

The Prevalence of Small Intestinal Bacterial Overgrowth in Diabetes Mellitus: A Systematic Review and Meta-analysis

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Research

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Abstract

Objective: The reported prevalence of small intestinal bacterial overgrowth (SIBO) among patients with diabetes mellitus (DM) is highly variable. We conducted this systematic review and meta-analysis to estimate the prevalence of SIBO in DM.

Methods: A comprehensive literature search of the PubMed, Cochrane Library and Embase databases from inception to December 2020 was conducted for studies correlating SIBO with DM. Studies were screened, and relevant data were extracted and analysed. The pooled prevalence of SIBO among DM patients and the odds ratio (OR) of SIBO among DM patients compared with controls were calculated. Publication bias was assessed using Egger's test and funnel plots.

Results: Fourteen studies including 1417 diabetes patients and 649 controls met the inclusion criteria. The pooled prevalence of SIBO in DM was 29% (95% CI 20–39%). The OR of SIBO in diabetes patients was 2.91 (95% CI 0.82–10.32, $p=0.1$) compared with controls. Subgroup analyses showed that the prevalence of SIBO in DM was higher in studies using jejunal aspirate culture (JAC) for diagnosis (39%, 95% CI 12–66%) than in those that used the lactulose breath test (LBT) (31%, 95% CI 18–43%) or glucose breath test (GBT) (29%, 95% CI 14–43%). The prevalence of SIBO in DM was higher in studies conducted in Western countries (35%, 95% CI 21–49%) than in those conducted in Eastern countries (24%, 95% CI 14–34%), and the prevalence of SIBO in type 1 DM (25%, 95% CI 14%–36%) was not significantly different from that in type 2 DM (30%, 95% CI 13%–47%).

Conclusion: Twenty-nine percent of diabetes patients tested positive for SIBO and had a significantly higher risk than the controls. The prevalence of SIBO in DM varied according to the diagnostic test performed and geographic area. DM could be a predisposing factor for the development of SIBO, especially among patients diagnosed by JAC or those in Western populations.

Introduction

Small intestinal bacterial overgrowth (SIBO) is a clinical syndrome that includes malnutrition, diarrhoea and abdominal distension caused by an increase in the number of bacteria and/or abnormal types of bacteria in the small intestinal tract^[1]. The gold standard for diagnosing SIBO is jejunal aspirate culture (JAC). A colony count in the proximal small intestine $\geq 10^5$ CFU/mL (normal value $\leq 10^4$ CFU/mL) or a coliform bacteria count in the small intestine $\geq 10^3$ CFU/mL is generally considered to indicate SIBO^[2]. Alternatively, the breath test, a widely used method for diagnosing SIBO, has the advantages of being simple, non-invasive and easily acceptable. Recent studies have shown that SIBO is closely associated with various diseases, including Crohn's disease^[3], irritable bowel syndrome^[4], functional dyspepsia^[5], hepatic encephalopathy^[6], and non-alcoholic fatty liver disease^[7].

Diabetes mellitus (DM) is a serious and growing global public health burden^[8]. DM was estimated to affect at least 382 million people worldwide in 2013, and this number will rise to 592 million by the year 2035^[9]. DM is a metabolic disease characterized by hyperglycaemia, which can cause multiple-organ damage. Furthermore, gastrointestinal complications are common among patients with DM^[10–11]. Studies on the relationship between DM and risk of SIBO have yielded inconsistent results. Notably, diabetes patients have been reported to exhibit increased risks of SIBO^[12], but several studies have reported inconsistent results^[13–14]. Therefore, we conducted a systematic review and meta-analysis to investigate the relationship between DM and the risk of SIBO by summarizing all of the available data.

Materials And Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations^[15].

Search strategy

We searched the PubMed, Cochrane Library and Embase databases from their inception to December 2020 using the following search terms: (diabetes mellitus OR diabetes OR diabetic OR T1DM OR T2DM) AND (small intestinal bacterial overgrowth OR small intestine bacterial overgrowth OR SIBO OR small bowel bacterial overgrowth OR breath test OR SBBO). The literature search had no language restrictions. We also screened the reference lists of the included studies and relevant reviews to identify all eligible articles. Two reviewers (X. Feng and XQ. Li) independently performed the literature search.

Study selection

Articles were eligible if they met the following criteria: (a) cohort study, case-control study or cross-sectional study investigated the relationship between SIBO and DM; (b) subjects were > 18 years old; (c) studies recruited subjects meeting the DM diagnostic criteria; (d) valid methods were used to assess SIBO, including the lactulose breath test (LBT), glucose breath test (GBT) or JAC; and (e) studies were in a full-text format. We excluded articles such as case reports, review articles, letters and those reporting animal research. In addition, we excluded studies that provided duplicate data. We did not determine the cut-off values for a positive test as long as the positive criteria were clarified. When a study used more than one test to diagnose SIBO, we extracted data from each method separately.

Data extraction and quality assessment

Two reviewers (X. Feng and XQ. Li) independently extracted the following data from the included studies: first author's surname, year of publication, origin of study, study design, diagnostic test for SIBO, SIBO diagnostic criteria, prevalence of SIBO in DM, type of diabetes (type 1, type 2 or both), average age, sex, and course of diabetes. Any discrepancies between the two reviewers were resolved by a third author (Z. Jiang). Two reviewers (X. Feng and XQ. Li) independently

evaluated the quality of the cohort studies or case-control studies with the Newcastle-Ottawa Scale (NOS)^[16] and assessed the quality of the cross-sectional studies with the modified Newcastle-Ottawa Scale^[17]. Studies with a score ≥ 7 were considered to be of high quality, while those with a score < 7 were considered to be of low quality.

Statistical analysis

The pooled prevalence of SIBO in diabetic patients was calculated. Subgroup analyses were conducted by SIBO diagnostic tests (LBT vs. GBT vs. JAC), geographic areas (Western countries vs. Eastern countries) and type of diabetes (type 1 [T1DM] vs. type 2 [T2DM]). For cohort studies or case-control studies, the number of patients with SIBO in the case group and control group was calculated separately, and then the odds ratios (ORs) and 95% confidence intervals (CIs) for the prevalence of SIBO in diabetic patients and their respective controls were calculated. P values < 0.05 were considered statistically significant. We used the Cochran Q statistic and I^2 statistic to assess heterogeneity. An I^2 value $> 50\%$ or a P value < 0.10 indicated statistically significant heterogeneity. The random-effects model was used with statistically significant heterogeneity across the studies; otherwise, the fixed-effects model was used. Furthermore, we used Egger's test or a funnel plot to assess any potential publication bias. $P > 0.05$ in Egger's test was considered indicative of no publication bias. We also performed sensitivity analyses by omitting one study in turn, which investigated the effect of an individual study on the overall prevalence of SIBO. All statistical analyses were performed using R 3.5.3 and RevMan 5.3.

