**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 64999

**Manuscript Type:** MINIREVIEWS

**Role of exercise in preventing and restoring gut dysbiosis in patients with inflammatory bowel diseases: A review**

Koutouratsas T *et al*. Gut dysbiosis

Tilemachos Koutouratsas, Anastassios Philippou, George Kolios, Michael Koutsilieris, Maria Gazouli

**Tilemachos Koutouratsas, Maria Gazouli,** Department of Basic Medical Sciences, Laboratory of Biology, Medical School, National and Kapodistrian University of Athens, Athens 11527, Greece

**Anastassios Philippou, Michael Koutsilieris,** Department of Basic Medical Sciences, Laboratory of Physiology, School of Medicine, National and Kapodistrian University of Athens, Athens 11527, Greece

**George Kolios,** Department of Medicine, Laboratory of Pharmacology, Democritus University of Thrace, Alexandroupolis 68100, Greece

**Author contributions:** Koutouratsas T, Philippou A, and Gazouli M performed the majority of the literature search and writing; Koutsilieris M, Kolios G, and Gazouli M conceived the study, made critical revisions, and wrote the manuscript; all the authors made critical revisions and provided approval of the final version of the manuscript to be published.

**Corresponding author: Maria Gazouli, PhD, Professor,** Department of Basic Medical Sciences, Laboratory of Biology, Medical School, National and Kapodistrian University of Athens, Michalakopoulou 176, Goudi, Athens 11527, Greece. mgazouli@med.uoa.gr

**Received:** February 26, 2021

**Revised:** April 19, 2021

**Accepted:** July 12, 2021

**Published online:**

**Abstract**

Inflammatory bowel diseases (IBD) include a spectrum of chronic inflammatory disorders of the gastrointestinal tract whose pathogenesis is yet to be elucidated. The intestinal microbiome has been studied as a causal component, with certain microbiotic alterations having been observed in subtypes of IBD. Physical exercise is a modulator of the intestinal microbiome, causing shifts in its composition that are partially corrective of those observed in IBD; furthermore, physical exercise may be beneficial in patients with certain IBD subtypes. This review studies the effects of physical exercise on the human gut microbiome while investigating pathophysiologic mechanisms that could explain physical activity’s clinical effects on patients with IBD.

**Key Words:** Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Pouchitis; Microbiome; Exercise

Koutouratsas T, Philippou A, Kolios G, Koutsilieris M, Gazouli M. Role of exercise in preventing and restoring gut dysbiosis in patients with inflammatory bowel diseases: A review. *World J Gastroenterol* 2021; In press

**Core Tip:** Inflammatory bowel diseases (IBD) are a spectrum of diseases that are characterized by their complex pathogenesis. The intestinal microbiome is thought to be a part of their pathogenesis, with certain alterations having been associated with IBD subtypes. Physical exercise is a modulator of the intestinal microbiome that has, furthermore, been associated with positive clinical outcomes in certain patients with IBD. Herein we discuss certain types of physical exercise, their effect on the intestinal microbiome, and its clinical effects on patients with IBD, as well as investigating underlying pathophysiologic mechanisms that could mediate the observed associations.

**INTRODUCTION**

Inflammatory bowel disease (IBD) comprises a spectrum of chronic inflammatory diseases that primarily but not exclusively affect the gastrointestinal tract, including ulcerative colitis (UC), Crohn’s disease (CD), and other related conditions[1]. Their pathogenesis is classically thought to include interactions between genetic, immune-mediated, and environmental factors[2]. Studies on the molecular epidemiology of IBD have shown that the gut microbiome composition is a biomarker of prognostic importance for CD and UC[3]. Other molecular phenotypes include *NOD2*, *MHC*, and *MST1* genotypes, which are correlated to disease location and activity, microRNA miR-215 levels, and DNA methylation, which are correlated to disease activity, *FOXP3* haplotype, which is of prognostic importance, and oncostatin M and IL-1β levels, which predict response to anti-tumor necrosis factor therapy[[3](#_ENREF_3),[4](#_ENREF_4)]; furthermore, serum C-reactive protein levels correlate to disease activity but are generally nonspecific[[4](#_ENREF_4)]. Increased serum miR-595 and miR-1246 levels are associated with active IBD[4]. Serum interleukin (IL)-2 and IL-6l and positivity for anti-bacterial flagellin, anti-outer membrane porin C, anti-A4-Fla2, and anti-Fla-X antibodies predict recurrence of disease[4]. The heterogeneity of IBD phenotypes underlines the need for new markers that can subclassify, diagnose, inform prognosis, and guide IBD treatment; but owing to the low sensitivity or specificity of known molecular markers, current knowledge is far from adequate to support their use in everyday clinical practice, a limitation that includes the microbiome as biomarker[[3](#_ENREF_3),[4](#_ENREF_4)].

