

Obesity and Irritable Bowel Syndrome: A Comprehensive Review

Octavia Pickett-Blakely, MD, MHS

Dr Pickett-Blakely is the director of the Small Bowel Disorders and Nutrition Program in the Division of Gastroenterology of the University of Pennsylvania Perelman School of Medicine in Philadelphia, Pennsylvania.

Address correspondence to:
Dr Octavia Pickett-Blakely
Division of Gastroenterology
University of Pennsylvania
9 Penn Tower
1 Convention Center Drive
Philadelphia, PA 19104
Tel: 215-349-8222
Fax: 215-349-5915
E-mail: octavia.pickett-blakely@uphs.
upenn.edu

Abstract: Obesity and irritable bowel syndrome (IBS) are prevalent in the United States and cause significant morbidity in those affected. However, it is unclear whether obesity is more prevalent in those affected by IBS or if IBS is more prevalent in obese persons. To evaluate the association between obesity and IBS, a comprehensive review was performed by searching MEDLINE and Embase from 1980 through July 2012. Studies were included if 1 of the outcomes examined the relationship between excess body weight or obesity and IBS. A total of 11 studies (2 pediatric and 9 adult) investigated the relationship between obesity and IBS. The prevalence of obesity in children with IBS ranged from 24.8% to 42%. In adults, the prevalence of IBS in obese subjects varied from 11.6% to 24%, depending on the study population. Two studies did not show increased odds of IBS in obese patients; however, 2 studies showed that symptoms were more severe in obese patients affected by IBS, while 1 of these studies demonstrated that IBS symptom severity improved after bariatric surgery. The findings of this comprehensive review of the literature suggest that the frequency of IBS in obese children and adults is variable and depends on the study population. Due to the heterogeneity in study populations, outcome assessment, and methodology in the existing literature, further studies are needed to determine whether obesity is associated with IBS.

Obesity affects approximately one-third of adults¹ in the United States and is associated with comorbid illnesses that affect multiple organ systems, including the gastrointestinal tract.^{1,2} Irritable bowel syndrome (IBS) is a chronic bowel disorder that occurs in up to 20% of adults in the United States and is characterized by abdominal pain or discomfort associated with altered bowel habits.^{3,4} IBS causes significant morbidity, with IBS-related symptoms accounting for 3.6 million annual physician visits, impaired quality of life, and decreased work productivity.⁵⁻⁷ Although the association between obesity and gastrointestinal diseases, such as gastroesophageal reflux disease, is well established, the data examining the association between obesity and IBS have not been well characterized.⁸

Keywords

Obesity, irritable bowel syndrome

Although the etiology of IBS is unclear, some researchers postulate that abnormal intestinal motility, diet, and/or altered gut microbiota may be involved.⁹ Animal studies suggest that body habitus is associated with altered lower gastrointestinal tract motility; however, the data are inconsistent.¹⁰⁻¹² Diets that are low in fiber (which modulates stool osmolarity), high in saturated fats (which increase motility), and high in fermentable carbohydrates (such as fructose and lactose) may contribute to IBS symptoms in obese persons. Furthermore, it has been postulated that IBS symptoms are linked to diet and may be more common in obese persons as a result of overeating in response to impaired satiation signals.¹³ Lastly, alterations in the composition of the gut microbiota have been reported in both obesity and IBS and may be a common link between the 2 disorders.⁴⁻²⁰

Establishing a link between obesity and IBS may lead to a greater emphasis on weight loss interventions for obese persons, with the goal of reducing the burden of IBS symptoms in this population. The purpose of this comprehensive review is to evaluate the association between obesity and IBS.

Methods

Electronic Search

The literature search was performed using MEDLINE and Embase for studies published in the English language from 1980 to July 2012. Literature prior to 1980 was not included because this time period predates the obesity epidemic. The search strategy included the following search terms: obesity, overweight, IBS, functional colonic disease, constipation, diarrhea, and gastrointestinal motility. Additionally, references were identified by a "hand search," in which reference lists of articles published on this subject were searched to identify potentially eligible studies not identified in the electronic database search.

