



Hrvatsko
Udruženje za
Neurogastroenterologiju i
Motilitet



ESNM
European Society
of Neurogastroenterology
& Motility

Učinak kombinacije probiotika na simptome i fekalnu mikrobiotu u bolesnika s pretilošću i sindromom iritabilnog crijeva

Eugen Javor, mag. pharm., spec. kliničke farmacije.

Poliklinika Solmed

Medicinski fakultet Sveučilišta u Rijeci, Rijeka, Hrvatska



University of Rijeka



SVEUČILIŠTE U RIJECI - MEDICINSKI FAKULTET








MEDRI



Figure 3: Global prevalence of inflammatory bowel syndrome according to the Rome IV criteria

Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. *Lancet*. 2020;396(10263):1675-1688.

Bristolska ljestvica stolice

Tip 1		Odvojene tvrde grudice, poput oraha (teško se prazne)
Tip 2		U obliku kobasice, ali grudičaste
Tip 3		Poput kobasice, ali s pukotinama na površini
Tip 4		Poput kobasice ili zmije, glatka i mekana
Tip 5		Mekani komadići jasnih rubova
Tip 6		Čupavi komadići neravnih rubova, kašasta stolica
Tip 7		Vodenasta, bez čvrstih dijelova, u potpunosti tekuća

Ford AC, Sperber AD, Corsetti M, Camilleri M. Irritable bowel syndrome. Lancet. 2020;396(10263):1675-1688.

Dijagnostički kriteriji

SIC

Ponavljajuća abdominalna bol, najmanje 1 dan u tjednu u prethodna 3 mjeseca, povezana s dva ili više od navedenog: povezano s defekacijom, promjena u učestalosti stolice, promjena u obliku stolice; kriteriji moraju biti zadovoljeni za zadnja 3 mjeseca, s nastupom simptoma najmanje 6 mjeseci prije postavljene dijagnoze

SIC s zatvorom

≥25% kretanja crijeva prema Bristolskoj ljestvici oblik tipa 1 ili 2 i <25% prema Bristolskoj ljestvici oblik tipa 6 ili 7

SIC s proljevom

≥25% kretanja crijeva prema Bristolskoj ljestvici oblik tipa 6 ili 7 i <25% prema Bristolskoj ljestvici oblik tipa 1 ili 2

SIC s mješovitim uzorkom stolice

≥25% kretanja crijeva prema Bristolskoj ljestvici oblik tipa 1 ili 2 i ≥25% prema Bristolskoj ljestvici oblik tipa 6 ili 7

Nerazvrstani SIC

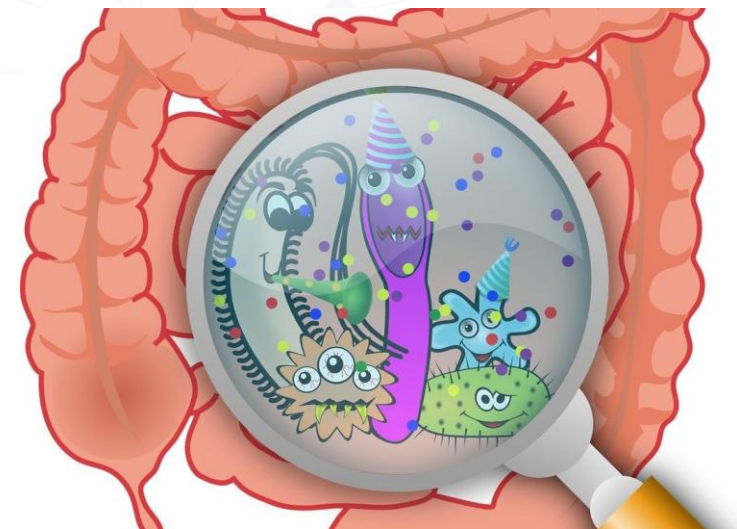
Zadovoljava dijagnostičke kriterije za SIC, ali crijevne navike se ne mogu precizno kategorizirati u niti jedan od podtipova prema Bristolskoj ljestvici

Terapija SIC-a

- Za niti jedan **terapijski pristup nije dokazano da mijenja prirodni tijek SIC-a.**
- Terapija često usmjerena prema **otklanjanju najneugodnijeg simptoma.**
- Većina terapija poboljšava simptome u otprilike **25-30% bolesnika** sa SIC-om i to se odnosi na liječenje u stacionarnim ustanovama.
- Većina randomiziranih kliničkih studija (RKS) u bolesnika sa SIC-om traje **do 12 tjedana** i zbog toga je njihova dugoročna učinkovitost nepoznata.

Mikrobiota crijeva

- **Patofiziologija SIC-a nije još u potpunosti razjašnjena**, ali je poznato da su uključeni višestruki periferni i središnji mehanizmi.
- **Mikrobiota crijeva** utječe na većinu fizioloških procesa povezanih s patofiziologijom SIC-a.



Stress



Brain-gut dysregulation

Altered motility of intestine

Altered gastrointestinal microbiome



Transient infection



Altered endocrine metabolism (serotonin)