Results

The initial literature search revealed 2629 potentially relevant studies (815 from PubMed, 1422 from Embase and 392 from Cochrane Library). Two studies were added by hand searching the references from the included studies. After excluding 661 duplicates, the titles and abstracts of 1970 unique articles were reviewed. Subsequently, we excluded 1925 studies that did not meet our inclusion criteria, which resulted in a full-text review of 45 studies. Twenty articles that did not report outcomes of interest were excluded after full-text review, while 10 articles were excluded because they were not full-text articles. One article was excluded because it duplicated data from another. Finally, 14 studies^[12-14,18-28] (9 cohort studies and 5 cross-sectional studies), including 2066 participants (1417 diabetic patients and 649 controls), were included in this meta-analysis (Fig. 1). Since two different diagnostic tests for SIBO were performed with different results in one study^[28], we separately calculated the prevalence of SIBO as two different studies. The characteristics and quality evaluation of the included studies are shown in Table 1. All 14 articles were of high quality.

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

Study	Country	Study design	SIBO diagnostic test	SIBO diagnostic criteria	Prevalence of SIBO	type of diabetes	Average age (years)	Gender (male/female)	Course of diabetes (year)
Yan et al ^[18] , 2020	China	cross-sectional	LBT	20g lactulose load is orally administered, 1) a baseline H ₂ concentration of > 10 ppm 2) H ₂ increase > 20 ppm or CH ₄ increase > 12 ppm above basal value within 90 minutes.	56/104 (53.8%)	T2DM	SIBO+:53.52 ± 10.5 SIBO-:53.69 ± 8.39	Overall 62/42 SIBO+: 34/22 SIBO-: 28/20	SIBO (13.0) SIBO (12.7%)
Malik et al ^[12] , 2020	India	cohort study	GBT	70g glucose load is orally administered, an increase of H ₂ ≥ 12 ppm above the baseline level within 2 hours	cases:43/300(14.3%) controls:1/200 (0.5%)	T2DM	cases: 54.6 ± 0.67 controls:55.4 ± 0.74	cases:142/158 controls:96/104	case: ± 0.2 contr none
Radionova et al ^[19] , 2020	Ukraine	cohort study	GBT	a rise of H ₂ ≥ 12 ppm above the basal level after glucose ingestion	cases: 69/92(75%) controls:33/80(41%)	T2DM	cases: 61.6 ± 9.0 controls:54.0 ± 13.5	cases: 63/29 controls: 46/34	not state
Malik et al ^[20] , 2018	India	cohort study	GBT	80g glucose load is orally administered, rise of H ₂ and/or CH ₄ ≥ 12 ppm over the baseline value within 2 hours	cases:17/75(22.7%) controls:1/75(1.3%)	T1DM	cases: 22.3 ± 5.2 controls: 23.1 ± 4.9	cases: 36/39 controls: 37/38	case: ± 3.6 contr none
Rana et al ^[21] , 2017	India	cohort study	GBT	80g glucose load is orally administered, rise of H ₂ and/or CH ₄ ≥ 12 ppm over the baseline value within 2 hours	cases:26/175(14.9%) controls:5/175(2.9%)	T2DM	not stated	cases: 87/88 controls: 89/86	case: ± 4.8 contr none
Adamska et al ^[13] , 2016	Poland	cohort study	LBT	20g lactulose load is orally administered, an elevated fasting H ₂ level > 20 ppm or a peak H ₂ level > 12 ppm in less than 60 minutes	cases:56/148(37.8%) controls: 30/41(73.2)	T1DM	cases: 45 (35–54) SIBO+: 44 (34–53) SIBO-: 45 (35–54) controls: 31 (27–39)	cases: 94/54 SIBO+: 35/21 SIBO-: 59/33 controls: 17/24	case: (13.5–28) SIBO (13–29) SIBO (13.5–29) contr none
Adamska et al ^[14] , 2015	Poland	cohort study	LBT	20g lactulose load is orally administered, H ₂ of first breath ≥ 20 ppm or an increase of H ₂ ≥ 12 ppm within 1 hour	cases: 82/200 (41%) T1DM: 36/91 (39.6%) T2DM:46/109(42.2%) controls: 15/20 (75%)	91 T1DM 109 T2DM	cases: 54(44–62) controls:37(29–41)	cases: 130/70 controls: 9/11	case: 15(11–23) contr none
Faria et al ^[22] , 2013	Brazil	cross-sectional	LBT	20g lactulose load is orally administered, an early peak (> 10mmHg) detected before 30 min or baseline H ₂ > 20 ppm	3/26 (11.5%)	T1DM	Overall 39 ± 9	6/22	case: ± 7

LBT, lactulose breath test; GBT, glucose breath test; JAC, Jejunal aspiration culture; ppm, parts per million; SIBO, small intestinal bacterial overgrowth; DM, dia

Study	Country	Study design	SIBO diagnostic test	SIBO diagnostic criteria	Prevalence of SIBO	type of diabetes	Average age (years)	Gender (male/female)	Control prevalence (year)
Rana et al ^[23] ,2011	India	cohort study	GBT	80g glucose load is orally administered, an increase of H ₂ and/or CH ₄ ≥ 12 ppm above the baseline in 2 consecutive readings	cases: 13/84(15.5%) controls: 1/45(2.2%)	T2DM	cases: 40.5 ± 12.6 controls: 43.4 ± 13.8	cases: 51/33 SIBO+: 6/7 SIBO-: 45/26 controls: 29/16	case: 10.5 contr none
Ojetti et al ^[24] ,2009	Italy	cross-sectional	LBT	10g lactulose load is orally administered, a rise of H ₂ > 20 ppm by 90 min or 180 min	13/50(26%)	T1DM	not stated	28/22	not state
Urita et al ^[25] ,2006	Japan	cross-sectional	GBT	75g glucose load is orally administered, an increase of H ₂ and/or CH ₄ ≥ 10 ppm above the baseline before the first 40 minutes	21/82 (25.6%)	not stated	Overall 62 (30–84)	Overall 40/42	not state
Zietz et al ^[26] ,2000	Germany	cross-sectional	GBT	70g glucose load is orally administered, an increase in breath H ₂ concentration > 20 ppm	17/50 (34%)	20 T1DM 30 T2DM	Overall 47.3 ± 2.2	not stated	14.4
Spengler et al ^[27] ,1989	Germany	cohort study	JAC	≥ 10 ⁴ microorganisms/ml of recovered fluid were considered to indicate increased bacterial growth.	cases: 10/19(52.6%) controls: 2/7(28.6%)	not stated	cases: 40–74 controls: 45–68	cases: 9/10 controls: 3/4	not state
Dooley et al ^[28] ,1988	USA	cohort study	LBT/JAC	10g lactulose load is orally administered, a short (15 min) peak ≥ 20 ppm of H ₂ before the sustained peak	cases: 1/3/12(25%) controls: 0/6 (0%)	T2DM	cases: 56 ± 8 controls: 36 ± 8	cases: 2/10 controls: none	case: ± 7 contr none