A single reviewer examined abstracts from studies obtained in the literature search for inclusion or exclusion criteria that were established a priori. Observational studies, including cross-sectional, case-control, and cohort studies, were eligible for inclusion. Studies eligible for inclusion in this review were pediatric or adult studies that examined the frequency or association of obesity in subjects with IBS or the frequency or association of IBS in obese subjects. Obesity was defined as a body mass index (BMI) greater than or equal to 30 kg/m². The presence of IBS was identified as an outcome of interest in all included studies.

Data Abstraction

Titles and abstracts from the initial search were reviewed by a single reviewer (OP-B) for content. Pertinent articles were then reviewed in full-text format by the

same reviewer. Data were abstracted by the reviewer and entered into an electronic database.

Quality Assessment

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for nonrandomized studies.¹³ The NOS was applied to case-control and cohort studies; however, it was not applied to cross-sectional studies and case series. The NOS scores for appropriate studies are listed in the Table.

Results

Of the studies obtained from the electronic searches, 51 full-text articles were reviewed. Forty full-text articles, including 2 animal studies, 2 duplicate studies, 30 articles that did not address the study question, and 6 review articles, were excluded. Data were abstracted from a total of 11 studies that were reported in this review.

Data from the 11 included studies are displayed in the Table. There were 2 studies that investigated obesity and IBS in children. Teitelbaum and colleagues reported a 25% prevalence of IBS among obese children and noted that obesity was significantly more prevalent in children with IBS compared with children without IBS.²¹ However, in a cohort of children with IBS, Bonilla and colleagues failed to show that obesity was more prevalent than nonobesity.²²

Nine studies investigated the relationship between obesity and IBS in adults. Crowell and colleagues published the earliest report of a positive association between obesity and IBS symptoms, which was confirmed by 2 subsequent studies.²³⁻²⁵ In a large, cross-sectional study of obese persons participating in a weight loss trial, the prevalence of IBS was 13%.²⁶ In a cohort of persons with IBS, symptom severity was positively associated with increased BMI.²⁷ Likewise, 3 studies reported that the frequency of IBS symptoms in obese subjects awaiting or undergoing weight loss surgery ranged from 12% to 24%.²⁸⁻³⁰ Clements and colleagues showed that IBS symptoms in obese subjects improved after weight loss surgery.²⁸ In contrast to the aforementioned studies, Talley and colleagues and Levy and colleagues failed to show increased odds of IBS in obese subjects in cross-sectional analyses of a birth cohort in New Zealand and a cohort of obese subjects enrolled in a medically supervised weight loss intervention trial, respectively.^{26,31}

Discussion

This review shows that, in children, the association between obesity and IBS remains unclear. In adults, the prevalence of IBS in obese persons is variable based on the population studied. Based on the current literature, the association between obesity and IBS in adults is unclear as well.