Neuronal plasticity



Genetic polymorphisms



Increased mucosa permeability



Bile acid malabsorption

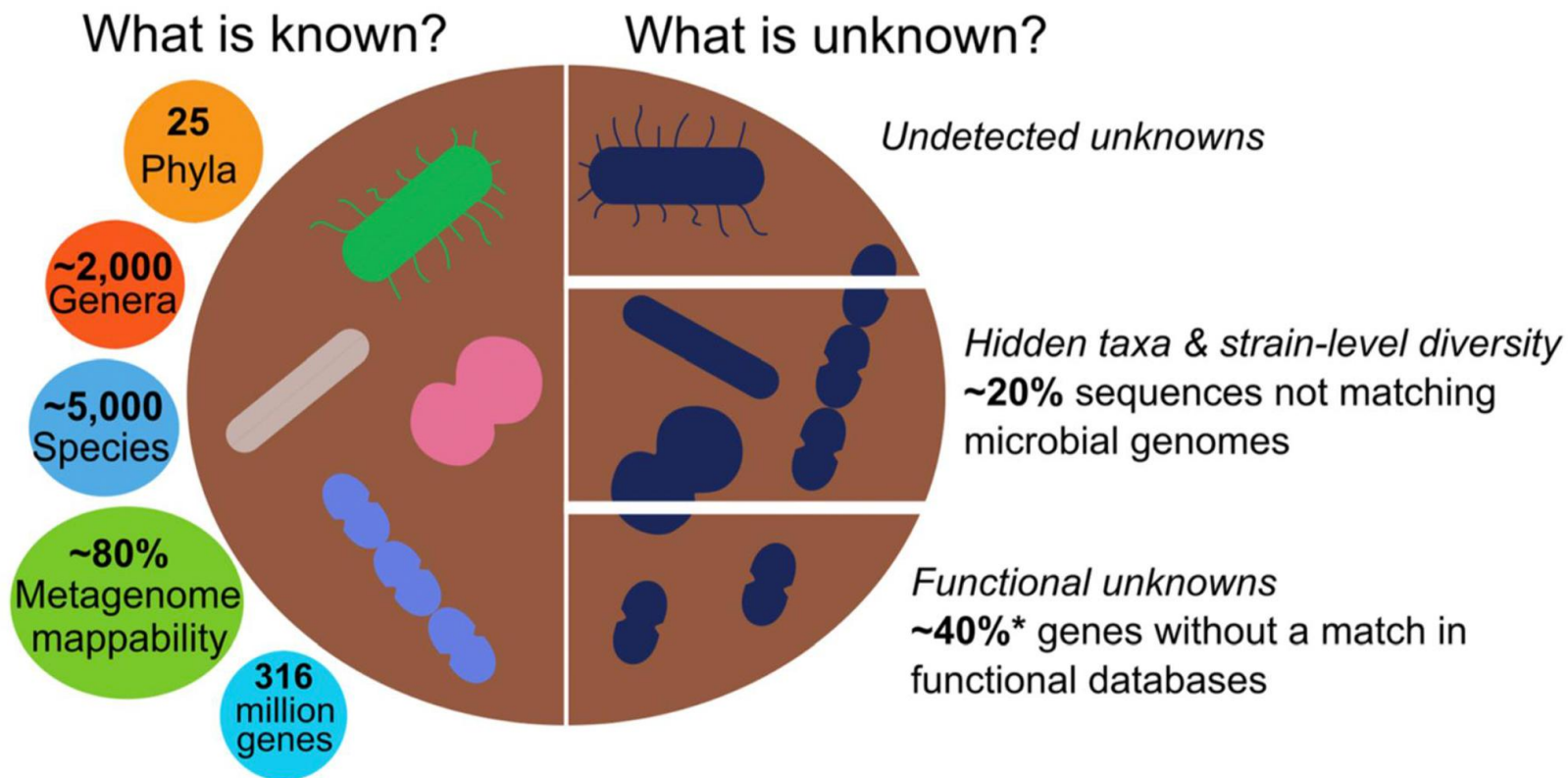


**Altered mucosal immune function
Food hypersensitivity**



Raznolikost ljudskog mikrobioma

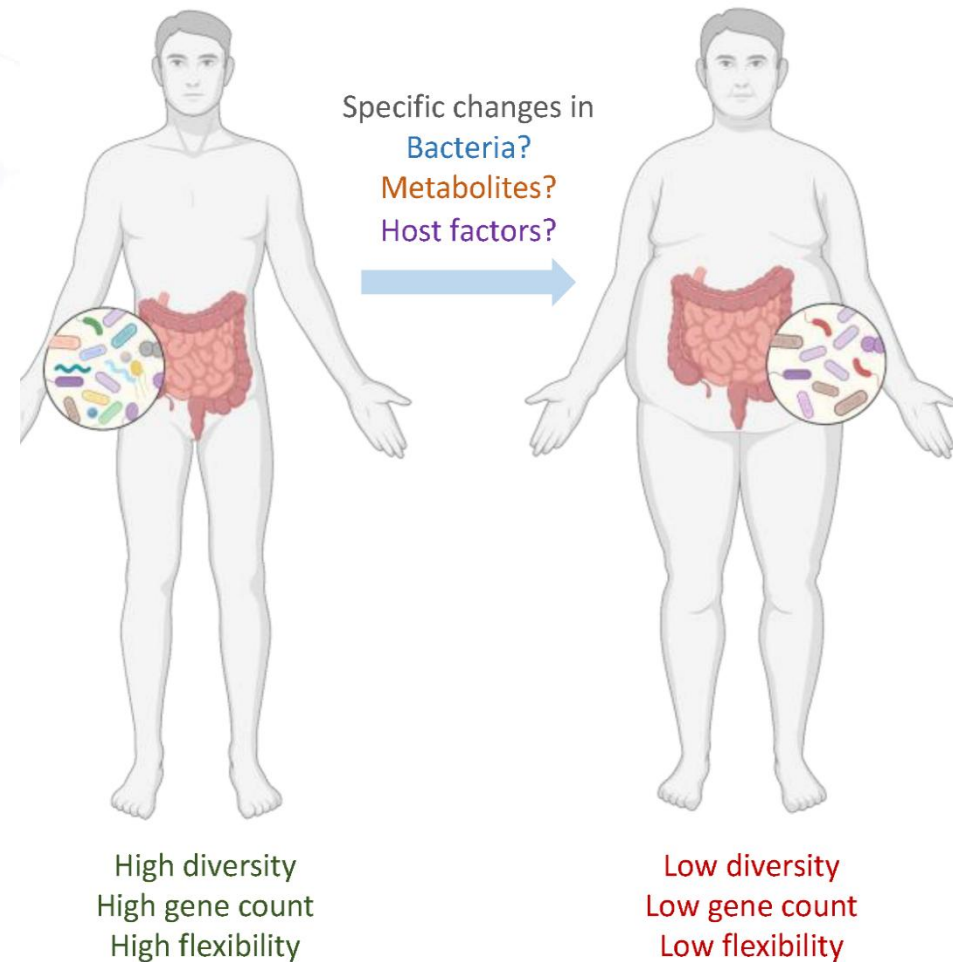
The human microbiome



- **25 koljena** (phyla) – visoka taksonomska razina koja pokazuje raznolikost.
- **~2.000 rodova** (genera) – niža taksonomska razina, detaljnija klasifikacija.
- **~5.000 vrsta** (species) – dosad identificirane vrste mikroorganizama.
- **~80% metagenoma mapirano** – većina genetskog materijala može se povezati s poznatim organizmima.
- **316 milijuna gena** – ogroman genski fond mikrobioma.

Mikrobiota crijeva i probiotici u SIC-u

- Postoji **razlika u sastavu mikrobiote crijeva** između bolesnika sa **SIC-om** i **zdrave kontrole**, što je ujedno i karakteristika za sve gastrointestinalne (GIT) poremećaje.
- **Mikrobna raznolikost crijevne mikrobiote** u bolesnika sa **SIC-om** je **smanjena** je u odnosu na mikrobiotu zdravih pojedinaca.
- **Raznolikost i obilatost crijevne mikrobiote** smatraju se mjerama „**zdrave mikrobiote**“, koje su važne za održavanje **homeostaze** i funkcije mikrobiote. Naročito tijekom izloženosti raznim stresorima mikrobiote.



Ringel Y, Ringel-Kulka T. The intestinal microbiota and irritable bowel syndrome. J Clin Gastroenterol. 2015;49 Suppl 1:S56-59.

Canli PD, Moens de Hase E, Van Hul M. Gut Microbiota and Host Metabolism: From Proof of Concept to Therapeutic Intervention.

Microorganisms. 2021; 9(6):1302

Mikrobiota crijeva i probiotici u SIC-u

- Upotreba **probiotika** jedna je od **nefarmakoloških** mjera koje su ispitivane u **randomiziranim kliničkim studijama (RKS)** u bolesnika sa **SIC-om**.
- **Rezultati RKS-a s probioticima** u bolesnika sa **SIC-om** su **nekonzistentni**.
- **RKS** imaju **značajan rizik od pristranosti**, upotrebljavane su različite vrste/sojevi probiotika, različite subpopulacije bolesnika i praćeni različiti konačni ishodi.

RCTs results in IBS

- Tri RKS testirali su *Saccharomyces boulardii* u 232 pacijenta sa SIC-om koristeći različite primarne ishode. **Abodminalni bolovi nisu bili različiti** u skupinama koje su koristile *S boulardii* u odnosu na one koje su koristile placebo.



1. Choi C, Jo S, Park H, et al. A randomized, double-blind, placebo-controlled multicenter trial of *Saccharomyces boulardii* in irritable bowel syndrome: effect on quality of life. *J Clin Gastroenterol* 2011;45:679–683.
2. Kabir M, Ishaque S, Ali M, et al. Role of *Saccharomyces boulardii* in diarrhea predominant irritable bowel syndrome. *Mymensingh Med J* 2011;20:397–401.
3. Abbas Z, Yakoob J, Jafri W, et al. Cytokine and clinical response to *Saccharomyces boulardii* therapy in diarrhea-dominant irritable bowel syndrome: a randomized trial. *Eur J Gastroenterol Hepatol* 2014;26:630–639.