LBT, lactulose breath test; GBT, glucose breath test; JAC, Jejunal aspiration culture; ppm, parts per million; SIBO, small intestinal bacterial overgrowth; DM, dia

Prevalence of SIBO in diabetic patients

The prevalence of SIBO in diabetic patients was reported in all included studies^[12–14,18–28] and ranged from 8–75%. The pooled prevalence of SIBO was 29% (95% CI 20–39%) with considerable heterogeneity ($I^2 = 92%$) (Fig. 2). We used a random-effects model. The results of Egger's test showed that there was no publication bias ($P = 0.6137$) (Fig. 3). To explore the variability in prevalence among the studies, we conducted subgroup analyses in this meta-analysis. The studies were subgrouped based on the SIBO diagnostic test used. The pooled prevalence of SIBO was 31% (95% CI 18–43%) in six studies^[13, 14, 18, 22, 24, 28] using the LBT and 29% (95% CI 14–43%) in seven studies^[12, 19–21, 23, 25, 26] using the GBT. Two studies^[27, 28] using JACs showed a prevalence of 39% (95% CI 12–66%) (Fig. 4). When subgrouped by geographic area, the prevalence of SIBO was 35% (95% CI 21–49%) in eight studies^[13,14,19,22,24,26–28] from Western countries and 24% (95% CI 14–34%) in six studies^[12, 18, 20, 21, 23, 25] from Eastern countries (Fig. 5). Furthermore, in subgroup analysis based on the type of diabetes, the prevalence of SIBO in type 2 diabetes (30%, 95% CI 13–47%)^[12, 18, 19, 21, 23, 28] was similar to the prevalence in type 1 diabetes (25%, 95% CI 14–36%)^[13, 20, 22, 24]. The prevalence of SIBO in studies including both type 1 and type 2 diabetes^[14, 26] was 40% (95% CI 33–46%) (Fig. 6).

SIBO in diabetic patients compared with controls

Nine cohort studies^[12–14,19–21,23,27,28] compared the event rate of SIBO between 1105 diabetic patients and 649 controls and were included in this analysis. The prevalence of SIBO among individuals with DM was higher than that among individuals without DM, with a pooled OR of 2.91 (95% CI 0.82–10.32), although the difference was not statistically significant ($p = 0.10$) (Fig. 7). We used random-effects models because of significant heterogeneity ($I^2 = 89%$). The funnel plot indicated a possibility of publication bias (Fig. 8).

A sensitivity analysis was also performed by excluding the study by Adamska et al^[13] from the meta-analysis. One reason is that almost half of the controls in the study were recruited from among the hospital personnel and their relatives, which may affect the reliability of the results. Another reason is that both studies^[13, 14] utilized the same laboratory database of the Poznan University of Medical Sciences during an overlapping period. Exclusion of this study increased the pooled OR to 4.18 (95% CI 1.34–13.05) and reached statistical significance ($p = 0.01$). The between-study heterogeneity was decreased with an I^2 of 81%.

Discussion

To the best of our knowledge, this study is the first systematic review and meta-analysis to investigate the association between DM and the risk of SIBO. Our meta-analysis revealed that (i) the overall pooled prevalence of SIBO in DM was 29% (95% CI 20–39%). The variability in SIBO prevalence seems to depend on the type of SIBO diagnostic test and geographic area. (ii) The risk of SIBO was 2.91-fold higher among individuals with DM than among individuals without DM. The risk increased 4.18-fold and reached statistical significance when we excluded the study that recruited from among the hospital personnel and their relatives as controls.

Mechanisms between DM and SIBO have not been well elucidated. On the one hand, autonomic neuropathy is a common complication in diabetic patients, and it occurs throughout the whole gastrointestinal tract, affecting gastrointestinal motility^[29, 30]. Dysfunction of the vagus nerve and intrinsic intestinal autonomic nerves may play a role in gastrointestinal autonomic neuropathy^[30]. Gastrointestinal hypomotility due to diabetic autonomic neuropathy can lead to small bowel stasis, thereby increasing the likelihood of SIBO. Ojetti et al^[24] found that diabetes patients with autonomic neuropathy have a significantly higher prevalence of SIBO than those without autonomic neuropathy. In addition, oxidative stress and inflammatory cytokines have been demonstrated in previous studies to take part in the progression of diabetes^[31, 32]. Some studies have reported that the levels of inflammatory cytokines (such as IL-6, TNF- α , and IL-10) and oxidative stress-related parameters were significantly higher in both T1DM patients and T2DM patients than in controls^[12, 20, 33–40]. There may be some association between oxidative stress, inflammatory cytokines and SIBO in diabetic patients. Malik et al also observed in their study that SIBO-positive T2DM patients have a significantly higher level of inflammatory cytokines and oxidative stress than SIBO-negative patients^[12]. One explanation is that increased oxidative stress in diabetic patients may lead to increased apoptosis of the inhibitory neuronal subpopulation of enteric neurons, which alters gut motility and makes patients more prone to SIBO^[41]. On the other hand, SIBO seems to have some impact on diabetic patients. A study by Yan et al^[18] indicated that T2DM patients with SIBO showed worse glycaemic control and a lower level of insulin release than those without SIBO. Similar conclusions were reported in another study in non-alcoholic steatohepatitis (NASH), which indicated that NASH patients with SIBO have a higher prevalence of impaired glucose tolerance than those without SIBO^[42]. These results suggest that SIBO could be associated with beta-cell function, although the mechanism remains unclear. One of the hypotheses is that activation of inflammatory pathways reduces insulin secretion by islet cells^[43]. However, further studies are needed to confirm whether the decreased insulin secretion seen in diabetic patients could be attributed to SIBO and whether SIBO treatment could improve glycaemic control and beta-cell function in this population. Malnutrition and gastrointestinal symptoms are also characteristics of diabetic patients with SIBO. Rana et al found that urinary d-xylose and lactose intolerance in SIBO-positive T2DM patients was more severe than that in SIBO-negative patients^[21]. This indicated that SIBO may aggravate malabsorption and malnutrition and cause various gastrointestinal symptoms. These results were consistent with a study by Yan et al^[18], which showed that T2DM subjects with SIBO had a significantly lower BMI than subjects without SIBO. Malabsorption in SIBO-positive patients might play a role in weight loss^[44]. In addition, Radionova et al found that chronic gastritis patients with T2DM and SIBO are more closely associated with symptoms such as bloating, nausea and belching than non-SIBO patients^[19].

