Association of small intestinal bacterial overgrowth with nonalcoholic fatty liver disease in children: A meta-analysis

Linghan Kuang, Wei Zhou, Yongmei Jiang

1 Department of Laboratory Medicine, West China Second University Hospital, Sichuan University, Chengdu, China, 2 Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China

* jym85501201@163.com

Abstract

It has been suggested that small intestinal bacterial overgrowth (SIBO) could cause nonalcoholic fatty liver disease (NAFLD), but this association was not examined in children by meta-analysis. This meta-analysis aimed to determine the association between SIBO and NAFLD in children. The electronic databases PubMed, Embase, and Cochrane Library were searched for studies published before April 22, 2021. The outcome was the association between SIBO and NAFLD. Three studies and 205 children were included. All three studies reported the association between SIBO and NAFLD. Children with SIBO were more likely to have NAFLD (odds ratio = 5.27, 95% confidence interval (CI): 1.66–16.68, P < 0.001; I² = 63.5%, P_heterogeneity = 0.065). When directly pooling the reported relative risks (RR) from two studies, children with NAFLD had an over 2-fold increased relative risk of developing SIBO (RR = 2.17, 05%CI: 1.66–2.82, P < 0.001; I² = 0.0%, P_heterogeneity = 0.837). This meta-analysis reports a possible association between SIBO and NAFLD in children.

Introduction

Nonalcoholic fatty liver disease (NAFLD) results from pathophysiological fatty liver changes unrelated to alcohol intake [1]. Histologic progression from steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis does not always correlate with clinical progression, especially in the early stages [1]. The causes of NAFLD include insulin resistance, obesity, weight gain, and diabetes [2]. The worldwide prevalence of obesity is 5.6% in girls and 7.8% in boys of 5–19 years of age, but the prevalence is >20% in many countries [3]. In addition, the prevalence of NAFLD is 7.6% in children [4].

The small intestinal bacterial overgrowth (SIBO) syndrome is a nutrient malabsorption condition associated with an excessive number of bacteria in the proximal small intestine [5, 6]. SIBO is often associated with bloating, pain, gas, and diarrhea [5, 6]. Predisposing factors for developing the SIBO syndrome include disorders of the protective antibacterial mechanisms, anatomic disorders such as blind loop or short bowel syndromes, and motility disorders [7]. The symptoms can be secondary to an underlying disease or due to the effects of toxic...
bacterial metabolites or nutritional complications such as fat malabsorption and vitamin deficiencies [7]. Its prevalence is unknown because of the non-specific symptoms of variable intensity (sometimes asymptomatic) that overlap with other diseases such as irritable bowel syndrome and inflammatory bowel disease [7].

According to recent epidemiologic studies, SIBO could be another risk factor for NAFLD [8–17]. The exact mechanisms linking SIBO and NAFLD are unknown but could involve increased intestinal permeability and bacterial toxins. Those toxins can trigger a low-grade inflammatory state that promotes insulin resistance and NAFLD [18–20]. In addition, endogenous ethanol production by the microbiota could predispose to NAFLD through lipid accumulation in the liver, oxidative stress, and gastrointestinal abnormalities allowing the passage of toxins through the gut liver axis [21, 22]. The gut microbiota can also cause choline deficiency, and choline is necessary for the secretion of very-low-density lipoproteins (VLDL), leading to triglyceride accumulation in the liver [23, 24].

A recent meta-analysis showed that there was a significant association between NAFLD and SIBO [27], but this meta-analysis included studies of patients of all age groups. Considering the epidemics of obesity in children and the prevalence of NAFLD in children, examining the association between NAFLD and SIBO in this age group is clinically relevant, especially in the context where SIBO is a manageable condition [5, 6, 28]. Therefore, the present meta-analysis aimed to determine the association between SIBO and NAFLD in children.

**Material and methods**

**Literature search**

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [29]. Since no original clinical raw data was collected or utilized, ethical approval was not required for this meta-analysis.

The eligibility criteria were 1) patients: children with obesity/overweight, 2) exposure: SIBO, 3) outcome: NAFLD, 4) study design: no limitation, and 5) full text published in English. The electronic databases PubMed, Embase, and Cochrane Library were searched for studies published before April 22, 2021, using the MeSH terms “Pediatric Obesity” and “small intestinal bacterial overgrowth” combined with relevant key words (S1 File). The reference lists of the retrieved articles were searched for additional potentially eligible studies.