RCTs results in IBS

- Dva RKS ispitivale su kombinaciju od **8 sojeva** (*Lactobacillus*, *Bifidobacterium*, *Streptococcus spp.*) u SIC-u i abdominalnim bolovima te su pokazale **smanjenje abdominalnih bolova**.
- **Kombinacija *Lactobacillus* probiotika poboljšava globalne simptome SIC-a (80,8% vs. 45,8%)** procijenjene prema subjektivnoj globalnoj procjeni (SGA) u bolesnika sa SIC-om bez zatvora.
- **Bio-Kult®**; kombinacija 14 različitih sojeva, u pacijenata s **umjerenim do teškim SIC-D smanjio je težinu abdominalnih bolova** na IBS-SSS skali (69% vs 47%).
- U RKS s tri skupine, ***L. acidophilus DDS-1* i *B. animalis subsp. lactis UABla-12* smanjili su abdominalnu bol i težinu simptoma (IBS-SSS), uz popratnu normalizaciju crijevnih navika** u odraslih osoba sa SIC-om.

1. Kim H, Vazquez RM, Camilleri M, et al. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterol Motil* 2005;17:687–696.
2. Drouault-Holowacz S, Bieuelet S, Burckel A, et al. A double blind randomized controlled trial of a probiotic combination in 100 patients with irritable bowel syndrome. *Gastroenterol Clin Biol* 2008;32:147–152.
3. Oh JH, Jang YS, Kang D, Chang DK, Min YW. Efficacy and safety of new lactobacilli probiotics for unconstipated irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *Nutrients*. 2019;11(12):2887.
4. Ishaque SM, Khosruzzaman SM, Ahmed DS, Sah MP. A randomized placebo-controlled clinical trial of a multi-strain probiotic formulation (Bio-kult®) in the management of diarrhea-predominant irritable bowel syndrome. *BMC Gastroenterol*. 2018;18(1):71.
5. Martoni CJ, Srivastava S, Leyer GJ. *Lactobacillus acidophilus dds-1* and *bifidobacterium lactis uabla-12* improve abdominal pain severity and symptomology in irritable bowel syndrome: randomized controlled trial. *Nutrients*. 2020;12(2):363.

A double blind, placebo-controlled, randomized clinical trial that breast milk derived-*Lactobacillus gasseri* BNR17 mitigated diarrhea-dominant irritable bowel syndrome

Suk Pyo Shin,¹ Yoon Mi Choi,² Won Hee Kim,² Sung Pyo Hong,² Jong-Min Park,³ Joohee Kim,⁴ Oran Kwon,^{4,*} Eun Hyun Lee⁵ and Ki Baik Hahm^{2,3,*}

- Kod bolesnika sa SIC-D, *Lactobacillus gasseri* BNR17 izoliran iz majčinog mlijeka **poboljšao** je **simptome proljeva**, pokazao značajno **smanjenje abdominalne boli, nadutosti, narušenog svakodnevnog života** te prosječne učestalosti defekacije. Analizom fekalne mikrobiote utvrđeno je da je BNR17 značajno **povećao** razine ***B. fecalis*, *E. rectale*, *C. aerofaciens*, *F. prausnitzii*** i ***B. stercoris***.
- Ova RKS je pokazala da probiotici **mogu smanjiti mikrobnu disbiozu** koja je izrazito prisutna kod bolesnika sa SIC-om.

Heat-inactivated *Bifidobacterium bifidum* MIMBb75 (SYN-HI-001) in the treatment of irritable bowel syndrome: a multicentre, randomised, double-blind, placebo-controlled clinical trial

Viola Andresen, Jürgen Gschossmann, Peter Layer

THE LANCET
Gastroenterology & Hepatology

- Združeni primarni ishod (kombinacija ↓ najmanje 30% boli u trbuhu i odgovarajućeg olakšanja simptoma SIC-a) postiglo je 74 (34%) od 221 bolesnika u skupini *B bifidum HI-MIMBb75* u usporedbi s 43 (19%) od 222 u skupini na placebo (omjer rizika 1.7, 95% CI 1.3-2.4; p=0.0007).
- Ova RKS je dokazala da su **korisni učinci probiotika** neovisni o **viabilnosti** samih stanica.

Andresen V, Gschossmann J, Layer P. Heat-inactivated *Bifidobacterium bifidum* MIMBb75 (SYN-HI-001) in the treatment of irritable bowel syndrome: a multicentre, randomised, double-blind, placebo-controlled clinical trial. *Lancet Gastroenterol Hepatol.* 2020;5(7):658-666.

REVIEW

Efficacy of Single-Strain Probiotics Versus Multi-Strain Mixtures: Systematic Review of Strain and Disease Specificity

Lynne V. McFarland¹

- Zasada **nema jasnih dokaza** da je **jedan soj** probiotika **inferiorniji od kombinacije sojeva** u raznim indikacijama, uključujući i u liječenju **SIC-a**.
- **RRR = 0.72, 95% CI 0.32, 1.58**

AGA SECTION

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders

Grace L. Su,^{1,2} Cynthia W. Ko,³ Premysl Bercik,⁴ Yngve Falck-Ytter,^{5,6} Shahnaz Sultan,⁷ Adam V. Weizman,⁸ and Rebecca L. Morgan⁹

¹Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan; ²Gastroenterology Section, Veterans Administration Ann Arbor Healthcare System, Ann Arbor, Michigan; ³Division of Gastroenterology, University of Washington Medical School, Seattle, Washington; ⁴Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; ⁵Division of Gastroenterology, Case Western Reserve University, Cleveland, Ohio; ⁶Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio; ⁷Division of Gastroenterology, University of Minnesota, Minneapolis, Minnesota; ⁸Division of Gastroenterology, Mount Sinai Hospital, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and ⁹Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

6. In symptomatic children and adults with irritable bowel syndrome, we recommend the use of probiotics only in the context of a clinical trial.

No recommendations

Knowledge gap


British Society of Gastroenterology guidelines on the management of irritable bowel syndrome

Dipesh H Vasant ,^{1,2} Peter A Paine,³ Christopher J Black ,⁴
Lesley A Houghton ,^{5,6} Hazel A Everitt,⁷ Maura Corsetti,⁸ Anurag Agrawal,⁹
Imran Aziz ,¹⁰ Adam D Farmer,^{11,12} Maria P Eugenicos,¹³ Rona Moss-Morris,¹⁴
Yan Yiannakou,¹⁵ Alexander C Ford ¹⁶

- ▶ Probiotics, as a group, may be an effective treatment for global symptoms and abdominal pain in IBS, but it is not possible to recommend a specific species or strain. It is reasonable to advise patients wishing to try probiotics to take them for up to 12 weeks, and to discontinue them if there is no improvement in symptoms **recommendation: weak, quality of evidence: very low**.

REVIEW

Evidence-based clinical practice guidelines for irritable bowel syndrome 2020

Shin Fukudo^{1,2}  · Toshikatsu Okumura¹ · Masahiko Inamori¹ · Yusuke Okuyama¹ · Motoyori Kanazawa¹ · Takeshi Kamiya¹ · Ken Sato¹ · Akiko Shiotani¹ · Yuji Naito¹ · Yoshiko Fujikawa¹ · Ryota Hokari¹ · Tatsuhiro Masaoka¹ · Kazuma Fujimoto¹ · Hiroshi Kaneko¹ · Akira Torii¹ · Kei Matsueda¹ · Hiroto Miwa¹ · Nobuyuki Enomoto¹ · Tooru Shimosegawa¹ · Kazuhiko Koike¹

CQ 3–6. Are probiotics effective in treating IBS?

- **Probiotics are effective in treating IBS. Probiotics are recommended for IBS. Strong recommendation, evidence level A, 100% agreed.**
- **Razlika u rezultatima** može se pripisati metodološkim razlikama među ispitivanjima.
- **Probiotici se smatraju korisnima za SIC zbog njihove relativno niske cijene i sigurnosti.**

Probiotics and prebiotics



February 2023



3.7 Irritable bowel syndrome (IBS)

- A reduction in abdominal bloating and flatulence as a result of probiotic treatments is a consistent finding in published studies; some strains may ameliorate pain and provide global relief. The literature suggests that certain probiotics may alleviate symptoms and improve the quality of life in persons with functional abdominal pain.

