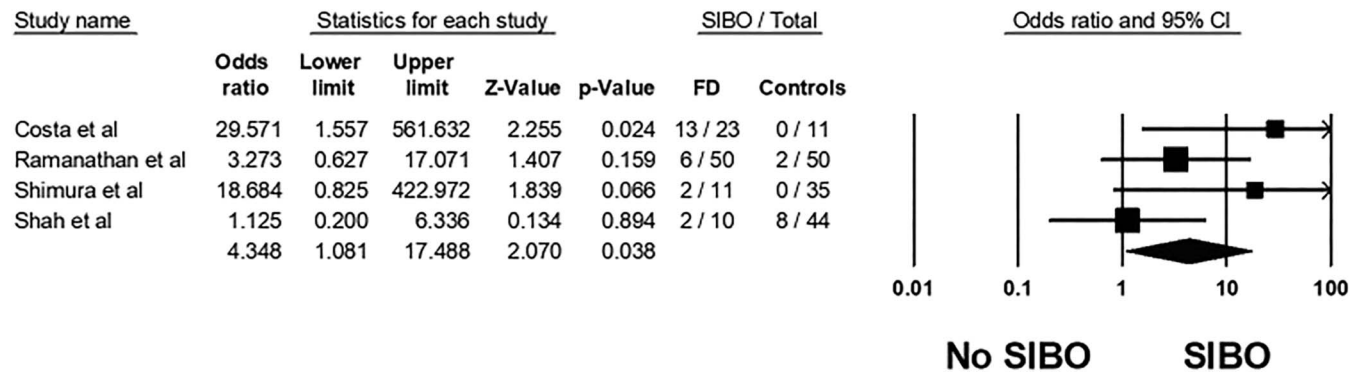

Figure 2. Forest plot of studies showing prevalence of SIBO in patients with FD, stratified according to the type of study. Overall, the prevalence of SIBO in FD is 31.6 (95% CI 15.9–53.2), $P = 0.093$) ($I^2 = 86.26$, $P = 0.0001$). SIBO prevalence in patients with FD in prevalence studies is 40.3(95% CI 15.5–71.4, $P = 0.556$) ($I^2 = 92.67$, $P = 0.0001$) and that in case-control studies is 24.7(95% CI 8.7–53.1, $P = 0.078$) ($I^2 = 79.80$, $P = 0.002$). CI, confidence interval; FD, functional dyspepsia; SIBO, small intestinal bacterial overgrowth.

was used to assess the quality of case-control studies (both patients with FD and controls) is outlined in Table S3(A), Supplementary Digital Content 1, http://links.lww.com/AJG/B898.

Of the 4, 3 case-control studies using GBT for SIBO diagnosis presented a low risk of bias/high methodological quality and 1 case-control study using LBT for SIBO diagnosis presented a moderate risk of bias/moderate methodological quality. All 3 prevalence studies presented a high risk of bias/low methodological quality. Therefore, conducting sensitivity analysis according to the quality of studies as assessed using the NOS, and the JBI critical appraisal tool, the pooled OR for SIBO in patients with FD as compared to healthy controls was 2.8 (95% CI 0.8–10.0), Figure S2, Supplementary Digital Content 1, http://links.lww.com/AJG/B898. Moreover, the heterogeneity was further reduced in the studies included in this analysis ($I^2 = 20.38$, $P = 0.285$, see Figure S2, Supplementary Digital Content 1, http://links.lww.com/AJG/B898).

By contrast, the 3 prevalence studies (22–24) included in this systematic review and meta-analysis presented a high risk of bias/low methodological quality, Table S3(B), Supplementary Digital Content 1, http://links.lww.com/AJG/B898. In prevalence studies, SIBO prevalence in patients with FD was 40.3% (95% CI 15.5–71.4, Figure 3, Table 3), was higher as compared to SIBO prevalence in patients with FD in the case-control studies 24.7(95% CI 8.7–53.1, Figure 2), with significant heterogeneity among the studies included in the overall analysis ($I^2 = 92.67$S3, $P = 0.0001$). Based on these findings, compared with the case-control studies, prevalence studies contributed to significant clinical heterogeneity.

