

Reviewer #1: In this review, the authors want to discuss the epidemiology of SIBO in functional dyspepsia, irritable bowel syndrome, functional abdominal bloating, functional constipation and other diseases. The content of this review is interesting and comprehensive. However, this review also has a few of shortcomings.

1. Abstract is inconsistent with the title and text. The abstract wants to describe the association of SIBO with various diseases, but the title and text focus on epidemiology. In addition, the abstract logic is not clear and language is not refined enough.

Authors' response.

Dear reviewer, thank you very much for your suggestion. We edited the abstract: " Small intestinal bacterial overgrowth (SIBO) is defined as an increase in the bacterial content of the small intestine above normal values. The presence of SIBO is detected in 33.8% of patients with gastroenterological complaints who underwent a breath test, and is significantly associated with smoking, bloating, abdominal pain, and anemia. Proton pump inhibitor therapy is a significant risk factor for SIBO. The risk of SIBO increased with age and did not depend on gender or race. SIBO complicates the course of a number of diseases and may be of pathogenetic significance in the development of their symptoms. SIBO is significantly associated with functional dyspepsia, irritable bowel syndrome, functional abdominal bloating, functional constipation, functional diarrhea, short bowel syndrome, chronic intestinal pseudo-obstruction, lactase deficiency, diverticular and celiac diseases, ulcerative colitis, Crohn's disease, cirrhosis, metabolic-associated fatty liver disease (MAFLD), primary biliary cholangitis, gastroparesis, pancreatitis, cystic fibrosis, gallstone disease, diabetes, hypothyroidism, hyperlipidemia, acromegaly, multiple sclerosis, autism, Parkinson's disease, systemic sclerosis, spondylarthropathy, fibromyalgia, asthma, heart failure, and other diseases. The development of SIBO is often associated with a slowdown in orocecal transit time that decreases the normal clearance of bacteria from the small intestine. The slowdown of this transit may be due to motor dysfunction of the intestine in diseases of the gut, autonomic diabetic polyneuropathy, portal hypertension, or a decrease in the motor-stimulating influence of thyroid hormones. In a number of diseases, including cirrhosis, MAFLD, diabetes, and pancreatitis, an association was found between disease severity

and the presence of SIBO. Further work on the effect of SIBO eradication on the condition and prognosis of patients with various diseases is required.”

2. The article provides some descriptions of the connection between SIBO and other diseases, but these are somewhat superficial, the intensive relationship is recommended, including the putative pathophysiological mechanisms linking SIBO and different diseases, as well as the description of how they interact.

Authors’ response.

Dear reviewer, thank you very much for your suggestion. Since the causes of SIBO development in various diseases are very similar, we discuss them in the Conclusions section. In particular, we write about the impact of slowing down transit through the small intestine, which occurs in many of the described diseases and leads to SIBO, as well as changes in the anatomy of the gastrointestinal tract after operations on it, which also leads to the development of SIBO after them:

«For many diseases, the development of SIBO is associated with a slowdown in OCTT that decreases the normal clearance of bacteria from the small intestine and is one of the mechanisms underlying the development of SIBO. The slowdown of this transit may be associated with motor dysfunction of the intestine in diseases of the gut, autonomic diabetic polyneuropathy, portal hypertension, or a decrease in the motor-stimulating influence of thyroid hormones.»

“In a number of diseases, including cirrhosis, MAFLD, diabetes mellitus, pancreatitis, and cystic fibrosis, an association was found between disease severity and the presence of SIBO. This may be due to the fact that intestinal motility is more severely disturbed in more severe diseases (in cirrhosis or autonomic diabetic polyneuropathy) or that the digestive capabilities of the gut are more affected (in severe pancreatitis and cystic fibrosis) in these cases, which increases the nutrients available for bacteria of small intestine, leading to their excess growth.”

“Bariatric surgery and gastrectomy lead to a decrease in the barrier function of the stomach which prevents the colonization of the small intestine by oral microbiota. Colectomy leads to a decrease in the barrier function of the ileocecal valve, which prevents the colonization of the small intestine by the colon microbiota. This may explain the increased risk of SIBO following these surgeries. “

We also give a brief description of the gut-liver axis, through which SIBO can influence the course of liver cirrhosis and MAFLD:

“ However, in SIBO, the overgrown bacteria themselves can, through their metabolic products, affect the metabolism of lipids and carbohydrates, aggravating the course of diabetes^[168] and MAFLD^[169], and also, through bacterial translocation and systemic inflammation, aggravate the course of portal hypertension in cirrhosis^[170-172].”