Efficacy and safety of probiotics in the treatment of irritable bowel syndrome: A systematic review and meta-analysis of randomised clinical trials using ROME IV criteria

[Georgios Konstantis](#)¹ • [Stylios Efstathiou](#)¹ • [Chryssa Pourzitaki](#)   • [Elisavet Kitsikidou](#) •

[Georgios Germanidis](#) • [Michail Chourdakis](#) • [Show footnotes](#)

Published: March 31, 2023 • DOI: <https://doi.org/10.1016/j.clnu.2023.03.01>

- Bez značajne redukcije u IBS-SSS (WMD -43.2 , 95% CI -87.5 to 1.0 , $I^2 = 82.9\%$)
- Nema korelacije za poboljšanje QoL s upotrebom probiotika (SMD -0.64 , 95% CI -1.27 to 0.00 , $I^2 = 93,9\%$)
- Značajna **redukcija nadimanja** (SMD -0.28 , 95% CI -0.47 to -0.09 , $I^2 = 36,0\%$).
- Značajna **smanjenje abdominalnih bolova** (SMD -0.94 , 95% CI -1.53 to -0.35 , $I^2 = 92,2$)

Mikrobiota crijeva i probiotici u bolesnika s pretilošću

- **Prisutna disbioza**, bolesnici s pretilošću imaju **↑više *Firmicutes* i ↓manje *Bacteroidetes*** od mršavih osoba. Korištenje samo koljena (npr. omjer *Firmicutes/Bacteroidetes*) je neprecizno. Kod pacijenata s pretilošću **povećana** je zastupljenost ***Firmicutes*** bakterija, uključujući rodove *Clostridium*, *Lactobacillus* i *Ruminococcus*, dok je *Faecalibacterium prausnitzii* — jedna od najzastupljenijih bakterija u zdravom ljudskom crijevu **smanjena**.
- **Bolesnici s pretilošću** koji su konzumirali dijetu s **niskim udjelom masti ili ugljikohidrata** kroz period od godinu dana su izgubili čak 25% svoje tjelesne težine, a u njihovom debelom crijevu je udio ***Firmicutes* pao ↓**, dok je ***Bacteroidetes* porastao ↑**. Međutim, razine ovih dviju vrsta bakterija nikada nisu dosegle razine onih u mršavih osoba.

Magne F, Gotteland M, Gauthier L, et al. The firmicutes/bacteroidetes ratio: a relevant marker of gut dysbiosis in obese patients? *Nutrients*. 2020;12(5):E1474..

Jumpertz R, Le DS, Turnbaugh PJ, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am. J. Clin. Nutr.* 2011;94:58–65.

Cani, Patrice D., Emilie Moens de Hase, and Matthias Van Hul. 2021. "Gut Microbiota and Host Metabolism: From Proof of Concept to Therapeutic Intervention." *Microorganisms* 9(6):1302

Effects of *Bifidobacterium breve* B-3 on body fat reductions in pre-obese adults: a randomized, double-blind, placebo-controlled trial

Junichi MINAMI^{1*}, Noriyuki IWABUCHI¹, Miyuki TANAKA¹, Koji YAMAUCHI¹, Jin-zhong XIAO², Fumiaki ABE¹ and Naoki SAKANE³

¹Food Ingredients & Technology Institute, Morinaga Milk Industry Co., Ltd., 5-1-83 Higashihara, Zama-shi, Kanagawa 252-8583, Japan

²Next Generation Science Institute, Morinaga Milk Industry Co., Ltd., 5-1-83 Higashihara, Zama-shi, Kanagawa 252-8583, Japan

³Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, 1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan

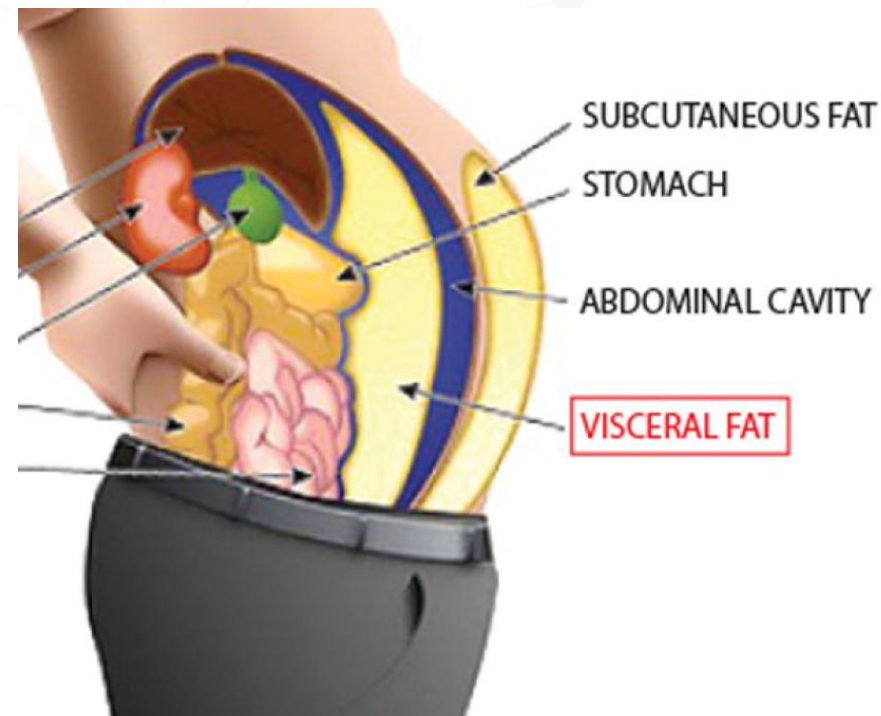
- **Visceralna masnoća** značajno se povećala nakon 4 i 8 tjedana u grupi s placeboom, dok u grupi s **B-3** nije bilo značajne promjene.
- Tjelesna masnoća i postotak tjelesne mase su **značajno smanjeni u B-3 grupi** u odnosu na placebo u 8 i 12 tjednu.

Probiotici u bolesnika s pretilošću i utjecaj na smanjenje tjelesne mase

- **Meta analiza** - od **27** uključenih RKS u meta analizu, njih **23** je prijavilo **pozitivan učinak na gubitak težine**.
- **Uzimanje probiotika i sinbiotika** može dovesti to **značajnog gubitka na težini** u uvjetima da životne navike ostaju nepromijenjene ili u kombinaciji s restrikcijom unosa energije i/ili povećanom fizičkom aktivnosti kroz period od 12 tjedana.
- Najviše upotrebljavani i s najboljim rezultatima na redukciju tjelesne težine su specifični sojevi iz vrsta ***Lactobacillus*** i ***Bifidobacterium*** koji su pokazali najbolje rezultate u **smanjenju tjelesne težine**.
- **Probiotici i sinbiotici** mogu biti od **pomoći u mršavljenju** kod osoba s **prekomjernom tjelesnom težinom i s pretilošću**.

Pretilost i SIC

- **Pretilost** se smatra kao **čimbenik rizika** za različite **GIT simptome**.
- **Indeks tjelesne mase (ITM) i potkožno masno tkivo nisu** rizični faktor za razvoj SIC-a.
- **Visceralna abdominalna pretilost i opsega struka** su rizični faktor za razvoj SIC-a .



Lee CG, Lee JK, Kang Y-S, et al. Visceral abdominal obesity is associated with an increased risk of irritable bowel syndrome. Am J Gastroenterol. 2015;110(2):310-319.