**Data extraction and quality assessment**

Potentially relevant publications were screened and evaluated independently by two reviewers (LH,K and W,Z), with a third reviewer (YM,J) resolving any disagreement and confirming data extraction. A structured data collection sheet was developed. Two researchers independently extracted data, including authors, year of publication, country, study design, sample size, age, percentage of males, and the diagnostic criteria of NAFLD and SIBO. The observational studies were evaluated according to the Newcastle-Ottawa scale (NOS) [30]. For cohort studies, the NOS evaluates the representativeness of the exposed cohort (2 points), the selection of the non-exposed cohort (1 point), the ascertainment of exposure (2 points), the demonstration that the outcome of interest was not present at the start of the study (1 point), the comparability of cohorts on the basis of the design or analysis (2 points), the assessment of the outcome (2 points), whether follow-up long enough for outcomes to occur (1 point), and the adequacy of follow up of cohorts (2 points). For case-control studies, the NOS evaluates the adequacy of the case definition (2 points), the representativeness of the cases (1 point), the selection of controls (2 points), the definition of controls (1 point), the comparability of cases
and controls on the basis of the design or analysis (2 points), the ascertainment of intervention (2 points), the same method of ascertainment for cases and controls (1 point), and the non-response rate (2 points). The maximum score is 9 points. A study is considered of good quality when having 3–4 points in the selection domain (items 1–4) and 1–2 points in the comparability domain (item 5), and 2–3 stars in the outcome/exposure domain (items 6–8) [30].

Statistical analysis
All analyses were performed using STATA MP 14.0 (StataCorp, College Station, Texas, USA). Odds ratios (ORs) with 95% confidence intervals (CIs) were combined for statistical analysis. Statistical heterogeneity among studies was calculated using Cochran’s Q-test and the I² index. An I² >50% and a Q-test P<0.10 indicated high heterogeneity, and the random-effects model was used; otherwise, the fixed-effects model was applied. P-values <0.05 were considered statistically different. Potential publication bias was not assessed due to too few studies being included [31].

Results
Selection of the studies
Twenty-seven records were retrieved from the databases (PubMed, n = 13; Embase, n = 9), and 20 records were left after removing the duplicates. Ten records were excluded after assessing the titles (one was a letter, four were conference abstracts, and five were reviews), and ten full-text papers were assessed. Seven were excluded because of study aim/design (n = 3; the objective was not related to the present meta-analysis), population (n = 3; those studies only included adults, not children), and because of duplicate study populations (n = 1) (Fig 1).

Finally, three studies were included [32–34] (Table 1). The three studies included 205 children. The mean age ranged 10.8–14.2 years, and 62.4% were boys. There were two case-control studies [32, 34] and one cohort study [33]. The cohort study [33] scored 7 on the NOS, and the two case-control studies [32, 34] scored 8 on the NOS (S1 Table).

Association between SIBO and NAFLD in children
All three studies [32–34] reported the association between SIBO and NAFLD. Children with SIBO were more likely to have NAFLD (OR = 5.27, 95%CI: 1.66–16.68, P = 0.005) (Fig 2). Moderate heterogeneity was observed (I² = 63.5%, P_heterogeneity = 0.065).

Risk of SIBO in children with NAFLD
When directly pooling the reported relative risks (RR) from two studies [33, 34], children with NAFLD had over 2-fold increased relative risk of developing SIBO (RR = 2.17, 95%CI: 1.54–2.81, P<0.001) (Fig 3). No heterogeneity was observed (I² = 0.0%, P_heterogeneity = 0.857).

Sensitivity analysis
The sensitivity analysis indicated that none of the three studies influenced the outcome (Fig 4).

Discussion
It has been suggested that SIBO could be a cause of NAFLD [8–17], but this association was not examined in children by meta-analysis. Therefore, this meta-analysis was performed to determine the association between SIBO and NAFLD in children. The results indicate a
significant association between SIBO and NAFLD in children. This is supported by a meta-analysis of ten studies, irrespective of patients' age [27].

Biologically, the explanation for this association is currently unknown. Nevertheless, some hypotheses are being explored. Intestinal leakage might be a major culprit because of the dysregulated tight junctions observed in SIBO [11, 35]. Impaired tight junctions will allow bacterial products such as endotoxins (including lipopolysaccharides (LPS) and unmethylated DNA
sequences) to enter the circulation, causing a low-grade systemic inflammatory reaction [36]. Low-grade endotoxemia in SIBO will activate the TLR-4 and CD14 receptors, which will activate the NF-κB pathway and lead to the expression of inflammatory cytokines [8, 36]. These inflammatory cytokines can directly participate in the pathogenesis of NASH [37], insulin resistance, and hepatic fibrosis [8, 38–40]. The chronic inflammatory state can lead to dysregulated lipid storage in the adipose tissue and insulin resistance [41, 42].