Table. Studies Included in the Review

Year	First Author	N	Population/ Location	Study Design	Outcome Measurement Tool	Results	Comments
1994	Crowell ²³	196	Weight management center cohort/United States	Cross-sectional	Questionnaire with Manning criteria	<ul style="list-style-type: none"> – Prevalence of IBS in obese and nonobese binge eaters: 23.3% and 21.4%, respectively – Prevalence of IBS in obese and nonobese nonbinge eaters: 11.6% and 4.9%, respectively 	<ul style="list-style-type: none"> – NOS score²: n/a – 3-month symptom recall – IBS symptoms linked to binge eating activity
2002	Svedberg ²⁴	1321	Twin cohort: monozygotic twins discordant for IBS/Sweden	Case-control	GI symptom questionnaire	<ul style="list-style-type: none"> – Prevalence of IBS: 5.4% in study sample – Prevalence of obesity in IBS cases: 6.9% – Prevalence of obesity in controls: 5.1% – OR of obesity in IBS cases vs controls: 2.6 (95% CI, 1.0-6.4) – OR of obesity in discordant twin pairs: 1.5 (95% CI, 0.2-8.9) 	<ul style="list-style-type: none"> – NOS score: 4 – IBS outcome assessment not standardized – Inadequate BMI variation in twins
2003	Clements ²⁸	43	Bariatric surgery cohort/United States	Case series	GSRS	<ul style="list-style-type: none"> – Severity scores for IBS higher in obese cases than controls (21.9 ± 14.6 vs 15.6 ± 13.3) at baseline – Severity scores for IBS cases higher in the preoperative cohort vs postoperative cohort (21.9 vs 14.5 ± 13.5) 	<ul style="list-style-type: none"> – NOS score: 2 – Control group not clearly defined – No adjustment for confounders (eg, amount of weight loss) – Laparoscopic RYGB – Symptoms assessed 6 months postoperatively
2004	Talley ³¹	929	Birth cohort/ New Zealand	Cross-sectional	Manning criteria	<ul style="list-style-type: none"> – OR of IBS in obese subjects: 1.16 (95% CI, 0.69-1.96) 	<ul style="list-style-type: none"> – NOS score: n/a – Outcome assessment at age 26
2005	Aro ²⁵	973	General population/Sweden	Cross-sectional	ASQ	<ul style="list-style-type: none"> – OR of IBS in obese subjects: 1.58 (95% CI, 1.05-2.38) 	<ul style="list-style-type: none"> – NOS score: n/a
2005	Levy ²⁶	983	Subjects in a weight-loss intervention trial/ United States	Cross-sectional	Rome II criteria	<ul style="list-style-type: none"> – Prevalence of IBS in study sample: 13.3% – OR of IBS status with increasing BMI: 1.02 (95% CI, 0.98-1.05) 	<ul style="list-style-type: none"> – NOS score: n/a – Additional data on food intake and eating habits obtained
2009	Teitelbaum ²¹	1448	Pediatric GI practice (cases) and general pediatric practice, middle and high school students (controls)/United States	Case-control	Rome II criteria	<ul style="list-style-type: none"> – Obesity prevalence in subjects with IBS: 24.8% 	<ul style="list-style-type: none"> – NOS score: 5 – No prevalence data given for controls

(continued on page 414)

Table. (continued from page 413) Studies Included in the Review

Year	First Author	N	Population/Location	Study Design	Outcome Measurement Tool	Results	Comments
2010	Roberson ²⁹	404	Bariatric surgery cohort/United States	Cross-sectional	Rome II criteria	– Prevalence of IBS in obese females: 24% – Prevalence of IBS in obese males: 12%	– NOS score: n/a – No standard weight loss surgery
2010	Sadik ²⁷	96	Cohort of IBS subjects/Sweden	Cross-sectional	Rome II criteria	– Overweight and obese subjects with IBS had greater symptom severity compared with normal-weight subjects with IBS	– NOS score: n/a – Transit studied: colonic, descending, and rectosigmoid transit faster in overweight/obese compared with health controls – Symptoms examined as secondary endpoint
2011	Bonilla ²²	180	Tertiary-care center pediatric GI clinic (abdominal pain-related functional GI disorders)/United States	Case series	Rome II criteria	– Obesity prevalence in IBS cases: 42% – Obesity prevalence in subjects with IBS and persistent pain on follow-up: 20%	– NOS score: n/a – No control group – 12-15 months of follow-up
2012	Fysekidis ³⁰	2011	Cohort awaiting bariatric surgery/United States	Cross-sectional	Rome III criteria	– Prevalence of IBS in obese subjects: 18%	– NOS score: n/a

*NOS score: maximum score is 8.

ASQ, abdominal symptom questionnaire; BMI, body mass index; GI, gastrointestinal; GSRS, gastrointestinal symptom rating scale; IBS, irritable bowel syndrome; NOS, Newcastle-Ottawa Scale; OR, odds ratio; RYGB, Roux-en-Y gastric bypass.