Visceral Obesity Measured By Dual X-Ray Absorptiometry And Bioimpedance As The Predictor For IBS In Obese Patients

**Goran Hauser¹, S. Klobucar Majanovic², A. Belancic³, S. Pletikosic Toncic²,
M. Krpina⁴, M. Tkalcic²**

1. Clinical Hospital Centre Rijeka; Faculty of Health Studies, Rijeka, Croatia

2. University of Rijeka, Rijeka, Croatia

3. Clinical Hospital Centre Rijeka; Faculty of Medicine, Rijeka, Croatia

4. Student, Faculty of Medicine, Rijeka, Croatia

CONCLUSIONS

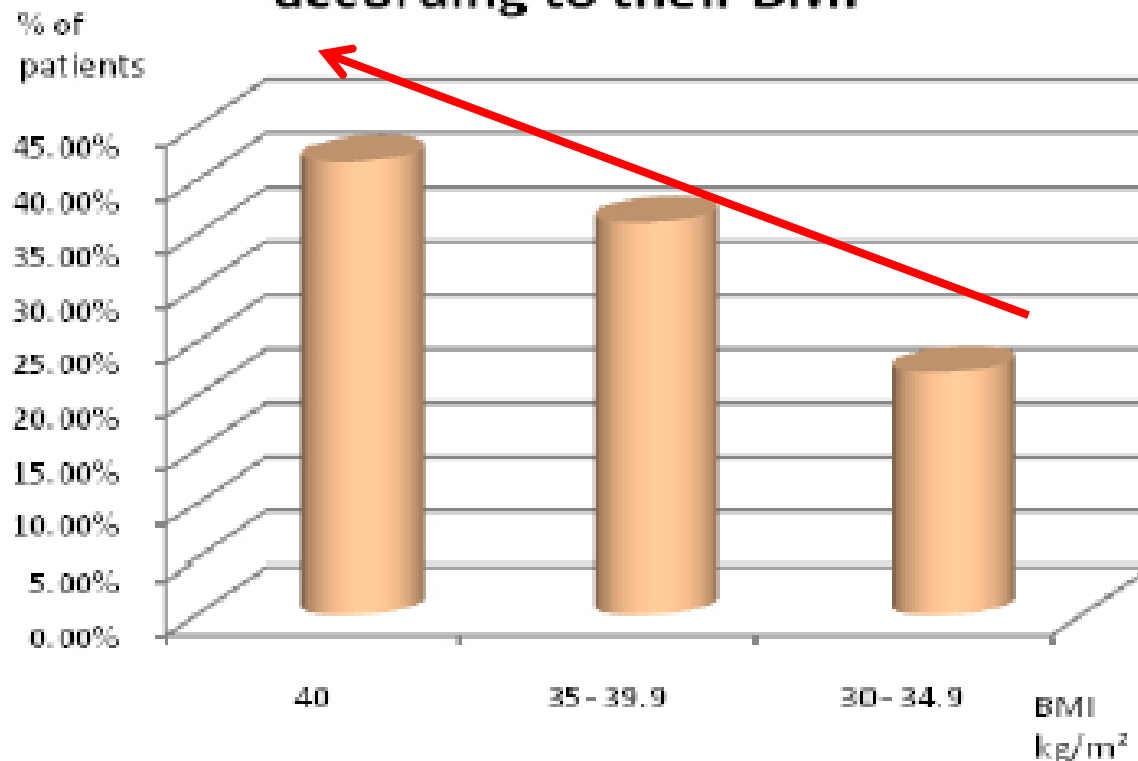
Visceral adiposity measured by the simple and non-invasive method is associated with an increased risk of IBS. Bioimpedance and DEXA are reliable methods for VAT measurement. However, neither FFM, FM, BMI and WC are associated with an increased risk of IBS.

G. Hauser, S. Klobučar Majanović, A. Belančić, S. Pletikosić Tončić, M. Krpina, M. Tkalčić. Visceral obesity measured by dual X-ray absorptiometry and bioimpedance as the predictor for IBS in obese patients. *Neurogastroenterology & Motility*. 2019;31(S4):e13671.

Prevalencija SIC-a u bolesnika s pretilošću

- Prevalencija SIC-a u bolesnika s pretilošću je blizu **30%** i raste proporcionalno s ITM.
- RKS s probioticima u ovoj subpopulaciji su **oskudna**.

Distribution of IBS patients according to their BMI



S. Oubaha, S. El Yazal, N. Bouznad, et al. Prevalence of Irritable Bowel Syndrome in Obese People. Archives of Gastroenterology and Hepatology. 2018; 1(2):16-19.

Schneck AS, Anty R, Tran A, et al. Increased prevalence of irritable bowel syndrome in a cohort of french morbidly obese patients candidate for bariatric surgery. Obes Surg. 2016;26(7):1525-1530.

Probiotici utjecaj na smanjenje težine

- **Kišobran meta analiza - 29 meta analiza** na 14,366 pacijenata, uključujući **112, 78, i 38 studija** za **indeks tjelesne mase (ITM), tjelesna težina (TT) i opseg struka (OS)**.
- Kvaliteta u metodologiji (AMSTAR2) je bila umjerena u 83%, niska u 10% i kritično niska u 7% uključenih studija.
- **Značajno učinkoviti u smanjenju ITM, TT i OS.**
- **Značajniji učinak na TT** je bio zapažen kod intervencija koje su trajale **>8 tjedana** i u **bolesnika s pretilošću**.



ESPEN Guideline

European guideline on obesity care in patients with gastrointestinal and liver diseases – Joint ESPEN/UEG guideline[☆]

Stephan C. Bischoff ^{a,*}, Rocco Barazzoni ^b, Luca Busetto ^c, Marjo Campmans-Kuijpers ^d, Vincenzo Cardinale ^e, Irit Chermesh ^f, Ahad Eshraghian ^g, Haluk Tarik Kani ^h, Wafaa Khannoussi ^{i,j}, Laurence Lacaze ^{k,l}, Miguel Léon-Sanz ^m, Juan M. Mendive ⁿ, Michael W. Müller ^o, Johann Ockenga ^p, Frank Tacke ^q, Anders Thorell ^r, Darija Vranesic Bender ^s, Arved Weimann ^t, Cristina Cuerda ^u

Recommendation 24

Selected probiotics can be recommended for achieving symptom relief in overweight and patients with IBS and obesity. Grade of recommendation 0 – strong consensus 93% agreement Commentary

A large number of studies and several meta-analyses have investigated the effect of different probiotics and their combinations on IBS symptoms, including pain and discomfort, bloating, flatulence, and global symptoms scores [153–155]. Administered probiotics included *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* strains [155]. Interpretation of study results is hindered by relevant limitations such as large variability in treatment dose, duration, strain combination, and high risk of bias in some studies [153,155]. However, selected probiotics have been recommended for patients with IBS at a recommendation grade B [156], and this recommendation can be extrapolated to IBS patients with obesity at grade 0 because of the extrapolation. For the scope of this guideline, it should be pointed out that no studies have directly addressed microbiota treatment in patients with IBS and overweight or obesity. Some studies have included patients with overweight or obesity with no reported subgroup analyses [157–160]. There is however no evidence for exclusion of patients with overweight or obesity from reported benefits of selected probiotic treatments.

Prebiotics and synbiotics including inulin, fructan, galactooligosaccharides, and oligosaccharides along with probiotics have been investigated in a smaller number of studies [153,161], making conclusions even more difficult on overall treatment efficacy as well as the superiority of specific combinations [162]. Studies have also investigated the effect of fecal microbiota transplantation on IBS symptoms with published meta-analyses showing no definitive evidence for efficacy [163–165].