Other possible mechanisms for the development of NAFLD in SIBO include the production of ethanol as a bacterial metabolic byproduct, leading to the hepatic accumulation of triglycerides and oxidative stress, and mucosal abnormalities that facilitate the entry of toxins into the

Table 1. Characteristics of the included studies.

| Author, Year | Troisi, 2017 [32] | Belei, 2017 [33] | Stepanov, 2019 [34] |
|--------------|------------------|-----------------|-------------------|
| Country      | Italy            | Romania         | Ukraine           |
| Study type   | Case-control study | Cohort study   | Case-control study |
| Sample size (n) | 22               | 125             | 58                |
| Without SIBO (n) | 10               | 78              | 28                |
| SIBO (n)     | 12               | 47              | 30                |
| Without SIBO age (years) | 11.6±2.1 (not reported according to SIBO) | 14.2 ± 2.2 | 10.8±2.8 |
| SIBO age (years) | 15.5 ± 2.4     | 11.8 ± 2.7      |
| Without SIBO F/M | 9/13           | 27/51           | 11/17             |
| SIBO F/M     | 18/29           | 12/18           |
| Without SIBO BMI | 27.6±4.6 (not reported according to SIBO) | 27.4 ± 3.1 | 24.4±3.8 |
| SIBO BMI     | 27.9 ± 3.1      | 24.4±3.8        |

Diagnostic criterion of NAFLD

- Children with ultrasonographic bright liver ± hypertransaminasemia underwent transaminase retesting, creatine phosphokinase determination, and laboratory exclusion of the most frequent causes of pediatric liver disease other than NAFLD (autoimmune hepatitis, Wilson disease, celiac disease, alpha-antitrypsin deficiency, viral hepatitis A, B, and C, Cytomegalovirus, and Epstein Barr virus).
- The diagnosis of NAFLD was made according to the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines based on abdominal imaging methods.
- Diagnosis of NAFLD was established according to CAP and exclusion of secondary steatosis in children with overweight/obesity.

Diagnostic criteria of SIBO

- Small intestinal bacterial overgrowth was identified using a hydrogen breath test (H2BT) apparatus. H2 basal values >40 ppm or an increase of 20 ppm over baseline within the first 120 min were considered suggestive of SIBO.
- The diagnosis of SIBO was based on a positive GHBT.
- The diagnosis of SIBO was determined from GHBT and data using the Gastro+Gastrolyzer gas analyzer.

Inclusion/exclusion criteria

- The inclusion criteria were 1) age between 5 and 16 years, 2) normal weight (BMI from the 25th to 85th percentile), 3) obese (BMI >95th percentile), and 4) absence of acute intercurrent or chronic illness.
- The inclusion criteria were 1) consecutive overweight and obese children and adolescents, and 2) aged 10–18 years old with BMI between the 85th and 95th percentile and >95th percentile, respectively.
- The exclusion criteria were 1) children diagnosed with different liver disorders caused by other conditions than NAFLD (infectious hepatitis, autoimmune hepatitis, drug-induced liver injuries, Wilson’s disease, hemochromatosis, celiac disease, mucoviscidosis, alpha-antitrypsin deficiency) or 2) adolescents with a history of alcohol intake.

SIBO: small intestinal bacterial overgrowth; NAFLD: nonalcoholic fatty liver disease; GHBT: glucose hydrogen breath test.

https://doi.org/10.1371/journal.pone.0260479.t001
The intestinal bacteria also produce short-chain fatty acids (SCFAs) that will reduce intestinal motility, increase the absorption of bacterial products [43] and participate in dysregulated glucose metabolism [40, 44, 45]. In addition, the overpopulation of bacteria in the small intestine will lead to the catabolism of choline by the bacteria, preventing its absorption. Choline is required for the secretion of VLDL particles by the liver, and impaired VLDL secretion will prevent the liver from exporting exogenous and endogenous lipids and will lead to hepatic lipid accumulation, steatosis, and NAFLD [23–26].

In fact, the mechanisms of SIBO are poorly understood. The pathogenesis of SIBO includes disorders of the protective antimicrobial mechanisms (achlorhydria, pancreatic exocrine insufficiency, and immunodeficiency syndromes), anatomical abnormalities (stricture, diverticula, fistulae, surgical blind loop, and previous ileocecal resections), motility disorders (secondary to systemic sclerosis, autonomic neuropathy, postradiation enteropathy, and small intestinal pseudoobstruction), and the long-term use of proton pump inhibitors [7]. In addition, SIBO involves multiple strains of bacteria, and the exact proportions might vary among individuals [46]. Still, which mechanisms are responsible for SIBO specifically in children is unknown. In addition, the causes of SIBO in the included studies were not reported. Furthermore, SIBO is a heterogeneous condition with variable clinical presentation and variable microorganisms involved [5–7], resulting in different rates of progression of NAFLD in different patients. The traditional model of NAFLD development is the two-hit model, but current evidence and hypotheses suggest that it is likely that the various mechanisms involved in NAFLD, including

Fig 2. Forest plot of NAFLD.

https://doi.org/10.1371/journal.pone.0260479.g002
SIBO, participate in parallel to the development of NAFLD but with different proportions of involvement in different individuals [36, 47, 48]. Additional studies are necessary to examine the causes and mechanisms of SIBO in the pathogenesis of NAFLD.