The pooled prevalence of SIBO in patients with DM was 29% in our study. However, there was a significant difference in the prevalence of SIBO. The discrepancies in these studies may be a result of the different SIBO diagnostic tests used, geographic areas and type of diabetes. The gold standard for diagnosing SIBO has long been JAC. Two studies in our analysis used JAC to diagnose SIBO, with a prevalence of 39%^[27, 28]. The limitations of JAC are its invasiveness, cost, difficulty accessing the distal small bowel, possible contamination by oral flora, and false negatives for obligate anaerobes^[45, 46]. Breath tests are non-invasive and inexpensive methods for evaluating SIBO compared to JAC, although diagnostic reliability is influenced by the substrates used and variable diagnostic criteria. Breath tests include the LBT and GBT. Previous studies have shown that rapid intestinal transit delivering lactulose to colonic bacteria can produce excess hydrogen gas and cause a higher false-positive result^[47–49]. In contrast, glucose has a lower sensitivity for diagnosing SIBO because of its rapid absorption in the proximal small intestine^[49, 50]. However, the prevalence of SIBO diagnosed by the LBT in our study was not significantly different from the GBT (31% vs. 29%). Additional studies with a larger sample size are needed to confirm this result. The different geographic areas also account for the variance in reported SIBO prevalence rates in DM. We found that the SIBO prevalence in DM was higher in Western countries than in Eastern countries (35% vs. 24%). One possible explanation for this result is the differences in dietary habits in different countries. High-fat and carbohydrate-rich foods in Western countries can decrease beneficial gut microbes and increase total anaerobic microflora and counts of Bacteroides and Enterobacteriales^[51]. Another explanation is the inherently different metabolism and physiology among different ethnic groups. In addition, we observed that the pooled prevalence of SIBO in T1DM was not significantly different from T2DM (25% vs. 30%). This suggests that the type of diabetes seems to be not significantly associated with the prevalence of SIBO. The effect of the type of diabetes on SIBO needs to be further investigated in more well-designed studies. Data from the present study suggest that the risk of SIBO is almost three times higher in patients with DM than in controls, although the difference was not statistically significant. Two studies in this meta-analysis reported that the prevalence of SIBO in diabetic patients was lower than that in controls^[13, 14], which was not consistent with other studies. A possible explanation is that Adamska et al^[13] recruited controls from among hospital personnel and their relatives. In addition, all participants in the two studies^[13, 14] were from the same medical institution. The selection of participants in the study may play a role in the results of the study. When we excluded the study by Adamska et al^[13], the risk of SIBO in DM increased to 4.18-fold compared with controls and reached statistical significance.

This study had several limitations: 1) a relatively small sample size due to the limited number of patients in each of the included studies; 2) the result of the funnel plot, which calculates the OR comparing the prevalence of SIBO in DM and controls, suggesting the possibility of publication bias in a number of the studies; and 3) different diagnostic tests and different geographic areas of subjects may cause heterogeneity in the results. These limitations have likely affected the reliability of the results, suggesting that new research must take these factors into consideration.

Conclusions

In summary, approximately 29% of diabetic patients tested positive for SIBO. Moreover, the increased risk of SIBO appears to be greater in patients diagnosed by JAC or those in Western populations. There was no significant difference in the prevalence of SIBO between T1DM and T2DM. The risk of SIBO in diabetic patients is almost three times higher than that in patients without diabetes. These results suggest that DM could be a predisposing factor for the development of SIBO, especially in patients diagnosed by JAC or those in Western populations. Future studies should address the association of SIBO with glycaemic control and nutritional status in diabetic patients.

Declarations

Ethics approval and consent to participate: The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met.

Consent for publication: The publication has been approved by all the authors.