Prevalence of SIBO and FD subtypes

Four (14,25–27) of the 7 studies reported the prevalence of SIBO in FD subtypes (PDS, EPS, or overlap of PDS and EPS); however, in 1 study (14), these data could not be extracted (Table 2). Overall, there was no significant difference in SIBO prevalence in FD patients with EPS (25.3% 95% CI 16.4–36.0) as compared to SIBO in FD patients with PDS (25.7%, 95% CI 12.5–43.3) or that in FD patients with an overlap of EPS and PDS (24.0%, 95% CI 9.4–45.1).

SIBO prevalence in FD patients with concomitant IBS

Two studies (14,27) reported on SIBO prevalence in patients with FD alone, IBS alone, and in those with an overlap of FD and IBS. SIBO prevalence was numerically higher in patients with FD (14.3%, 95% CI 3.1–36.2) as compared to those with an overlap of FD and IBS (11.5, 95% CI 4.4–23.4). Moreover, none of the 10 IBS patients (without concomitant FD) were positive for SIBO on the breath test.

Methane positivity of breath tests in patients with FD

Only 2 studies (22,27) reported the prevalence of methane-positive SIBO in patients with FD. Twelve (38.7% 95% CI 21.9–57.8) of 31 patients with FD diagnosed with SIBO met criteria for methane-positive SIBO on the breath test.

Effect of PPIs on the prevalence of SIBO in FD

Similarly, only 2 studies (25,27) assessed the effect of PPI use on SIBO prevalence in patients with FD. The prevalence of SIBO in 10/15 (66.7%, 95% CI 38.4–88.2) patients with FD on PPI was higher compared with 5/18 (27.8%, 95% CI 9.7–53.5) patients with FD not on a PPI, but this failed statistical significance.

Effect of antibiotic treatment on symptoms in FD patients with SIBO

Two case-control studies (14,26) reported treatment effects in 8 patients with FD and 2 controls with SIBO, who received antibiotic treatment (rifaximin and levofloxacin) for variable durations (7 to 10 days). Antibiotic treatment resulted in normalization of breath tests in all patients with FD and control subjects, and symptom improvement was noted in all treated patients.

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis reporting the prevalence of SIBO in patients with FD. The meta-analysis includes 7 studies (4 case-control and 3 prevalence studies) conducted in 7 countries, with 263 patients with FD and 84 healthy controls. Overall, there is a significant increase (OR 4.3, 95% CI 1.1–17.5) of SIBO prevalence in patients with FD compared with healthy controls. Furthermore, the data reveal that there was no significant difference in SIBO prevalence in different FD subtypes.

We found statistically significant heterogeneity in the primary analysis reporting SIBO prevalence in FD. This is very similar to our recently published systematic review and meta-analysis of the SIBO prevalence in IBS (4). We thus conducted subgroup analyses according to the study type. Overall, SIBO prevalence in patients with FD was higher in prevalence studies as compared to that in case-control studies. We also found higher heterogeneity scores when only prevalence studies were included in the