The management of SIBO involves the treatment of the underlying diseases or abnormalities, eradicating bacterial overgrowth, and maintenance of remission [6, 7, 28], and correcting vitamin B12 deficiency and other associated nutritional deficiencies [6, 7, 28]. The options for eradicating bacterial overgrowth (induction of remission) include antibiotics to selectively target bacterial strains causing SIBO syndrome if possible (e.g., rifaximin 1200 or 1600 mg/day for 7–10 days as one treatment course or as cyclic therapy [49]; other options include tetracycline, neomycin, norfloxacin, amoxicillin/clavulanate, or erythromycin) [6, 7, 28]. Other treatment options, but with limited evidence, include a 14-day elemental diet, which is reported to normalize lactulose breath tests in patients with irritable bowel syndrome and abnormal lactose breath test, use of prokinetics for motility-associated SIBO syndrome, and probiotic therapies [6, 7, 28, 50]. The strategies for maintenance of remission include watchful observation and the use of promotility medication [6, 7, 28]. Still, the antibiotics used in the management of SIBO, especially repeated exposure, can have a potential impact on NAFLD. Studies showed that alterations in the gut microbiota drive the progression of NAFLD and that targeting the gut microbiota using probiotics [51] or antibiotics [52, 53] can slow the progression of NAFLD. Therefore, the relationship between SIBO and NAFLD is probably affected by the treatments undertaken in the patients. Furthermore, there is a risk of liver injury in patients with repeated antibiotic exposure [54–56] that could mimic the inflammatory changes.

![Fig 3. Forest plot of NAFLD (pooled from RR and 95%CI directly).](https://doi.org/10.1371/journal.pone.0260479.g003)
observed in NAFLD [57]. Unfortunately, a major limitation of the present meta-analysis is that the included studies present very limited information about past treatments in their patients. Therefore, this issue remains unsolved and will have to be examined in future studies.

A meta-analysis is limited by the included studies. The study by Troisi et al. [32] was designed to analyze the urinary metabolomic of gut liver axis abnormalities. They diagnosed SIBO using a hydrogen breath test (H2BT) apparatus. H2 basal values >40 ppm or an increase of 20 ppm over the baseline within the first 120 min were considered suggestive of SIBO. The study by Belei et al. [33] directly examined the association between SIBO and the risk of developing NAFLD in children. SIBO was diagnosed using the glucose hydrogen test. In Stepanov et al. [34], the association between SIBO and obesity and overweight was examined in children. The diagnosis of SIBO was determined using the glucose hydrogen breath test and Gastro+Gastrolyzer gas analyzer. Although all studies used hydrogen production to diagnose SIBO, different methods have different sensitivity and specificity [58, 59]. Still, SIBO can be caused by non-hydrogen-producing bacteria, and such tests would yield false-negative results [58, 59]. Future studies should use reliable and comprehensive diagnostic methods for SIBO.

Nevertheless, SIBO is a manageable condition [5, 6, 28]. Since the present study reported an association between SIBO and NAFLD, managing SIBO might be a target to prevent NAFLD development and progression in children. Developing NAFLD during childhood carries a potentially worst prognosis than developing it during adulthood, and managing NAFLD as early as possible should yield a better prognosis [60–62]. The world is currently seeing
epidemics of childhood obesity [63]. Screening for and managing SIBO, especially in obese children, could be a way to prevent childhood NAFLD. Indeed, although NAFLD is multifactorial and depends upon BMI [4], not all obese children will develop NAFLD, and some non-obese children can also develop NAFLD. Since SIBO is preventable, it could be targeted to prevent NAFLD and its morbidity in adulthood. The use of antibiotics, prebiotics, probiotics, and synbiotics could be explored in the future [64–66].

This meta-analysis has limitations. Only observational studies were included, and their sample size was generally small, resulting in a small number of patients that could be included. The estimates were non-adjusted, preventing the accurate determination of the ORs and RRs. The studies used different diagnostic methods. Some of those methods are known to be less reliable than others [58, 67], and it is possible that some studies missed some children who should have been included. The use of different diagnostic methods, different study designs, and different study populations resulted in heterogeneity, which could affect the conclusions. It was also unclear whether the criteria for SIBO were the same among the four studies, especially for the study by Belei et al. [33]. Obesity is a strong confounder of NAFLD, and it is not clear if SIBO alone affects both obesity and NAFLD or SIBO affects obesity resulting in NAFLD development. Unfortunately, the small number of studies and patients included in this meta-analysis prevented the inclusion of only normal-weight children with SIBO. Most of all, the present meta-analysis highlights the lack of data regarding the association between SIBO and NAFLD in children.