Both IBS and obesity have considerable impact on the healthcare system and society.^{5-7,32} Medical therapies and the clinical evidence supporting the efficacy of existing therapies for IBS are limited, while the most durable and effective treatment for obesity is bariatric surgery, which is reserved for severe categories of obesity.^{33,34} If IBS symptoms are indeed associated with obesity, gastroenterologists will be uniquely positioned to emphasize weight loss as a potential therapeutic modality for IBS.

There are many potential mechanisms whereby IBS symptoms develop in obese persons. First, altered small bowel and colonic transit in obese persons may explain IBS symptoms, but the data in this area are limited. Moos and colleagues reported shorter total gastrointestinal transit times in obese rats compared with their lean counterparts, while Kiely and colleagues reported longer overall transit times in leptin-deficient obese mice compared with their lean counterparts.¹⁰⁻¹²

In human studies, Basilisco and colleagues reported delayed orocecal transit times in obese subjects using the

lactulose breath test, while a later study failed to reproduce this finding using scintigraphy.^{35,36} Sadik and colleagues, however, reported an inverse correlation between BMI and colonic transit time in subjects with IBS.²⁷ It should be noted that this study also reported faster descending and rectosigmoid transit in obese compared with normal-weight subjects with IBS. These findings suggest that, while delayed colonic transit is a plausible explanation for constipation symptoms, segmental colonic motility disturbances may explain diarrheal symptoms in obese patients with IBS. Given the limited data with regard to altered intestinal motility in obesity, additional investigation is warranted before altered motility can be evoked as an explanation for the development of IBS symptoms in this population.

Low-fiber and high-refined-carbohydrate diets are linked to obesity and are another potential contributor to IBS symptoms in obese persons, although there are little data to support this theory. As many as 67% of persons with IBS complain of food intolerance, which raises the possibility that ingested food products are an underlying cause of

both obesity and IBS symptoms.³⁷ An early population-based study failed to demonstrate a significant difference in the diet macronutrient composition or ingestion of certain “culprit” foods (eg, wheat, fructose, dairy, and lactose) in those subjects with IBS compared with controls.³⁸ Furthermore, a more recent study showed that patients with IBS frequently consumed canned food, processed meats, and foods such as cakes and ice cream as well as grains, fruits, and vegetables.³⁹ Based on the data available, diet remains a potential factor linking IBS to obesity.

Gut microbiota shifts may explain a possible connection between obesity and IBS and have been reported in both obesity and IBS.¹⁴⁻¹⁹ Small intestinal bacterial overgrowth (SIBO) may be a potential mechanism whereby IBS symptoms manifest in obese persons. In a cohort of patients awaiting bariatric surgery, SIBO was present in 41%.⁴⁰

Although the mechanisms of altered gut flora in obesity are unclear, diet (such as high-fat “Western-type” diets) has been shown to influence the gut microbiota in some studies and may contribute to subsequent IBS symptoms in obese patients.⁴¹ Although the current data are provocative, they are insufficient to establish a causal relationship between gut microbiota shifts and IBS symptoms in obese patients.

When interpreting the literature that evaluates the relationship between obesity and IBS, some limitations must be considered. First, there is considerable heterogeneity in the study populations included in this review. In particular, both pediatric and adult populations are included even though the definition of obesity is different in each population and has changed over time. Earlier studies using Metropolitan Life tables were unlikely to be representative of the US population, and, thus, the prevalence of obesity may have been underestimated. Underestimating the prevalence of obesity may have, in turn, resulted in an underestimation of the association between obesity and IBS. Furthermore, in some population-based studies, subjective as opposed to objective measures of obesity (eg, per-subject report vs measured height and weight, respectively) may have underestimated obesity as well. In addition, there is considerable heterogeneity in the assessment of the outcome of IBS in the studies reported in this review.

The lack of standardized assessment of IBS poses a challenge when interpreting the data. It has been shown that the prevalence of IBS is variable, depending on the criteria that are used.^{42,43} Although validated bowel symptom questionnaires and the Manning criteria were used to measure the outcome of IBS in some studies, the most commonly used outcome measure was the well-known Rome criteria. Nonetheless, future studies should utilize standardized criteria for IBS.