We also provide references to the concept of gut-brain and gut-joint axes, which can explain the relationship between SIBO and diseases of the nervous system and joints.

“Interestingly, the frequency of SIBO is increased in a number of nervous and rheumatic diseases, which may support the existence of the gut-brain^[157-159] and gut-joint^[160-162] axes, suggesting that the products of gut microbiota metabolism can directly or indirectly affect emotional-cognitive and immune function^[163], predisposing individuals to the development of these diseases, which is well illustrated by the example of hepatic encephalopathy^[164,165] and reactive arthritis^[166-167].”

We absolutely agree with you that a detailed description of the pathogenetic relationships between SIBO and the diseases described in the review would be very useful for readers, and we wanted to do it initially, but then we realized that it would take too much space and make this already large article just huge. We believe that a thorough consideration of the role of SIBO in the pathogenesis of diseases of the intestines, liver, pancreas, joint, endocrine glands, nervous system and other organs requires separate detailed reviews, which we plan to prepare over time.

3. The authors lack insight into the problems with the current research on SIBO and different diseases, and it is suggested to add their own insights.

Authors' response.

Dear reviewer, thank you very much for your suggestion. We added to the Conclusions section:

“Since SIBO is associated with many diseases, even those not related to the intestines, it seems useful to continue studying the association of SIBO with other diseases and their manifestations. It is also important to clarify the pathogenetic ways in which the underlying disease can contribute to the development of SIBO, and SIBO, in turn, can have a negative effect on the course of the underlying disease. Currently, such studies are being conducted in cirrhosis^[72], MAFLD^[79-81], diabetes^[118,119], and other diseases. An

important question is how the course of the underlying disease will respond to SIBO treatment. These results have already been obtained for some diseases^[49,154], but their presentation is the aim for the next review.”

4. The format of the references is inconsistent; it is recommended that they should be modified. Therefore, a major revision is suggested.

Authors’ response.

Dear reviewer, thank you very much for your suggestion. References are made in accordance with the recommendations of the journal. We used Pubmed's electronic tools to generate these references and further edited it as recommended by the journal. When forming an edited version of the manuscript, the correctness of the references is additionally checked and corrected by the artificial intellect of the journal.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Gut microbiota plays an important role in maintaining health. Once organic or functional diseases occur, intestinal bacteria overgrow and the increase the number or variety of bacteria will induce abdominal pain, bloating, diarrhea, and malnutrition symptoms. The diagnosis of SIBO mostly depends on the clinical findings of doctors, who decide whether to conduct further tests, such as intestinal fluid culture and imaging examinations to verify the diagnosis. Such a diagnosis pattern potentiates many problems, however, this review did not address such issue. Major concern: 1. The author did not address the heterogeneity and susceptibility of SIBO. In some cases, although there is SIBO, it may not have significant harmful effects. There are no symptoms, or the symptoms are atypical. Patients do not seek medical attention in a timely manner or doctors do not detect it in a timely manner, resulting in the statistical prevalence of SIBO may be lower than the actual level. Some other studies report that the incidence of SIBO in the healthy population ranges from 2.5% to 22%;

Authors’ response.

Dear reviewer, thank you very much for your suggestion. We added to the Conclusions section:

« In addition, we have observed pronounced heterogeneity in the frequency of SIBO detection in healthy individuals within the control groups, which ranged from fractions of a percent to several tens of percent. The reason for this is yet to be established. However, the detection of SIBO in such a large number of clinically healthy individuals shows that this disorder can be relatively harmless and often asymptomatic.»

2. SIBO symptoms often overlap with other diseases and may be incorrectly diagnosed as IBS. The prevalence of SIBO among patients who meet the diagnostic criteria for IBS is 30% to 85%;

Authors' response.

Dear reviewer, thank you very much for your suggestion. We added to the Conclusions section:

« Some diseases, such as IBS, functional diarrhea, and functional constipation, can be mimicked by SIBO with the same symptoms. In these cases, it is not clear what disease is present: SIBO, which manifests itself as IBS and other functional bowel diseases, or these diseases, which are aggravated by the development of SIBO.»