Table 1. Primary Endpoints Used in IBS Clinical Trials

Drug and Indication	Primary Endpoint	Questions (Single-Item) Used to Assess Efficacy	Responses
Alosetron — IBS-D ¹	Adequate relief	<i>In the past 7 days, have you had adequate relief of your IBS pain or discomfort?</i>	Binary (Yes/No)
Tegaserod — IBS-C ²	Satisfactory relief	<i>Did you have satisfactory relief of your overall IBS symptoms during the last week?</i>	Binary (Yes/No)
		<i>Did you have satisfactory relief of your abdominal discomfort or pain during the last week?</i>	Binary (Yes/No)
	Subject Global Assessment of Relief (SGA)	<i>Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit. Compared to the way you usually felt before entering the trial, how would you rate your relief of symptoms during the past week?</i>	5-Point Likert scale
Lubiprostone — IBS-C ³	Modified version of the SGA	<i>How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared with how you felt before you entered the trial?</i>	7-Point Likert scale

- 1.
- 2.
- 3.

Comparison of adequate relief with symptom, global, and responder endpoints in linaclotide phase 3 trials in IBS-C

United European Gastroenterology Journal

2015, Vol. 3(1) 53–62

© Author(s) 2014

Reprints and permissions:

sagepub.co.uk/journalsPermissions.nav

DOI: 10.1177/2050640614555946

ueg.sagepub.com



Michael Camilleri¹, Anthony J Lembo², Bernard J Lavins³,
James E MacDougall³, Robyn T Carson⁴, Valerie SL Williams⁵,
Lauren M Nelson⁵, Steven J Shiff⁴, Mark G Currie³, Caroline B Kurtz³
and Jeffrey M Johnston³

- Postoji **znatna podudarnost** tjednih procjena **AR rezultata s FDA i EMA kriterijima odgovora**. Kada se **AR** koristi kao referentna vrijednost, vrijednosti za klinički značajne promjene abdominalnih i crijevnih simptoma **dobro odgovaraju** vrijednostima potrebnima za postizanje FDA i EMA ishoda.



Effects of an oral synbiotic on the gastrointestinal immune system and microbiota in patients with diarrhea-predominant irritable bowel syndrome

Adrian Mathias Moser^{1,2} · Walter Spindelboeck^{1,2} · Bettina Halwachs^{2,3} · Heimo Strohmaier⁴ · Patrizia Kump^{1,2} · Gregor Gorkiewicz^{2,3} · Christoph Högenauer^{1,2}

- **Pilot studija** (ne randomizirana, otvorena, prospektivna, bez kontrolne skupine) oralni sinbiotik [sadrži prebiotike (maltodekstrin, inulin, fruktooligosaharide) i 9 ljudskih bakterijskih sojeva (*Lactobacillus casei* W56, *Lactobacillus acidophilus* W22, *Lactobacillus paracasei* W20, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactobacillus plantarum* W62, *Bifidobacterium bifidum* W23), s minimalno 7,5 milijardi bakterija (eng. colony forming units, CFU) u 1 dozi (3 g) i 15 milijardi bakterija u 2 doze (6 g).
- **Pozitivan utjecaj** na gastrointestinalni imunološki sustav, mikrobiotu i težinu simptoma SIC-a u bolesnika koji boluju od SIC-a s proljevom.

Učinak kombinacije probiotika na simptome i fekalnu mikrobiotu u bolesnika s pretilošću i sindromom iritabilnog crijeva

- **Trostruko slijepa RKS, multicentrična**
- Potreban broj bolesnika: **100 (64)**
 - **50 (32)** prima **probiotik** (*Lactobacillus casei* W56, *Lactobacillus acidophilus* W22, *Lactobacillus paracasei* W20, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactobacillus plantarum* W62, *Bifidobacterium bifidum* W23)
 - **50 (32)** prima **placebo**
- **Broj posjeta: 3**
 - period **probira** (screening): **-1. tjedan**
 - period **randomizacije**: **0. tjedan**
 - period **završetka tretmana**: **8. tjedan**

Uključujući kriteriji

- Muški ili ženski bolesnici
- U dobi između **18 i 65 godina**
- Bolesnici sa **sindromom iritabilnog crijeva (SIC)** prema Rimskim kriterijima IV (Rome IV).
- Bolesnici s indeksom tjelesne mase (**ITM**) **≥ 30 kg/m²**
- **Potpisani informirani pristanak**

Isključujući kriteriji

- **Trudnoća ili dojenje**
- **Teška sistemska bolest** (rak, gastrointestinalna bolest poput ulceroznog kolitisa, Crohnove bolesti, celijaklija, rekurentni divertikulitis) kronično zatajenje bubrega, endokrini poremećaji, metabolički poremećaji, angina, kongestivno zatajenje srca, nekontrolirana hipertenzija.
- **Prethodna abdominalna operacija** osim apendektomije, kolecistektomije i operacije abdominalne hernije.
-

Ciljevi studije

- **Primarni ciljevi:**

- ispitati učinak probiotika na **odgovarajuće olakšanje (OO)** od sveukupnih simptoma SIC-a. Smatra se da je ispitanik odgovorio na intervenciju ako odgovori s pozitivno „DA“ na najmanje 50% procjene OO 10-tjednog razdoblja ispitivanja (5 od 10 tjednih procjena).

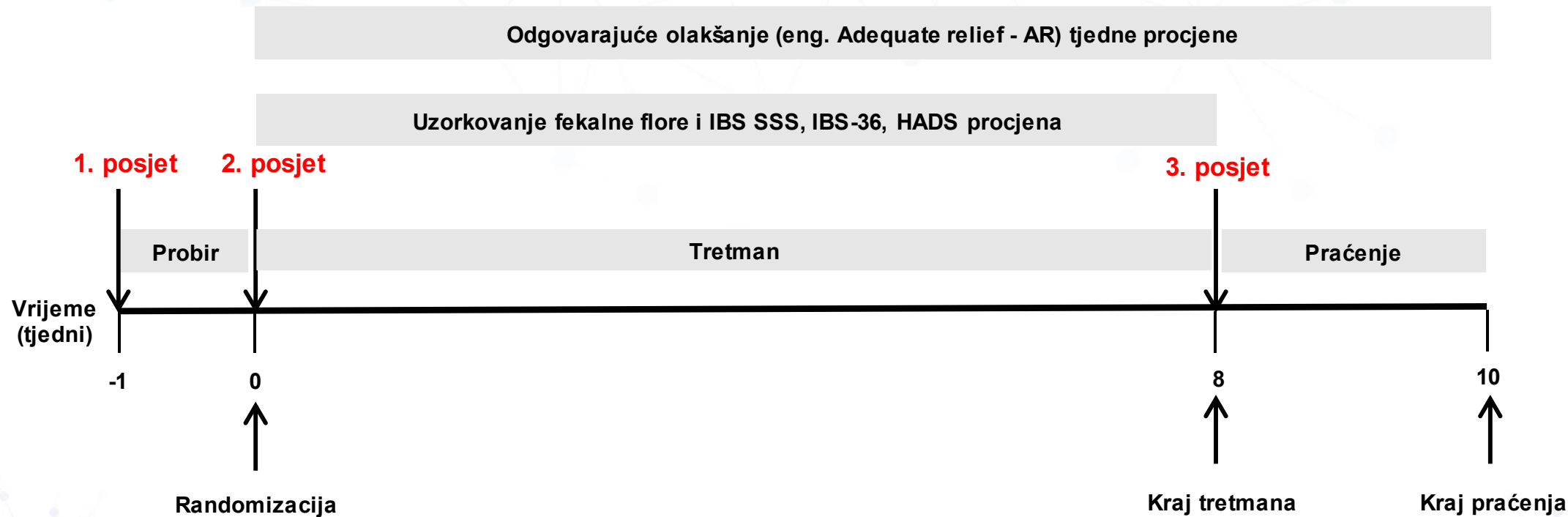
- **Sekundarni ciljevi:**

- ispitati učinak probiotika na **fekalnu floru**

- **Ostali ciljevi**

- ispitati učinak probiotika na **težinu simptoma SIC-a** (upitnik **IBS SSS**)
- ispitati učinak probiotika na **kvalitetu života bolesnika sa SIC-om** (upitnik **IBS-36**)
- ispitati učinak probiotika na **psihološko stanje** bolesnika (upitnik **HADS**)