Conclusions
In conclusion, the present meta-analysis determined that there might be an association between NAFLD and SIBO in children. Importantly, this meta-analysis highlights the lack of data available about SIBO and NAFLD in children. Still, this meta-analysis is hypothesis-generating and highlights the lack of data available in children on this topic. Future studies should explore the mechanisms linking SIBO and NAFLD and examine whether treating SIBO could prevent NAFLD in children. Future trials should be designed with the aim of exploring the causality relationship between SIBO and NAFLD and improving the diagnosis of SIBO. Standardized diagnostic criteria should be formulated for SIBO by an authoritative organization.

Supporting information
S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Table. Quality assessment of included studies based on NOS.
(DOCX)

S1 File. Electronic search strategy of PubMed.
(DOCX)

Author Contributions
Conceptualization: Linghan Kuang, Yongmei Jiang.
Data curation: Linghan Kuang, Wei Zhou.
Formal analysis: Linghan Kuang, Wei Zhou, Yongmei Jiang.
Funding acquisition: Yongmei Jiang.
Project administration: Yongmei Jiang.
Writing – original draft: Linghan Kuang.
Writing – review & editing: Wei Zhou, Yongmei Jiang.

References

1. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. Jama. 2015; 313(22):2263–73. https://doi.org/10.1001/jama.2015.5370 PMID: 26057287.

2. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology. 2012; 142(7):1592–609. https://doi.org/10.1053/j.gastro.2012.04.001 PMID: 22656328.

3. Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017; 390(10113):2627–42. https://doi.org/10.1016/S0140-6736(17)32129-3 PMID: 29029897; PubMed Central PMCID: PMC5735219.

4. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. PloS one. 2015; 10(10):e0140908. https://doi.org/10.1371/journal.pone.0140908 PMID: 26512983; PubMed Central PMCID: PMC4626023.

5. Rana SV, Bhardwaj SB. Small intestinal bacterial overgrowth. Scandinavian journal of gastroenterology. 2008; 43(9):1030–7. https://doi.org/10.1080/00365520801947074 PMID: 18609165.

6. Rezaie A, Pimentel M, Rao SS. How to Test and Treat Small Intestinal Bacterial Overgrowth: an Evidence-Based Approach. Current gastroenterology reports. 2016; 18(2):8. https://doi.org/10.1007/s11894-015-0482-9 PMID: 26780631.

7. Bures J, Cynary J, Kohoutova D, Forsti M, Rejhr S, Kvetina J, et al. Small intestinal bacterial overgrowth syndrome. World journal of gastroenterology. 2010; 16(24):2978–90. https://doi.org/10.3748/wjg.v16.i24.2978 PMID: 20572300; PubMed Central PMCID:PMC2890937.

8. Fialho A, Fialho A, Thota P, McCullough AJ, Shen B. Small Intestinal Bacterial Overgrowth Is Associated with Non-Alcoholic Fatty Liver Disease. Journal of gastrointestinal and liver diseases: JGLD. 2016; 25(2):159–65. https://doi.org/10.15403/jgld.2014.1121.252.lw g PMID: 27308646.

9. Ghoshal UC, Baba CS, Ghoshal U, Alexander G, Misra A, Saraswat VA, et al. Low-grade small intestinal bacterial overgrowth is common in patients with non-alcoholic steatohepatitis on quantitative jejunal aspirate culture. Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology. 2017; 36(5):390–9. https://doi.org/10.1007/s12664-017-0797-6 PMID: 29034439.

10. Lei Q, Yang L, Wang E, Chen D. The value of hydrogen and methane breath test to detect SIBO on exploring the role of intestinal flora in the incidence of nonalcoholic fatty liver disease. J Dig Dis. 2016; 17(Suppl 1):13–112.

11. Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology. 2009; 49(6):1877–87. https://doi.org/10.1002/hep.22848 PMID: 19291785.

12. Mohamed BSJ, Runkana A, Alhaddad R, Shatnawewu A. Characterization of patients undergoing breath testing for small intestinal bacterial overgrowth (SIBO). Am J Gastroenterol. 2015; 110(Suppl 1):S988–S9.

13. Nongthombam SNB, Kumar A, Roy N, Sachdev V, SHhalimar Acharya S. Prevalence of small intestinal bacterial overgrowth (SIBO) and insulin resistance in both obese and non obese non-alcoholic fatty liver disease (NAFLD) patients. J Clin Exp Hepatol. 2015; 5(Suppl 2):S23–S4.

14. Sajjad A, Motterhead M, Syn WK, Jones R, Smith S, Nwokolu CU. Ciprofloxacin suppresses bacterial overgrowth, increases fasting insulin but does not correct low acylated ghrelin concentration in non-alcoholic steatohepatitis. Alimentary pharmacology & therapeutics. 2005; 22(4):291–9. https://doi.org/10.1111/j.1365-2036.2005.02562.x PMID: 16097995.