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Figures

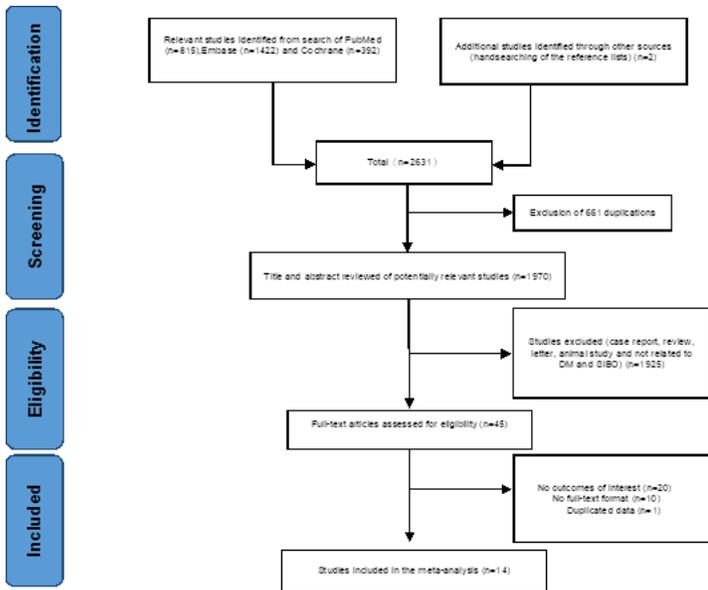


Figure 1

Flow chart of the selection process of articles

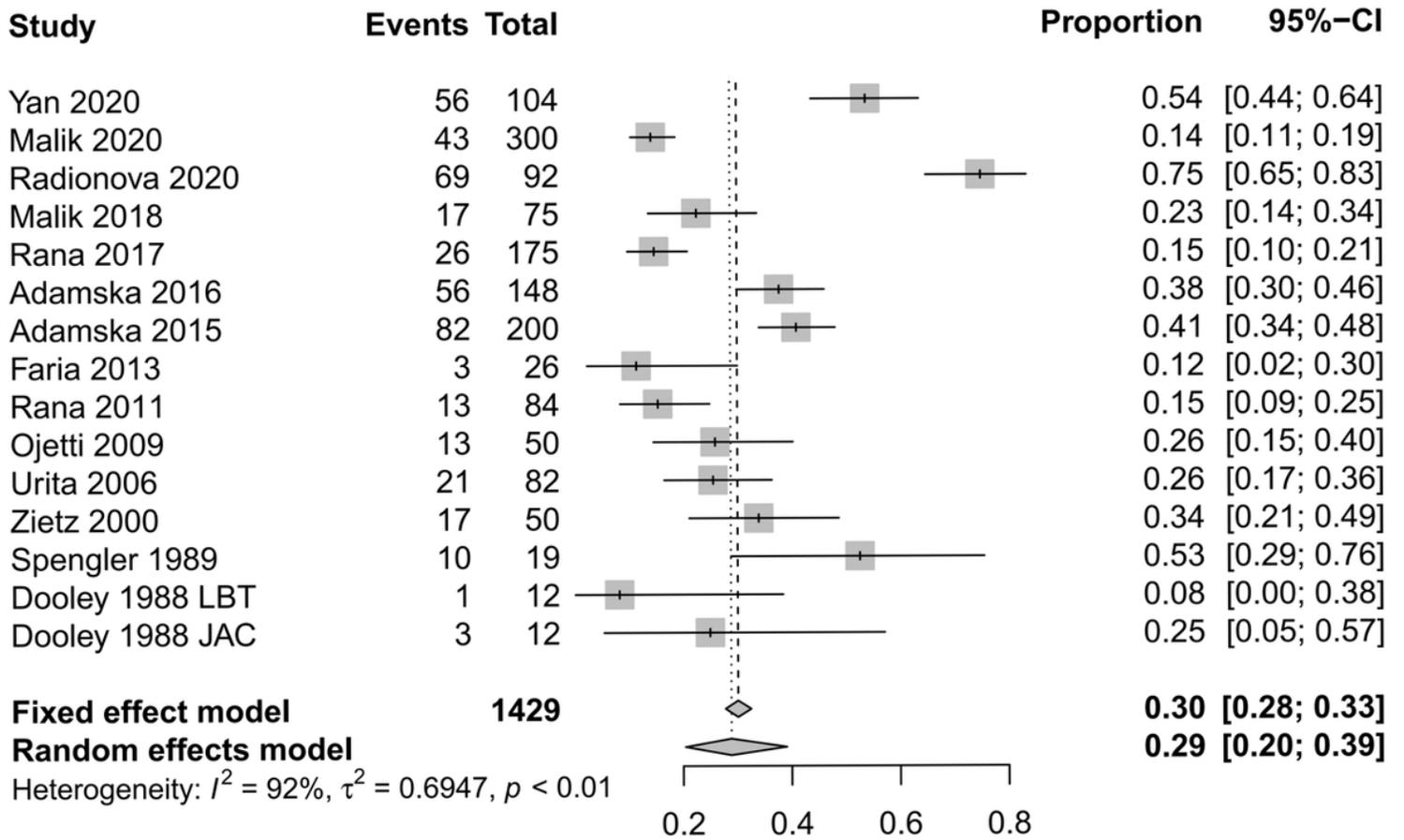


Figure 2

Forest plot of the pooled prevalence of SIBO in DM.