Shematski prikaz dizajna studije

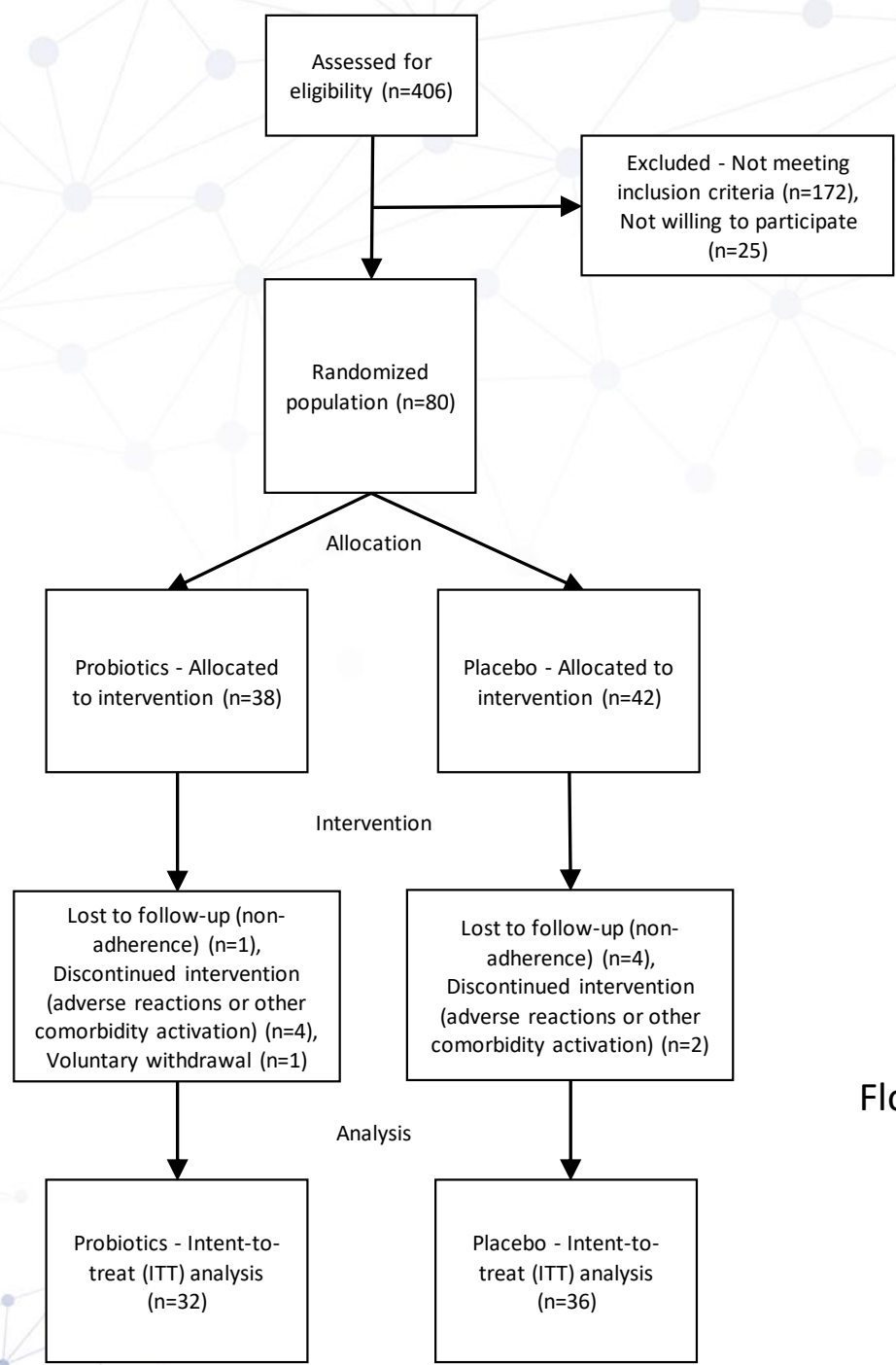


Statistička analiza

- Izračun uzorka: **36% razlika u OO simptoma SIC-a** između probiotika i placeba (stopa **OO 48%** u skupini na probiotiku i **12%** u skupini na placebo)
- Broj ispitanika potreban za istraživanje na razini statističke značajnosti od **0,05 (α)** sa snagom istraživanja od **80% (β)** je **64 (32 u svakoj skupini)**, a dobiven je testiranjem temeljen na hi (**χ^2**) kvadrat testu. S pretpostavkom osipanja od 36% potrebno je ukupno **100 ispitanika (50 ispitanika u svakoj skupini)**.

Status studije: **završena (LPLV)** - analize u tijeku

- **406** pacijenta bilo u probiru,
 - **105** (26%) bili kandidati za studiju
 - od toga 25 (21%) nije bilo zainteresirano za sudjelovanje
 - Uključeno **80** (20%) pacijenata
- **Završilo tretman: 68**
 - **Probiotik: 32**
 - **Placebo: 36**
- **Osipanje: 12** (15%)
- **Statističke analize do kraja Q4 2025.**



Flowchart of participants through the study protocol

Baseline Patient Characteristics of the intention-to-treat population

Characteristics	Probiotic (n = 32)	Placebo (n = 36)	P value
Age, median (IQR), years	47.6 (42.0-55.5)	47.9 (42.8-53.5)	0.91
Body mass index, median (IQR) ^a	39.2 (34.4-42.7)	37.4 (32.3-41.6)	0.24
Sex			0.57
Female	28 (87.5)	33 (91.7)	
Male	4 (12.5)	3 (8.3)	
IBS subtype			0.49
IBS-C	12 (37.4)	13 (36.1)	
IBS-D	10 (31.3)	8 (22.2)	
IBS-M	10 (31.3)	15 (41.7)	
IBS-U	0 (0)	0 (0)	
IBS-SSS			0.56
Remission (<75)	1/31 (3.2)	4/34 (11.8)	
Mild (75-174)	13/31 (41.9)	10/34 (29.4)	
Moderate (175 to 300)	15/31 (48.4)	16/34 (47.1)	
Severe (>300)	2/31 (6.5)	4/34 (11.8)	
IBS-SSS	195.00 ± 77.16 /31	196.21 ± 82.21 /33	0.95
IBS-36	101.10 ± 46.60 /31	87.91 ± 44.37 /33	0.27

Data are expressed as mean ± s.d. Or IQR or n (%). P-values indicate comparison between groups. (*P < 0.05).