Early studies on animal models have shown that immune cells could not cause inflammation in the absence of intestinal bacteria, therefore suggesting a putative role for the intestinal microbiome in the induction and/or maintenance of local inflammation and disease[5]. This was further supported by the observation that intestinal inflammation in IBD was greatest in parts of the bowel richer in bacteria[2]. Further studies have demonstrated that certain patterns of microbiotic alterations, including increases or reductions in the plethora of bacterial, fungal, and viral species, were likely linked to the risk for IBD[2].

Physical exercise is a possible modulator of intestinal microbiome composition, altering the functional activity of the gut ecosystem. Exercise is associated with increased biodiversity and a beneficial metabolic function, while exhaustive exercise training might be associated with dysbiosis of the gut microbiota, promoting negative metabolic effects and inflammation[[6](#_ENREF_6),[7](#_ENREF_7)]. Thus, physical activity/exercise has been studied as a significant modifier of the intestinal microbiome in animal[[8](#_ENREF_8),[9](#_ENREF_9)] and human[[6](#_ENREF_6),[7](#_ENREF_7),[10](#_ENREF_10)] studies. Specifically, more active individuals’ microbiomes tend to harbor a higher abundance in *Akkermansia muciniphila*, a health-promoting species, as well as decreased Bacteroidetes bacteria and increased bacterial diversity[[11](#_ENREF_11),[12](#_ENREF_12)]. Specific types of physical exercise have not only been associated with microbiotic signatures, but also with a reduction in endotoxemia and serum inflammatory markers[[11](#_ENREF_11),[13](#_ENREF_13),[14](#_ENREF_14)]. These alterations persist as statistically significant, even when normalizing for age, weight, body composition, and nutritional habits as confounding factors[15]. Nevertheless, it should be noted that researchers have also reported a lack of correlation between a certain type of exercise and changes in the microbiome[[16](#_ENREF_16),[17](#_ENREF_17)]; moreover, some contradictions as to the observed patterns of microbiotic alterations associated with exercise are evident[[18](#_ENREF_18)]. This ambiguity is, however, expected to be partly clarified when common definitions and detailed description of exercise characteristics [*i.e.* frequency, intensity, type (mode), time (duration), and volume/dose (duration x intensity)] and methods of fecal sampling are utilized among the same study groups.

Given the established pathobiological role for the microbiome in IBD and taking into account the more recent data assessing patterns of microbiotic alterations associated with exercise, this review aims to summarize and clarify the important findings linking dysbiosis in IBD to physical activity, with a focus on preventative medicine and therapeutics.

**METHODlogy**

Our literature search utilized the PubMed literature database. Search keywords included “inflammatory bowel disease”, “IBD”, “ulcerative colitis”, “Crohn’s disease”, “indeterminate colitis”, “microbiome”, “microbiota”, “physical activity”, “exercise”, as well as combinations of the aforementioned with the AND/OR operators. Articles were first filtered by title, followed by abstract screening, and the remaining were finally selected based on their full text.

**EXERCISE AND ITS INFLUENCE ON THE MICROBIOME**

In healthy mice, *Allobaculum* and *Clostridiales* are more abundant in exercised mice than in controls[19]. In diabetic mice, total intestinal bacteria and Enterobacteriaceae are lower in the exercise groups than in diabetic controls[9]. In high-fat diet obese mice, exercise increases Bacteroidetes as well as increases the Bacteroidetes/Firmicutes ratio in the cecum and colon[20]. In an early obesity and non-alcoholic fatty liver disease model, where male rats fed a control or a high-fat diet, a combined aerobic and resistance exercise training resulted in increased *Parabacteroides*, *Bacteroides*, and *Flavobacterium* genera, while *Blautia*, *Dysgonomonas*, and *Porphyromonas* exhibited an opposite pattern[[8](#_ENREF_8)] (Table 1).