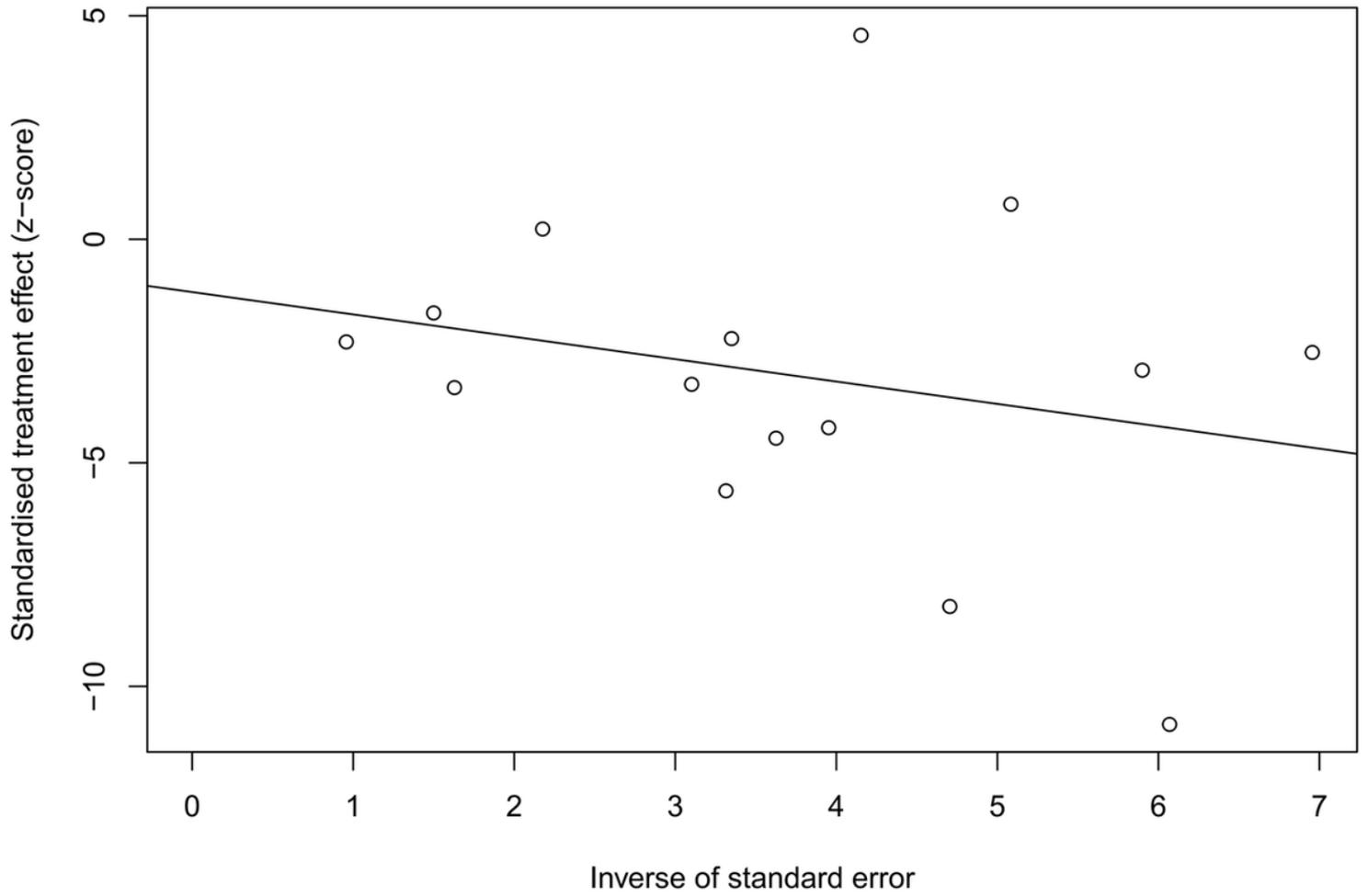


Figure 3

Egger test showing the publication bias of the pooled prevalence of SIBO in DM ($p=0.6137$)

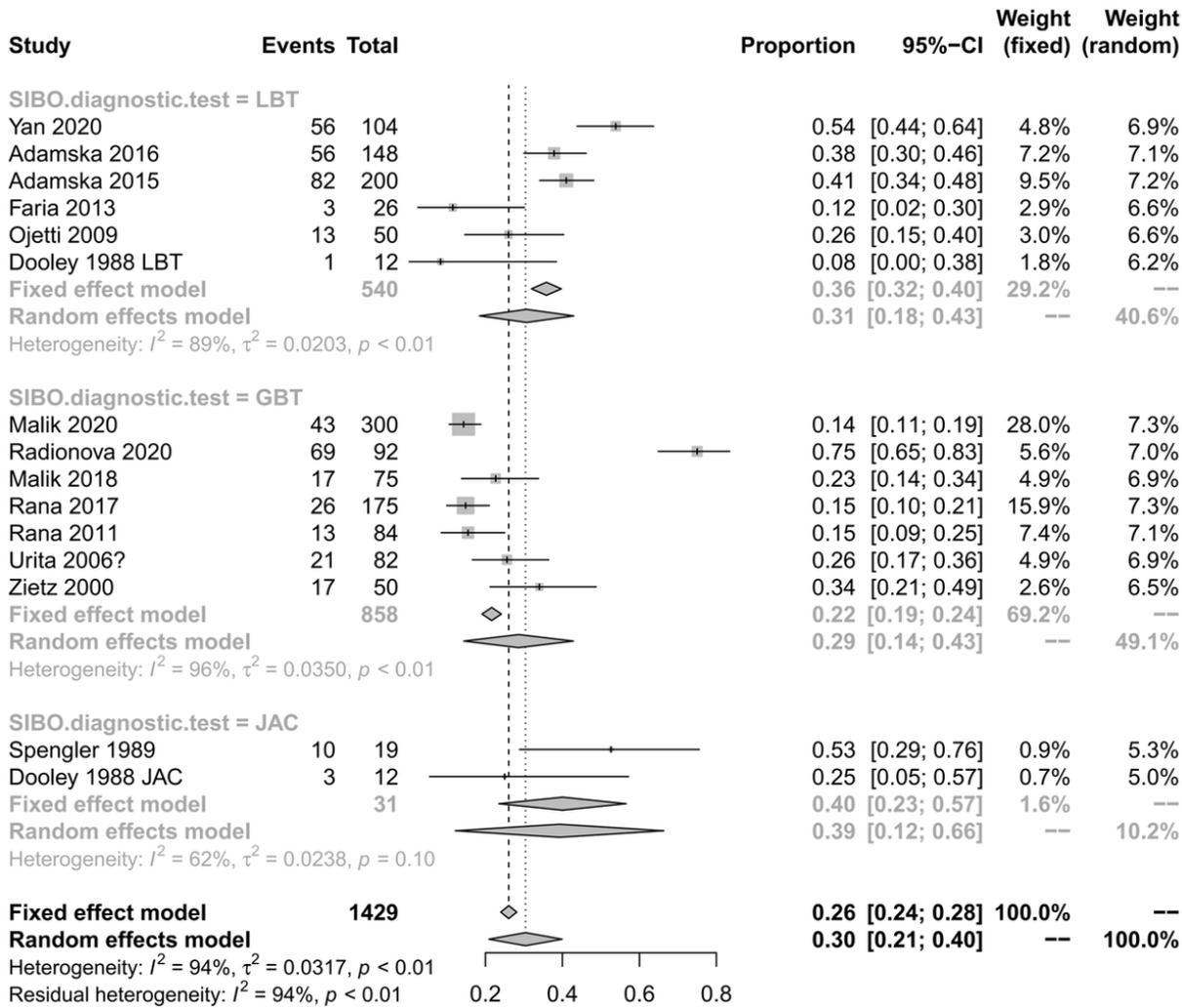


Figure 4

Forest plot of the prevalence of SIBO in DM based on the SIBO diagnostic test.