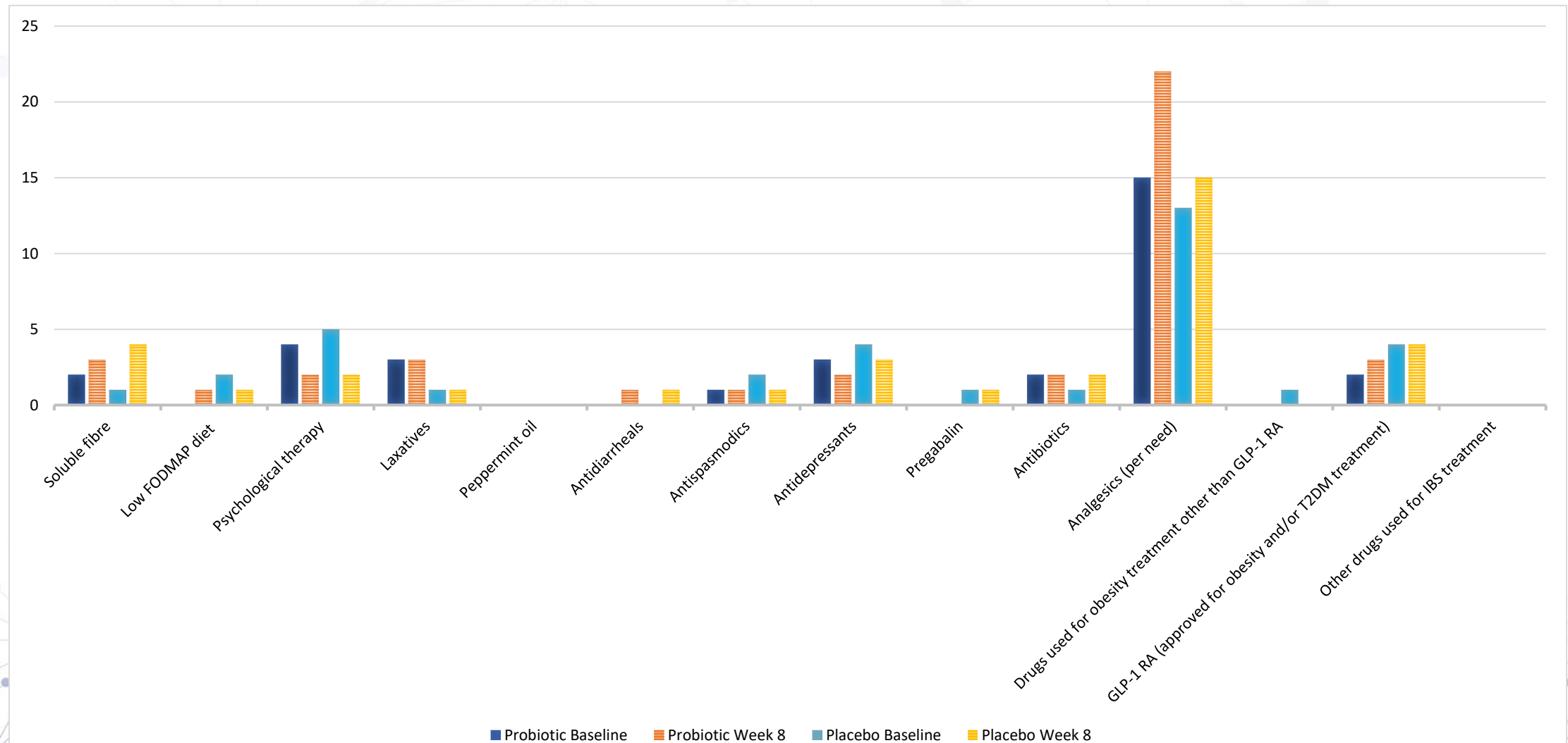
^a Calculated as weight in kilograms divided by height in meters squared.

Baseline Patient Characteristics of the intention-to-treat population

Characteristics	Probiotic (n = 32)	Placebo (n = 36)	P value
HADS			
Depression	11/31 ^b (35.5)	11/34 ^b (32.4)	0.79
Anxiety	16/31 ^b (51.6)	21/34 ^b (61.8)	0.41
Family history of intestinal disorders or diseases	8 (32)	4 (11.1)	0.13
Probiotic usage			0.61
Never	14 (44.8)	14 (38.9)	
Sometimes	18 (56.2)	21 (58.3)	
Daily	0 (0)	1 (2.8)	
Smoking			0.02*
Never	13 (40.6)	26 (72.2)	
Former smoker	9 (28.1)	7 (19.4)	
Smoker	10 (31.3)	3 (8.3)	
Alcohol consumption			0.68
Never	18 (56.3)	22 (61.1)	
Sometimes	14 (43.8)	14 (38.9)	
Daily	0 (0)	0 (0)	
Physical activity			0.80
No activity	10 (31.3)	12/35 ^b (34.3)	
<30 min 3 times per week	11 (34.4)	12/35 ^b (34.3)	
>30 min 3 times per week	11 (34.4)	11/35 ^b (31.4)	

Data are n/N (%), unless otherwise indicated. ^b Number of analysed participants. (*P < 0.05).

Konkomitanta terapija na početku i na kraju studije



Descriptive summary of primary and other efficacy parameters (not statistically analysed)

Outcomes	Probiotic (n = 32)	Placebo (n = 36)	Absolute difference
<i>Primary outcome</i>			
Adequate relief	28 (87.5)	28 (77.8)	9.7
<i>Other prespecified outcomes</i>			
IBS-SSS			
Improvement by ≥50 points	11/29 (37.9)	5/25 (20.0)	17.9
Improvement by ≥100 points	11/29 (37.9)	5/25 (20.0)	17.9
IBS-36			
Improvement by ≥ 36 points	10/29 (34.5)	12/27 (44.4)	9.9
HADS			
HADS improvement by ≥6 points	5/27 (18.5) ^a	6/28 (21.4) ^b	3.1
HADS-D improvement by ≥3 points	6/27 (22.2) ^a	8/28 (28.6) ^b	6.4
HADS-A improvement by ≥4 points	4/27 (14.8) ^a	5/28 (17.9) ^b	3.1

Data are n/N (%), unless otherwise indicated. Results are analysed in the intention to treat (ITT) population, unless otherwise indicated. IBS-SSS=irritable bowel syndrome-severity scoring system. HADS= Hospital Anxiety and Depression Scale. HADS-A=HADS anxiety. HADS-D=HADS depression.

Incidence of adverse events reported by patients during follow-up

Adverse event	Probiotic (n = 32)	Placebo (n = 36)	P value
Abdominal distension	1 (3.1)	1 (2.8)	1.0
Abdominal pain	2 (6.3)	2 (5.6)	1.0
Bloating	1 (3.1)	2 (5.6)	1.0
Constipation	2 (6.3)	1 (2.8)	0.60
Diarrhea	0 (0)	3 (8.3)	0.24
Aggravated irritable bowel syndrome	1 (3.1)	0 (0)	0.47
Nausea	1 (3.1)	0 (0)	0.47
Increased appetite	0 (0)	1 (2.8)	1.0
Rash	0 (0)	1 (2.8)	1.0

Data are n/N (%). Adverse events are graded as Grade 1 (mild) to Grade 2 (moderate) according to Common Terminology Criteria for Adverse Event (CTCAE).

Patient reported adverse events are probably due to the irritable bowel syndrome (IBS) itself, less likely intervention related.

The Effect of a Probiotic Mixture in Obese Patients With Irritable Bowel Syndrome

ClinicalTrials.gov ID ⓘ NCT04760353

Sponsor ⓘ University Hospital Rijeka

Information provided by ⓘ Goran Hauser, University Hospital Rijeka (Responsible Party)

Last Update Posted ⓘ 2025-09-25

Official Title

The Effect of a Probiotic Mixture on the Symptoms and Fecal Microbiota in Obese Patients With Irritable Bowel Syndrome, Randomised, Double-blind, Controlled Study

Conditions ⓘ

IBS - Irritable Bowel Syndrome

Obesity

Intervention / Treatment ⓘ

- Dietary Supplement: Probiotic mixture (OMNi-BiOTiC STRESS)
- Other: Placebo

Other Study ID Numbers ⓘ

- Omni Stress 1.1

Study Start (Actual) ⓘ

2021-11-10

Primary Completion (Estimated) ⓘ

2025-10-20

Study Completion (Estimated) ⓘ

2025-10-20

Enrollment (Estimated) ⓘ

100

Study Type ⓘ

Interventional

Phase ⓘ

Not Applicable