15. Shanab AA, Scully P, Crosbie O, Buckley M, O’Mahony L, Shanahan F, et al. Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8. Digestive diseases and sciences. 2011; 56(5):1524–34. https://doi.org/10.1007/s10620-010-1447-3 PMID: 21046243.

16. Volynets V, Kuper MA, Strahl S, Maier IB, Spruss A, Wagnerberger S, et al. Nutrition, intestinal permeability, and blood ethanol levels are altered in patients with nonalcoholic fatty liver disease (NAFLD).
Digestive diseases and sciences. 2012; 57(7):1932–41. https://doi.org/10.1007/s10620-012-2112-9 PMID: 22427130.

17. Wigg AJ, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG. The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis. Gut. 2001; 48(2):206–11. https://doi.org/10.1136/gut.48.2.206 PMID: 1156641; PubMed Central PMCID: PMC1728215.

18. Brandt A, Jin CJ, Nolte K, Sellmann C, Engstler AJ, Bergheim I. Short-Term Intake of a Fructose-, Fat- and Cholesterol-Rich Diet Causes Hepatic Steatosis in Mice: Effect of Antibiotic Treatment. Nutrients. 2017; 9(9). https://doi.org/10.3390/nu9091013 PMID: 28906444; PubMed Central PMCID: PMC5622773.

19. Creely SJ, McTernan PG, Kusminski CM, Fisher f M, Da Silva NF, Khanolkar M, et al. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. American journal of physiology Endocrinology and metabolism. 2007; 292(3):E740–7. https://doi. org/10.1152/ajpendo.00302.2006 PMID: 17090751.

20. Rorato R, Borges BC, Uchoa ET, Antunes-Rodrigues J, Elias CF, Elias LLK. LPS-Induced Low-Gra d Inflammation Increases Hypothalamic JNK Expression and Causes Central Insulin Resistance Ir irrelevant of Body Weight Changes. International journal of molecular sciences. 2017; 18(7). https://doi. org/10.3390/jms18071431 PMID: 28677618; PubMed Central PMCID: PMC5535922.

21. Masarone M, Rosato V, Dallio M, Gravina AG, Agli tti A, Loguercio C, et al. Role of Oxidative Stress in Pathophysiology of Nonalcoholic Fatty Liver Disease. Oxidative medicine and cellular longevity. 2018; 2018:5947613. https://doi.org/10.1155/2018/5947613 PMID: 29991976; PubMed Central PMCID: PMC6016172.

22. Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, et al. Characterization of gut microbiomes in non-alcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology. 2013; 57(2):601–9. https://doi.org/10.1002/hep.26093 PMID: 23055147.

23. Dumas ME, Barton RH, Toye A, Cloarec O, Blan cher C, Rothwell A, et al. Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103(33):12511–6. https://doi.org/10.1073/pnas.0601056103 PMID: 16895997; PubMed Central PMCID: PMC1567909.

24. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. Gastroenterology. 2014; 146(6):1513–24. https://doi.org/10.1053/j.gastro.2014.01.020 PMID: 24440671; PubMed Central PMCID: PMC3996054.

25. Buchman AL, Dubin MD, Moukarzel AA, Jend en DJ, Roch M, Rice KM, et al. Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. Hepatology. 1995; 22(5):1399–403. PMID: 7590654.

26. Jin X, Yu CH, Li YM. Increased intestinal permeability in pathogenesis and progress of nonalcoholic steatohepatitis in rats. World journal of gastroenterology. 2007; 13(11):1732–6. https://doi.org/10.3748/wjg.v13.i11.1732 PMID: 17461479; PubMed Central PMCID: PMC4146951.

27. Wijarnpreecha K, Lou S, Watthanasu nton K, Kroner PT, Cheungpasitporn W, Lukens FJ, et al. Small intestinal bacterial overgrowth and nonalcoholic fatty liver disease: a systematic review and meta-analysis. European journal of gastroenterology & hepatology. 2020; 32(5):601–8. https://doi.org/10.1097/MEG.0000000000001541 PMID: 31567712.

28. Ponziani FR, Gerardi V, Gasbarrini A. Diagnosis and treatment of small intestinal bacterial overgrowth. Expert review of gastroenterology & hepatology. 2016; 10(2):215–27. https://doi.org/10.1586/14772558.2016.1097133.

29. Selcuk AA. A Guide for Systematic Reviews: PRISMA. Turkish archives of otorhinolaryngology. 2019; 57(1):57–8. https://doi.org/10.5152/tao.2019.4058 PMID: 31049257; PubMed Central PMCID: PMC6461330.

30. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers’ to authors’ assessments. BMC medical research methodology. 2014; 14:45. https://doi.org/10.1186/1471-2288-14-45 PMID: 24690082; PubMed Central PMCID: PMC4021422.

31. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2017). London: Cochrane Collaboration; 2019.