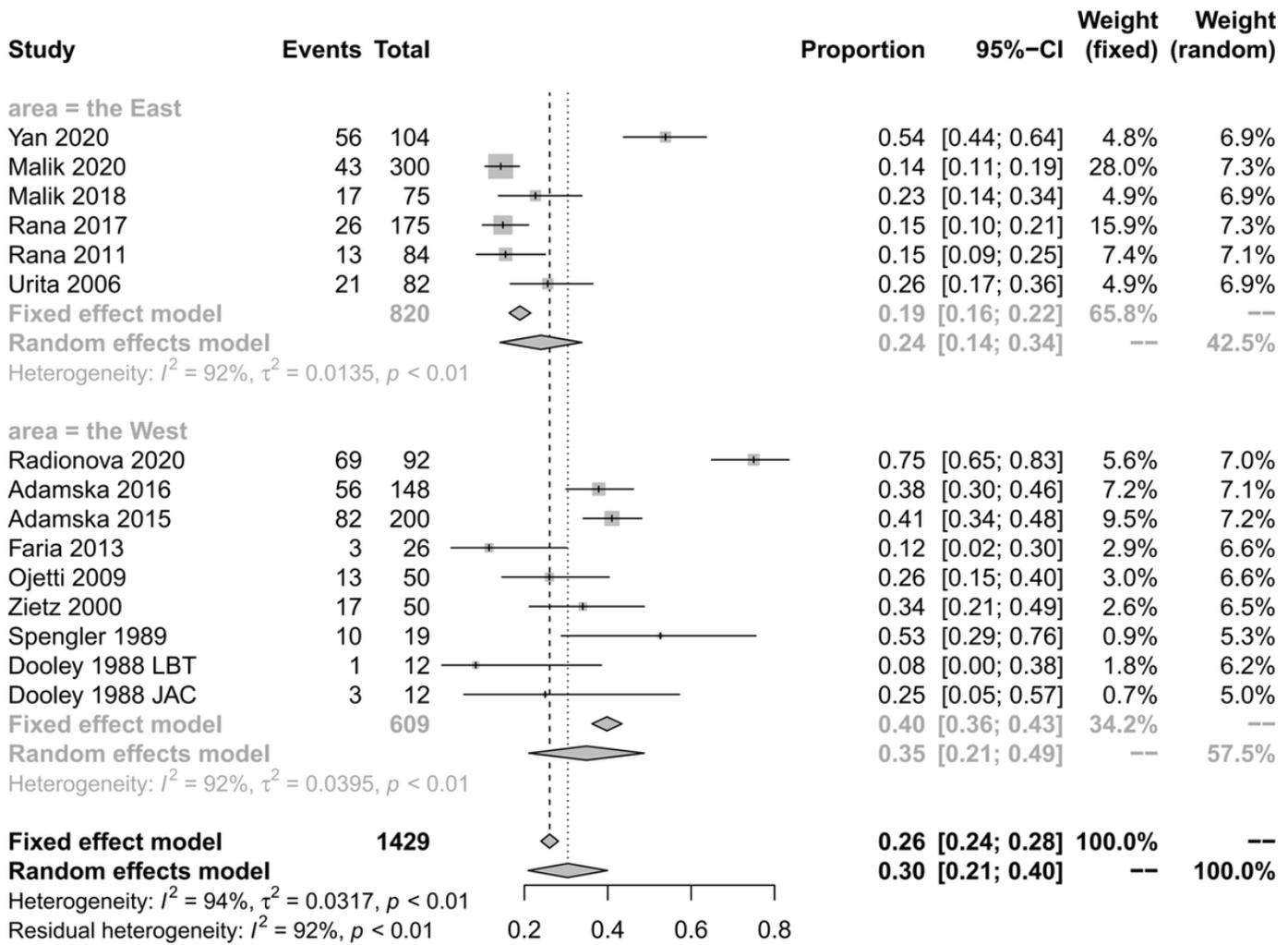


Figure 5

Forest plot of the prevalence of SIBO in DM based on geographic areas

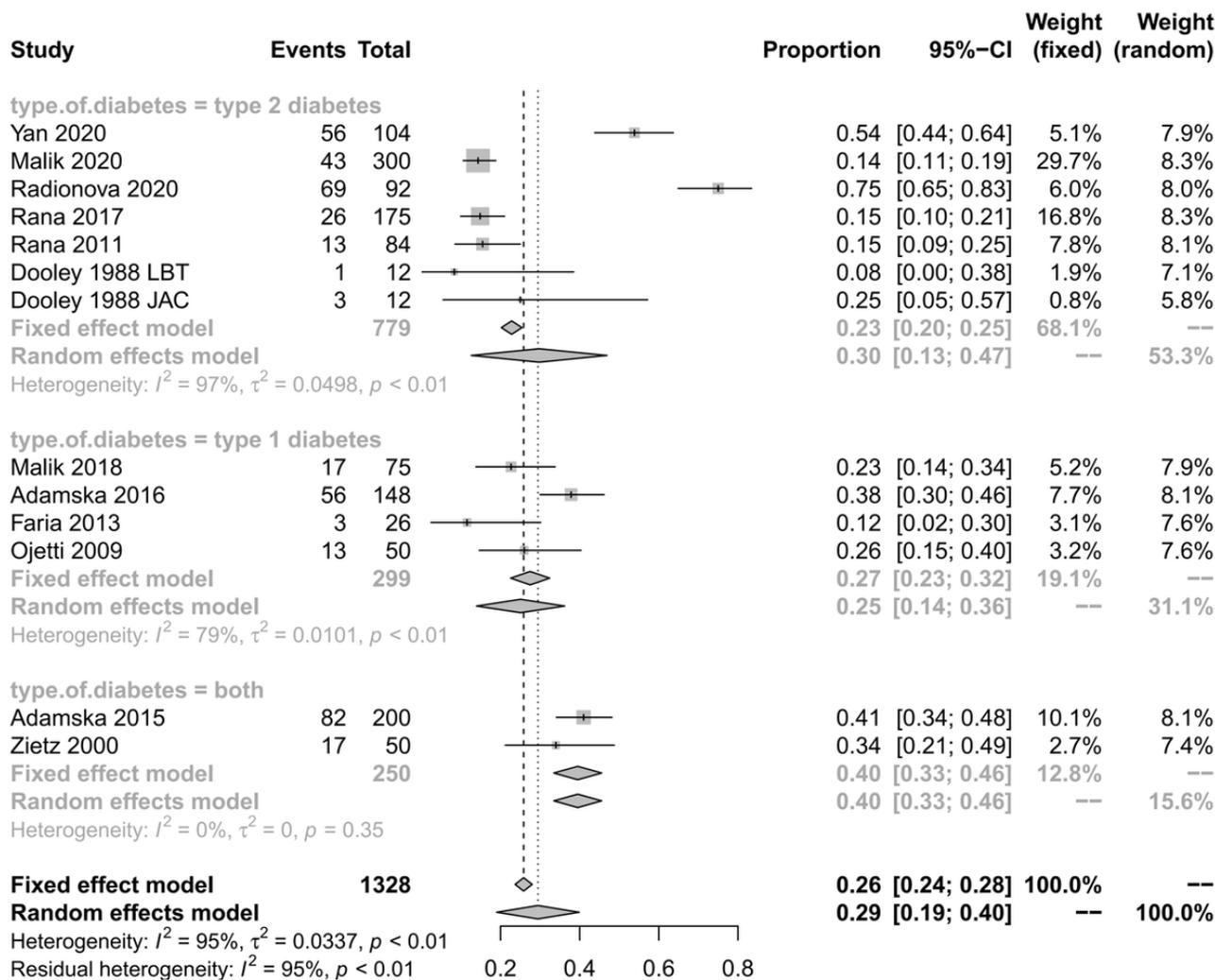


Figure 6

Forest plot of the prevalence of SIBO in DM based on type of diabetes

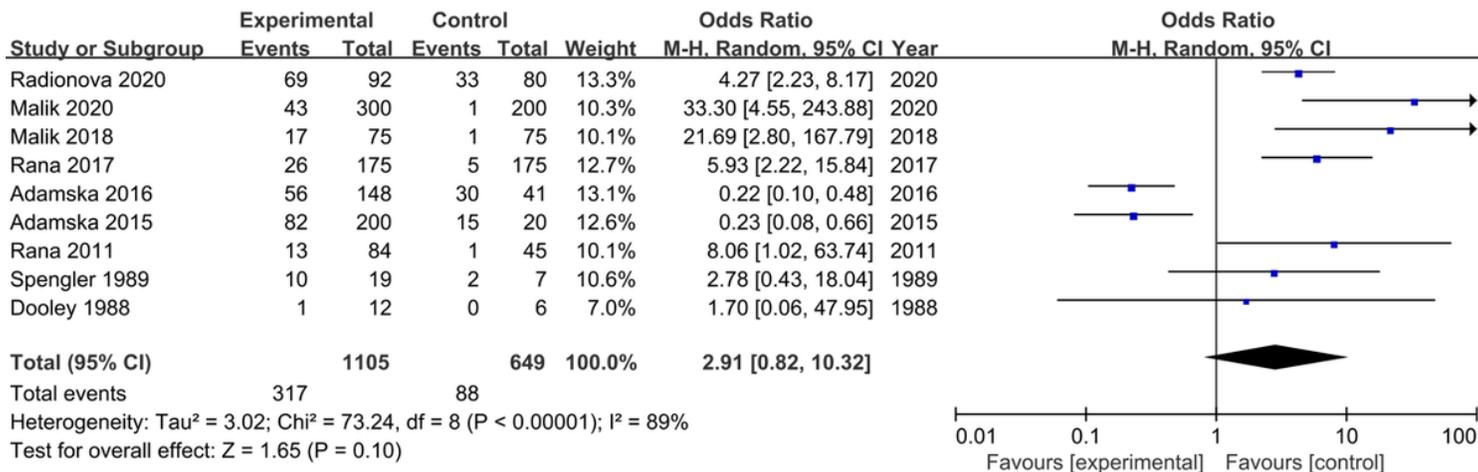