Lastly, this review included only studies in which the association between body weight and IBS was the primary

outcome. Therefore, publication bias is an additional limitation of the present study, given that studies examining the association between body weight and IBS as a secondary outcome are unlikely to report a negative association.

If, indeed, obesity is associated with IBS, it should be determined whether the association between body weight and IBS symptoms is linear in an effort to predict the severity of IBS symptoms according to obesity class. Likewise, future studies should evaluate the impact of voluntary weight loss on IBS symptoms in obese persons. Obese patients may be more likely to pursue, and providers more likely to recommend, weight loss interventions if voluntary weight loss is shown to improve IBS symptoms. Conversely, if weight loss, such as that observed after bariatric surgery, is shown to worsen IBS symptoms, this information may be used by healthcare providers to select the most appropriate weight loss modality for individual patients.

Conclusions

Obesity and IBS may be linked; however, a true association and its underlying mechanisms remain to be elucidated. Future investigation using standardized assessments of obesity and IBS should focus on determining whether IBS is more common in obese persons, understanding the mechanisms whereby obesity is linked to IBS symptoms, understanding the clinical course of IBS in obese persons, and determining the effect of weight loss interventions on IBS symptoms.

Dr Pickett-Blakely has no relevant conflicts of interest to disclose.

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 2010;303(3):235-241.
2. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. *Arch Intern Med*. 2000;160(7):898-904.
3. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology*. 2002;123(6):2108-2131.
4. Rey E, Talley NJ. Irritable bowel syndrome: novel views on the epidemiology and potential risk factors. *Dig Liver Dis*. 2009;41(11):772-780.
5. Dean BB, Aguilar D, Barghout V, et al. Impairment in work productivity and health-related quality of life in patients with IBS. *Am J Manag Care*. 2005;11(1 suppl):S17-S26.
6. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology*. 2009;136(3):741-754.
7. DiBonaventura M, Sun SX, Bolge SC, Wagner JS, Mody R. Health-related quality of life, work productivity and health care resource use associated with constipation predominant irritable bowel syndrome. *Curr Med Res Opin*. 2011;27(11):2213-2222.
8. El-Serag H. The association between obesity and GERD: a review of the epidemiological evidence. *Dig Dis Sci*. 2008;53(9):2307-2312.
9. El-Salhy M. Irritable bowel syndrome: diagnosis and pathogenesis. *World J Gastroenterol*. 2012;18(37):5151-5163.
10. Moos AB, McLaughlin CL, Baile CA. Effects of CCK on gastrointestinal function in lean and obese Zucker rats. *Peptides*. 1982;3(4):619-622.
11. Pecora P, Suraci C, Antonelli M, De Maria S, Marrocco W. Constipation and obesity: a statistical analysis. *Boll Soc Ital Biol Sper*. 1981;57(23):2384-2388.
12. Kiely JM, Noh JH, Graewin SJ, Pitt HA, Swartz-Basile DA. Altered intestinal