32. Troisi J, Pierri L, Landolfi A, Marciano F, Bisogn o A, Belmonte F, et al. Urinary Metabolomics in Pediatric Obesity and NAFLD Identifies Metabolic Pathways/Metabolites Related to Dietary Habits and Gut-Liver Axis Perturbations. Nutrients. 2017; 9(5). https://doi.org/10.3390/nu9050485 PMID: 28492501; PubMed Central PMCID: PMC5452215.

33. Belei O, Olariu L, Dobrescu A, Marcovici T, Marginean O. The relationship between non-alcoholic fatty liver disease and small intestinal bacterial overgrowth among overweight and obese children and
adolescents. Journal of pediatric endocrinology & metabolism: JPEM. 2017; 30(11):1161–8. https://doi.
org/10.1515/jpep-2017-0252 PMID: 28988228.

34. Stepanov YM, Zavhorodnia NY, Lukianenko OY, Zygalov EV, Yagmur VB. Association of small intestinal bacterial overgrowth and non-alcoholic fatty liver disease in children. Gastroenterolog. 2019; 53 (4):266–72.

35. Ferolla SM, Armiliato GN, Couto CA, Ferrari TC. The role of intestinal bacteria overgrowth in obesity-related nonalcoholic fatty liver disease. Nutrients. 2014; 6(12):5583–99. https://doi.org/10.3390
nu6125583 PMID: 25479248; PubMed Central PMCID: PMC4276985.

36. Augustyn M, Gris I, Kukia M. Small intestinal bacterial overgrowth and nonalcoholic fatty liver disease. Clinical and experimental hepatology. 2019; 5(1):1–10. https://doi.org/10.5114/ceh.2019.83151 PMID: 30915401; PubMed Central PMCID: PMC6431096.

37. Kapil S, Duseja A, Sharma BK, Singla B, Chakraborti A, Das A, et al. Small intestinal bacterial overgrowth and toll-like receptor signaling in patients with non-alcoholic fatty liver disease. Journal of gastroenterology and hepatology. 2016; 31(1):213–21. https://doi.org/10.1111/jgh.13058 PMID: 26212089.

38. Majewska M, Szczepanik M. [The role of Toll-like receptors (TLR) in innate and adaptive immune responses and their function in immune response regulation]. Postepy higieny i medycyny doświadczal
nej, 2006; 60;52–63. PMID: 16474276.

39. Marra F, Lotersztajn S. Pathophysiology of NASH: perspectives for a targeted treatment. Current pharmaceutical design. 2013; 19(29):5250–69. https://doi.org/10.2174/13816128113199990344 PMID: 23394092; PubMed Central PMCID: PMC3984586.

40. Marra F, Svegliati-Baroni G. Lipotoxicity and the gut-liver axis in NASH pathogenesis. Journal of hepatology. 2018; 68(2):280–95. https://doi.org/10.1016/j.jhep.2017.11.014 PMID: 29154964.

41. Ota T. Obesity-induced inflammation and insulin resistance. Frontiers in endocrinology. 2014; 5:204. https://doi.org/10.3389/fendo.2014.00204 PMID: 25538683; PubMed Central PMCID: PMC4255620.

42. Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. The Journal of clinical investigation. 2017; 127(1):43–54. https://doi.org/10.1172/JCI88880 PMID: 28045398; PubMed Central PMCID: PMC5199705 Sanofi-Synthelabo, and has a provisional patent (no. 61721475 entitled “Biomarkers to improve prediction of heart failure risk,” filed by Baylor College of Medicine and Roche.

43. de Faria Ghetti F, Oliveira DG, de Oliveira JM, de Castro Ferreira L, Cesar DE, Moreira APB. Influence of gut microbiota on the development and progression of nonalcoholic steatohepatitis. European journal of nutrition. 2018; 57(3):861–76. https://doi.org/10.1007/s00394-017-1524-x PMID: 28875318.

44. Zhu L, Baker RD, Baker SS. Gut microbiome and nonalcoholic fatty liver diseases. Pediatric research. 2015; 77(1–2):245–51. https://doi.org/10.1038/pr.2014.157 PMID: 25310763.

45. Riviere A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteri a and Butyrate -Producing Colon Bacte-
ria: Importance and Strategies for Their Stimulation in the Huma n Gut. Frontiers in microbiology. 2016;
68(2):2015.12.012 PMID: 26823198.

46. Bouhnik Y, Alain S, Attar A, Flourie B, Raskine L, Sanson-Le Pors MJ, et al. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol. 1999; 94(5):1327 –31. Epub 1999/05/11. https://doi.org/10.1111/j.1572-0241 .1999.01016. x

47. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholi c fatty liver disease (NAFLD). Metabolism: clinical and experimental. 2016; 65(8):1038–48. https://doi.org/10.1016/j.
m metab.2015.12.012 PMID: 26823198.