Figure 7

Forest plot of odds ratios of SIBO in diabetes patients compared with controls

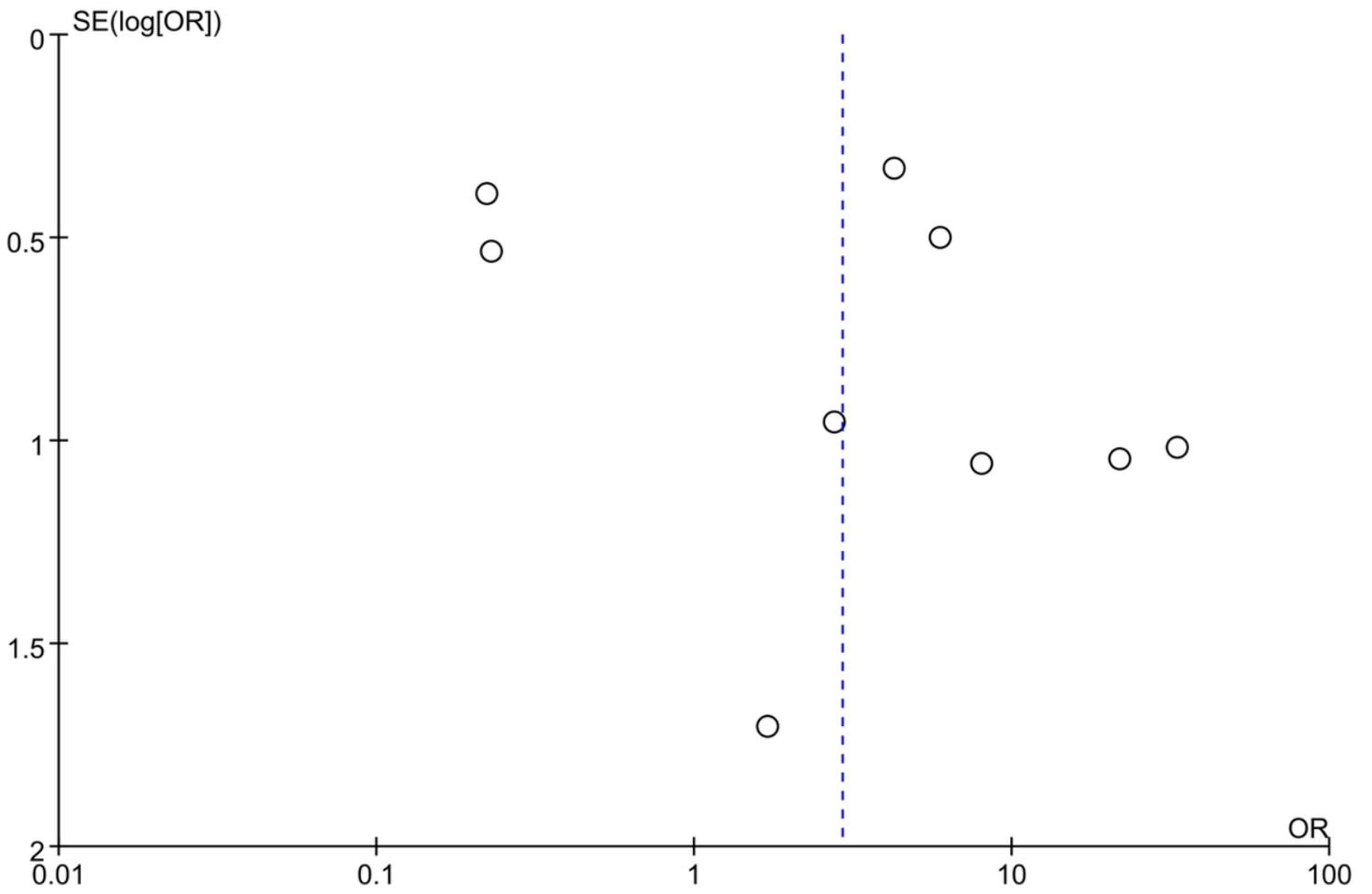


Figure 8

Funnel plot showing the publication bias of odds ratios of SIBO

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