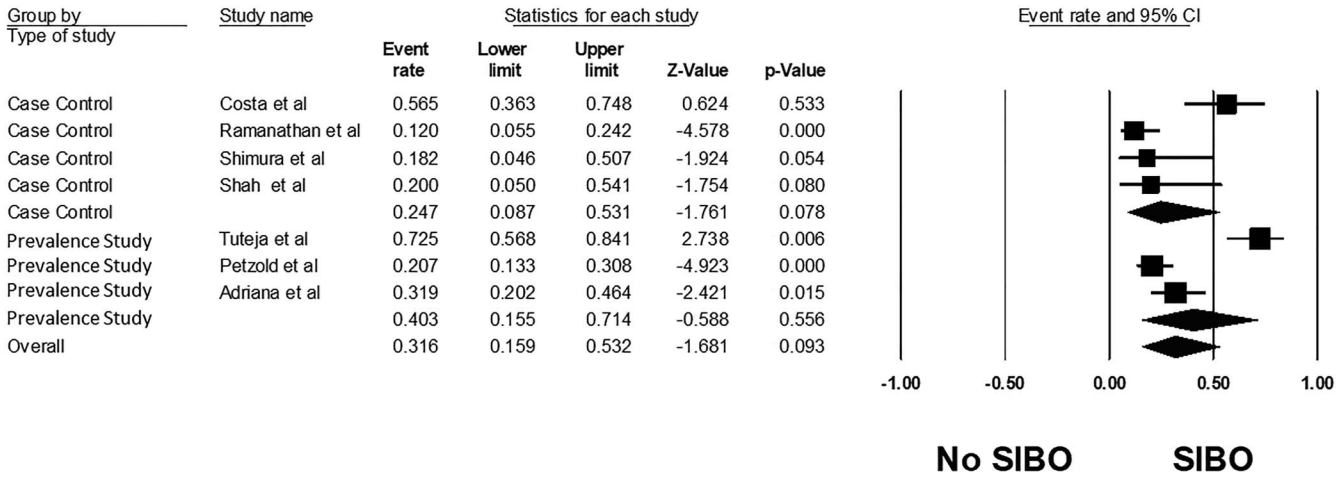

Figure 3. Forest plot of studies showing prevalence of small intestinal bacterial overgrowth in patients with functional dyspepsia and controls, using breath tests (odds ratio = 4.3 [95% confidence interval 1.1–17.5], $P = 0.038$) ($I^2 = 37.33$, $P = 0.188$). CI, confidence interval; SIBO, small intestinal bacterial overgrowth.

subgroup analysis, contributing to the overall heterogeneity we observed in the primary analysis. By contrast, minimal heterogeneity was seen in the subgroup analysis including only case-control studies. Potentially, this could be explained by the fact that the 4 case-control studies included healthy subjects in the control groups, minimizing the risk of bias. Another contributing factor could be the quality of the studies included in this systematic review and meta-analysis as assessed by NOS and the JBI critical appraisal tool. All case-control studies using GBT for SIBO diagnosis scored high on the NOS and on the JBI critical appraisal tool, reflecting that these are high-quality studies. On the other hand, the included prevalence studies were of low quality pointing toward inherent limitations of these studies. Furthermore, the prevalence studies were retrospective audits of insufficiently defined study cohorts with limited information regarding FD subtype or overlap with other functional gastrointestinal disorders such as IBS. More importantly, all 3 prevalence studies did not control for potential risk factors for SIBO (e.g., PPI or antibiotic use and previous surgery). This could potentially explain why they overestimate SIBO prevalence in patients with FD as compared to that in case-control studies.

Another limitation of the included studies is the failure to systematically assesses methane positivity. Only 2 (22) of the 7 studies measured both methane and hydrogen positivity on breath tests to diagnose SIBO, and in these studies, approximately one-third of the SIBO-positive FD patients were methane-positive on the breath test. Although methane is produced by Archea and not bacteria, it is now recognized that hydrogen and methane positivity are diagnostic for microbial colonization of the small intestine (28). In our recent systematic reviews and meta-analysis, we have shown a link between methane positivity on the breath test and IBS, constipation subtype (4), and an inverse association in patients with inflammatory bowel disease (6). To highlight the significance of measuring methane in patients with suspected intestinal dysbiosis, the most recent American College Guidelines for SIBO (28) have coined the term, intestinal methanogen overgrowth, to indicate methane production by methanogens (archae) on the breath test rather than SIB(bacteria) O. Thus, by not including analysis of methane production during breath testing, the prevalence of SIBO in 5 of 7 studies included in this meta-analysis may have been underestimated.

Although limited by the small size, we did not find any significant difference in the SIBO prevalence in patients with FD according to FD subtype. On the other hand, there have been speculations that PPI treatment is a risk factor for SIBO in patients with functional gastrointestinal disorders. Only 2 studies (25) included in this systematic review and meta-analysis assessed the effect of PPI use on SIBO prevalence in patients with FD and found PPI to be a risk factor for SIBO. Regarding treatment effects with antimicrobial therapy, limited data were available; however, 2 small studies reported improvement of symptoms in all SIBO-positive FD patients and normalization of breath tests in all treated subjects. Although there are data suggesting that only a subgroup of patients with FD responds to antibiotic therapy (29), it might be speculated that patients with FD who respond to antibiotic therapy have underlying small intestinal dysbiosis.