- motility in leptin-deficient obese mice. *J Surg Res*. 2005;124(1):98-103.
13. Talley NJ, Quan C, Jones MP, Horowitz M. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. *Neurogastroenterol Motil*. 2004;16(4):413-419.
14. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005;102(31):11070-11075.
15. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006;444(7122):1022-1023.
16. Kassinen A, Krogius-Kurikka L, Mäkituokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007;133(1):24-33.
17. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe*. 2008;3(4):213-223.
18. Rajilić-Stojanović M, Biagi E, Heilig HG, et al. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology*. 2011;141(5):1792-1801.
19. Jeffery IB, Quigley EM, Öhman L, Simrén M, O'Toole PW. The microbiota link to irritable bowel syndrome: an emerging story. *Gut Microbes*. 2012;3(6):572-576.
20. Simrén M, Barbara G, Flint HJ, et al; Rome Foundation Committee. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut*. 2013;62(1):159-176.
21. Teitelbaum JE, Sinha P, Micale M, Yeung S, Jaeger J. Obesity is related to multiple functional abdominal diseases. *J Pediatr*. 2009;154(3):444-446.
22. Bonilla S, Wang D, Saps M. Obesity predicts persistence of pain in children with functional gastrointestinal disorders. *Int J Obes (Lond)*. 2011;35(4):517-521.
23. Crowell MD, Cheskin LJ, Musial F. Prevalence of gastrointestinal symptoms in obese and normal weight binge eaters. *Am J Gastroenterol*. 1994;89(3):387-391.
24. Svedberg P, Johansson S, Wallander MA, Hamelin B, Pedersen NL. Extra-intestinal manifestations associated with irritable bowel syndrome: a twin study. *Aliment Pharmacol Ther*. 2002;16(5):975-983.
25. Aro P, Ronkainen J, Talley NJ, Storskrubb T, Bolling-Sternevald E, Agréus L. Body mass index and chronic unexplained gastrointestinal symptoms: an adult endoscopic population based study. *Gut*. 2005;54(10):1377-1383.
26. Levy RL, Linde JA, Feld KA, Crowell MD, Jeffery RW. The association of gastrointestinal symptoms with weight, diet, and exercise in weight-loss program participants. *Clin Gastroenterol Hepatol*. 2005;3(10):992-996.
27. Sadik R, Björnsson E, Simrén M. The relationship between symptoms, body mass index, gastrointestinal transit and stool frequency in patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2010;22(1):102-108.
28. Clements RH, Gonzalez QH, Foster A, et al. Gastrointestinal symptoms are more intense in morbidly obese patients and are improved with laparoscopic Roux-en-Y gastric bypass. *Obes Surg*. 2003;13(4):610-614.
29. Roberson EN, Gould JC, Wald A. Urinary and fecal incontinence after bariatric surgery. *Dig Dis Sci*. 2010;55(9):2606-2613.
30. Fysekidis M, Bouchoucha M, Bihan H, Reach G, Benamouzig R, Catheline JM. Prevalence and co-occurrence of upper and lower functional gastrointestinal symptoms in patients eligible for bariatric surgery. *Obes Surg*. 2012;22(3):403-410.
31. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. *Am J Gastroenterol*. 2004;99(9):1807-1814.
32. Finkelstein EA, Strombotne KL. The economics of obesity. *Am J Clin Nutr*. 2010;91(5):1520S-1524S.
33. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292(14):1724-1737.
34. Trinkle KE, Nahata MC. Treatment of irritable bowel syndrome. *J Clin Pharm Ther*. 2011;36(3):275-282.
35. Basile G, Camboni G, Bozzani A, Vita P, Doldi S, Bianchi PA. Orocecal transit delay in obese patients. *Dig Dis Sci*. 1989;34(4):509-512.
36. French SJ, Murray B, Rumsey RD, Sepple CP, Read NW. Preliminary studies on the gastrointestinal responses to fatty meals in obese people. *Int J Obes Relat Metab Disord*. 1993;17(5):295-300.
37. Eswaran S, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. *Gastroenterol Clin North Am*. 2011;40(1):141-162.
38. Saito YA, Locke GR III, Weaver AL, Zinsmeister AR, Talley NJ. Diet and functional gastrointestinal disorders: a population-based case-control study. *Am J Gastroenterol*. 2005;100(12):2743-2748.
39. Chirila I, Petrariu FD, Ciortescu I, Mihai C, Drug VL. Diet and irritable bowel syndrome. *J Gastrointest Liver Dis*. 2012;21(4):357-362.
40. Madrid AM, Poniachik J, Quera R, Defilippi C. Small intestinal clustered contractions and bacterial overgrowth: a frequent finding in obese patients. *Dig Dis Sci*. 2011;56(1):155-160.
41. Kootte RS, Vrieze A, Holleman F, et al. The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. *Diabetes Obes Metab*. 2012;14(2):112-120.
42. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Thjodleifsson B. Stability of the irritable bowel syndrome and subgroups as measured by three diagnostic criteria—a 10-year follow-up study. *Aliment Pharmacol Ther*. 2010;32(5):670-680.
43. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(7):712-721.e4.