48. Gatta L, Scarpignato C. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. Alimentary pharmacology & therapeutics. 2017; 45 (5):604–16. Epub 2017/01/13. https://doi.org/10.1111/apt.13928 PMID: 28078798; PubMed Central PMCID: PMC5299503.

49. Zhong C, Qu C, Wang B, Liang S, Zeng B. Probiotics for Preventing and Treating Small Intestinal Bacterial Overgrowth: A Meta-Analysis and Systematic Review of Current Evidence. J Clin Gastroenterol. 2017; 51(4):300–11. Epub 2017/03/08. https://doi.org/10.1097/MCG.0000000000000814 PMID: 28267052.

50. Zhou Y, Zheng T, Chen H, Li Y, Huang H, Chen W, et al. Microbial Intervention as a Novel Target in Treatment of Non-Alcoholic Fatty Liver Disease Progression. Cell Physiol Biochem. 2018; 51(5):2123–35. Epub 2018/12/07. https://doi.org/10.1159/000495830 PMID: 30522122.
52. Grabherr F, Grander C, Effgenberger M, Adolph TE, Tilg H. Gut Dysfunction and Non-alcoholic Fatty Liver Disease. Frontiers in endocrinology. 2019; 10:611. Epub 2019/09/27. https://doi.org/10.3389/fendo.2019.00611 PMID: 31555219; PubMed Central PMCID: PMC6742654.

53. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology. 2010; 52(5):1836–46. Epub 2010/11/03. https://doi.org/10.1002/hep.24001 PMID: 21038418.

54. Ferrajolo C, Verhamme KM, Trifiro G, t Jong GW, Picelli G, Giaquinto C, et al. Antibiotic-Induced Liver Injury in Paediatric Outpatients: A Case-Control Study in Primary Care Databases. Drug Saf. 2017; 40(4):305–15. Epub 2016/12/28. https://doi.org/10.1002/dra.20464 PMID: 28025733; PubMed Central PMCID: PMC5362651.

55. Lim R, Choudry H, Conner K, Karnsakul W. A challenge for diagnosing acute liver injury with concomitant/sequential exposure to multiple drugs: can causality assessment scales be utilized to identify the offending drug? Case Rep Pediatr. 2014; 2014:156389. Epub 2014/12/17. https://doi.org/10.1155/2014/156389 PMID: 25506455; PubMed Central PMCID: PMC3112029.

56. Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother. 2011; 66(7):1431–46. Epub 2011/05/19. https://doi.org/10.1111/j.1365-2958.2011.05685.x PMID: 21860825; PubMed Central PMCID: PMC3155069.

57. Ghoshal UC. How to interpret hydrogen breath tests. Journal of neurogastroenterology and motility. 2011; 17(3):312–7. https://doi.org/10.5056/jnm.2011.17.3.312 PMID: 21860825; PubMed Central PMCID: PMC3155069.

58. Simren M, Stotzer PO. Use and abuse of hydrogen breath tests. Gut. 2006; 55(3):297–303. Epub 2006/02/14. https://doi.org/10.1136/gut.2005.075127 PMID: 16474100; PubMed Central PMCID: PMC1856094.

59. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). Journal of pediatric gastroenterology and nutrition. 2017; 64(2):319–34. https://doi.org/10.1097/MPG.0000000000001482 PMID: 28107283; PubMed Central PMCID: PMC5413933.

60. Hambardzumyan K, Zmuda JM, Kleinman JM, Shi K, Loos RJ, Pradhan TM, et al. The accuracy of obesity classifications derived from self-reported weight and height: comparison of the 2013–2014 National Health and Nutrition Examination Survey with the 2013–2014 National Health Interview Survey. Obes Res Clin Pract. 2016; 10:241–50. https://doi.org/10.1016/j.orcp.2016.09.005 PMID: 27762402; PubMed Central PMCID: PMC5083378.

61. Chen WC, Quigley EM. Probiotics, prebiotics & symbiotics in small intestinal bacterial overgrowth: opening up a new therapeutic horizon! Indian J Med Res. 2014; 140(5):582–4. Epub 2015/01/13. PMID: 25579137; PubMed Central PMCID: PMC4311309.

62. Shi J, Gao F, Zhang J. Effect of Combined Live Probiotics Alleviating the Gastrointestinal Symptoms of Functional Bowel Disorders. Gastroenterology research and practice. 2020; 2020:4187148. Epub 2020/10/06. https://doi.org/10.1155/2020/4187148 PMID: 33014039; PubMed Central PMCID: PMC7519468.

63. Sachdev AH, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. Ther Adv Chronic Dis. 2013; 4(5):223–31. Epub 2013/09/03. https://doi.org/10.1177/204062213496126 PMID: 2399726; PubMed Central PMCID: PMC3752184.

64. Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome and its relationship with oro-cecal transit time. Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology. 2006; 25(1):6–10. PMID: 16567886.