3. Using hydrogen breath test alone cannot detect methanogenic SIBO, leading to missed diagnosis and reducing the detection rate of SIBO;

Authors' response.

Dear reviewer, thank you very much for your suggestion. We added in the Introduction section:

“In addition, while SIBO was initially associated with hydrogen release, it is now accepted that SIBO can also accompany the formation of methane. Methane SIBO and hydrogen SIBO are not only detected with different frequencies, but can also have different effects. It is important that the test for hydrogen SIBO does not detect methane SIBO and vice versa^[8,9].”

Also in the text, we focus the attention of readers on the frequency of detection of methane SIBO and its association with it as symptoms of the disease separately. For example, in the section on IBS, we write that:

“Separately, a meta-analysis of studies investigating methane SIBO in IBS was performed. It showed that the incidence of methane SIBO in patients with IBS was

25.0% (95%CI=18.8–32.4%), not significantly different from that in the control group (OR=1.2 [95%CI=0.8–1.7]). In patients with IBS, LBT provided positive results for methane SIBO almost three times as often as GBT (29.0% [95%CI=20.9–38.6%] *vs.* 11.5% [95%CI=5.0–24.3%]). In contrast with hydrogen SIBO, the prevalence of methane SIBO in patients with IBS-C was higher than in those with IBS-D (37.7% [95%CI=33.5–42.1%] *vs.* 12.4% [95%CI=10.2–14.9%]; OR=3.1 [95%CI=1.7–5.6])^[31].”

4. Age is an important risk factor for SIBO. The incidence rate of SIBO in different age groups is different. The prevalence of SIBO in the elderly is generally higher than that in other age groups.

Authors’ response.

Dear reviewer, thank you very much for your suggestion. We added:

“The risk of SIBO increased with age (OR=1.04 [95%CI=1.01–1.07])^[11] and did not depend on gender or race^[11,12].”

“The third meta-analysis revealed that among patients with IBS, female gender (OR=1.5 [95%CI=1.0–2.1]), older age (standard mean difference 3.1 years [95%CI=0.9–5.4]), and IBS-D (OR=1.7 [95%CI=1.3–2.3]) compared with other IBS subtypes increased the odds of SIBO^[30].”

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)**Conclusion:** Major revision

Specific Comments to Authors:

What are the new concepts that this study proposes?

Authors’ response.

Dear reviewer, thank you very much for your suggestion. We wrote in the Introduction section:

“The aim of this review is to provide up-to-date information on the association of SIBO with various diseases and their manifestations.”

Although many reviews have been published on SIBO, our review is the only one that comprehensively covers the epidemiology of SIBO based on recent research. How we wrote in the Conclusions section:

“In conclusion, we have summarized almost all published information on the association of SIBO with various diseases and their manifestations. Almost one third of cited studies were published within the last 2 years, highlighting the recent interest in the field and the importance of our review.”

What are the future directions of the topic described in this manuscript?

Dear reviewer, thank you very much for your suggestion. We wrote in the Conclusions section:

“However, further study on SIBO in various diseases, and particularly on the effect of its eradication on the condition and prognosis of patients, is required.”

Reviewer #4:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: It is not an interesting manuscript. Authors cannot succeed to present their idea in a clear way adding information to the existing literature.

Authors' response.

Dear Reviewer. We are very sorry that our manuscript did not seem interesting to you. However, we believe that it will be of great interest to readers for the following reasons. First, as we have shown in Figure 1, the number of publications on SIBO is constantly growing, which indicates a growing interest in this disorder. Secondly, despite the existence of reviews on SIBO, most of them are either devoted to this disorder in general, with only one or a couple of pages describing its epidemiology, or SIBO in a particular disease. Our review is the only one that comprehensively covers the epidemiology of SIBO based on recent research. In our article, we described the epidemiology of SIBO in more than 50 diseases, as well as the associated manifestations of these diseases, which have not yet been done in a single article ever. In addition, we provided a unique table that, based on the latest data and presented the incidence and OR of developing SIBO in these more than 50 diseases. Thus, our publication can be used as a reference with numerical data on this issue. Another advantage of our work was that almost one third of cited studies were published within the last 2 years, thus it represents significantly updated information compared to previous reviews.