A limitation of the studies available for this systematic review and meta-analysis that needs to be considered is that all studies have only used breath tests (indirect testing), which are surrogate markers for diagnosing bacterial overgrowth. None of the studies used small bowel aspirate and culture (direct testing) which are the traditionally accepted gold standard for diagnosing SIBO. Culture-based tests are invasive, require an endoscopy with specialized equipment, and are prone to cross-contamination by oropharyngeal microbes, and most importantly, there is debate on the site of sampling in the small intestine and appropriate thresholds of microbial density for diagnosing SIBO (13). Hence, culture tests have been replaced by breath tests in routine clinical setting for SIBO diagnosis. However, it is well recognized that breath tests have significant methodological limitations and lack sensitivity and specificity for SIBO diagnosis (11,30).

When we conducted a sensitivity-analysis based on the type of the breath test used for SIBO diagnosis, we found that the prevalence of SIBO in patients with FD diagnosed by LBT was more than three-times higher than that by GBT (53.4% vs 17.2%). There was significantly high heterogeneity in the studies included in the analysis using LBT and zero heterogeneity in the studies included in analysis that used GBT. So, the question remains

whether LBT overestimates or GBT methods underestimate the prevalence of SIBO. Furthermore, there have been concerns that LBT reflects orocecal transit time rather than truly measuring SIBO (31). On the other hand, glucose is readily absorbed in the proximal small bowel; hence, a negative GBT cannot exclude SIBO affecting the distal small bowel. This highlights that the diagnosis of SIBO in various gastrointestinal conditions is hampered by the lack of universally accepted and validated diagnostic tests.

Finally, a key limitation is the paucity of studies available in the literature assessing the presence of SIBO in FD while there are many studies (including 4 systematic review and meta-analyses) assessing SIBO in IBS (4,32–34). In addition, it is worth noting that in all the case-control studies included this systematic review and meta-analysis, the sample size is relatively small with less than 50 participants per arm.

Functional gastrointestinal disorders often exist with a spectrum of symptoms, and the overlap of various functional gastrointestinal disorders such as FD and IBS (35) is frequently seen in clinical practice and could potentially be caused by intestinal dysbiosis. Thus, it would be clinically relevant to compare SIBO prevalence in FD patients with and without concomitant IBS-type symptoms. In the current systematic review and meta-analysis, 2 studies assessed SIBO prevalence in FD patients with and without concomitant IBS. They found a numerically higher SIBO prevalence in FD patients without IBS as compared to that in FD patients with concomitant IBS.

The data of this systematic review and meta-analysis suggest an association between FD and SIBO and the possibility that treatments targeting SIBO can improve FD symptoms. This is also well aligned with our recent experimental work using quantitative polymerase chain reaction to determine bacterial loads of small intestinal mucosal biopsies. In patients with FGID, as compared to asymptomatic controls, the duodenal bacterial load is significantly increased irrespective of PPI use (27). In addition, the symptom response to a standardized meal challenge is significantly correlated with the duodenal bacterial load and inversely correlated with quality of life in patients with FD (5). Moreover, a study testing effects of antimicrobial therapy in patients with FD revealed that in SIBO-positive FD patients, the initially augmented symptom response to a standardized meal challenge was reduced after antimicrobial therapy (36).

In summary, this is the first systematic review and meta-analyses of FD and SIBO. Based on the available data using breath tests as the diagnostic modality, the prevalence of SIBO is significantly increased in patients with FD, as compared to healthy controls. Although SIBO prevalence in patients with FD was numerically higher as compared to that in FD patients with concomitant IBS, this failed statistical significance. Although limited by the small sample size (and the small number of studies), we did not find any significant difference in SIBO prevalence according to FD subtypes. Although only limited data are available, PPI use seemed to be a risk factor for SIBO in patients with FD. Antibiotic therapy resulted in symptomatic improvement and normalization of a positive breath test results. Although this systematic review and meta-analysis suggests a link between SIBO and FD, the quality of evidence is low, and this can be attributed mainly to the low sensitivity and specificity of diagnostic tests for SIBO diagnosis, in particular the LBT and to substantial clinical heterogeneity seen in the prevalence studies. Finally, the available data—in combination with other experimental data—are encouraging but thus far insufficient to firmly conclude that antimicrobial therapy should be prescribed in breath test–positive patients or should be expected to result in the long-term symptom improvement. Thus, appropriately powered case-control studies and clinical trials and are required that not only assess the prevalence of SIBO or treatment effects, but also to better characterize intestinal dysbiosis (e.g., microbial load and function) linked to symptom manifestation.

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CONFLICTS OF INTEREST

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