Several factors that modify the human gut microbiome have been identified; those include country of residence, specific genotypes (such as those affecting the ABO antigens), delivery by caesarian section, diet, cigarette smoking, breastfeeding, gastroenteritis, increased hygiene, use of antibiotics, obesity, immune response, as well as physical exercise[[2](#_ENREF_2),[13](#_ENREF_13),[21](#_ENREF_21),[22](#_ENREF_22)]. Human studies have shown that sedentary individuals have a predominance of *Bacteroides* and *Parabacteroides* in their gut microbiome, while participants with a higher level of activity, as gauged by accelerometers, have a predominance of *Coprococcus*, *Blautia*, and *Eubacterium*[23]. Women with an active lifestyle have a higher proportion of *Faecalibacterium prausnitzii*, *Roseburia hominis,* and *Akkermansia muciniphila* bacteria in their gut than sedentary women[24]. Aerobic brisk walking increases *Bacteroides* species in healthy elderly women[25]. Endurance training has been observed to reduce *Streptococcus*, *Proteobacteria*, *Porphyromonadaceae*, *Odoribacter*, *Desulfovibrionaceae*, and *Enterobacteriaceae* and to increase *Verrucomicrobiaceae*, *Bifidobacteriaceae*, *Dorea*, *Anaerofilum*, and *Akkermansia* bacteria in overweight women[26]. In obese children, a strength and endurance combined training program led to an increase in *Blauti*a, *Dialister,* and *Roseburia* species, accompanied by a reduction in inflammasome activation[14]. In elderly men, endurance exercise has been observed to reduce *Clostridium difficile* and increase intestinal populations[[27](#_ENREF_27)] Male elite rugby players have been found to have a more diverse microbiome than body mass index (BMI)-matched controls, with the athletes having higher proportions of *Akkermansiaceae* and *Akkermansia* than high-BMI controls and lower proportions of *Lactobacillaceae*, *Bacteroides,* and *Lactobacillus* than low-BMI controls[[10](#_ENREF_10)]. In swimmers, a reduction in training volume is accompanied by a significant reduction in *Coprococcus* and *Faecalibacterium* populations[28]. In marathon runners, *Lentisphaerae* and *Acidobacteria* increase in intestinal population after running[29]. Ultra-endurance exercise has been observed to increase butyrate-producing bacteria, such as *Subdoligranulum* and *Roseburia hominis*, which are thought to reduce intestinal inflammation by producing butyrate[30]. In martial arts athletes, *Parabacteroides, Phascolarctobacterium, Bilophila, and Oscillibacter* are higher in higher-level athletes than in lower-level ones, with *Allisonella*, *Citrobacter,* and *Megasphaera* found at lower levels[31]. Other researchers have reported no change in gut bacterial diversity or composition after short-term high-intensity interval training in lean and overweight men[16]. Exercise has also been found to induce microbial transformations in the context of damaging intestinal conditions, such as a high-fat diet and toxic substances[32] (Table 1). These changes could in part be attributed to increased gut motility during exercise, which promotes shedding of loosely bound bacteria and the growth of health-promoting species[33].

**ROLE OF THE MICROBIOME IN IBD**

Patients with CD have a diminished diversity of the fecal intestinal microbiome, with Lachnospiraceae, Bacteroidetes, and the species *Clostridium leptum* being decreased, with Proteobacteria, Actinobacteria, and the genus *Prevotella* being increased[[13](#_ENREF_13)]. Patients with inflammatory bowel disease also have increased *Fusobacterium*, *Pasturellaceae*, *Ruminococcus* *gnavus*, *Veillonellaceae*, *Candida* *albicans*, *Candida* *tropicalis*, *Clavispora* *lusitaniae*, *Cyberlindnera* *jadinii*, *Kluyveromyces* *marxianus,* and *Caudivirales* in their gut microbiota, as well as decreased *Bacteroides*, *Bifidobacterium*, *Clostridium* XIVa, *Clostridium* IV, *Faecalibacterium* *prausnitzii*, *Roseburia*, *Suturella*, and *Saccharomyces cerevisiae*[[2](#_ENREF_2)]. Therefore, it can be argued that intestinal dysbiosis may be a component of IBD pathogenesis[34].

The involvement of the microbiome in the pathogenesis of IBD is further supported by the effectiveness of antibiotic therapy in the treatment of certain IBD phenotypes, such as perianal CD and pouchitis, and in the prevention of postoperative relapse in patients with CD[2].

Fecal microbiota transplantation involves the transfer of feces from a donor to the GI tract of a recipient, as an attempt to enrich the recipient’s gut microbiota and correct any dysbiosis. Fecal microbiota transplantation is currently systematically used in the treatment of *Clostridium difficile* colitis[35]. Some researchers have also investigated its implementation in IBD therapeutics, with some promising findings having been reported, although no concrete conclusions can yet be drawn about its efficacy and safety, plausibly owing to the dissimilarities between the associated studies[35].

**ANIMAL CLINICAL DATA**

Gut microbiota transplant from exercise-trained mice leads to a reduction in inflammatory markers in the distal colons of sedentary mice, combined with an attenuated colitis histology score[36]. In mouse models of colitis, voluntary treadmill exercise has been found to reduce inflammation while forced exercise exacerbates tissue damage and leads to increased mortality[37]. The same researchers then attributed part of this effect to an increase in *Tenericutes* bacteria in the large intestine in the forced-exercise group, since the family *Mollicutes*, a member of the phylum *Tenericutes*, hasbeen linked to UC in humans[38]. In another study, exercise was shown to ameliorate the symptoms of chemically induced colitis and to alter significantly gut microbiota, with decreased populations of *Bacteroides vulgatus* and increased numbers of *Akkermansia muciniphila*[39]. In mice born without a normal mucus layer in their intestines due to a genetic knockout of mucin-2, exercise neither significantly alters the gut microbiome nor reduces the severity of chronic colitis, in contrast to wild-type mice where both effects have been observed[[40](#_ENREF_40)].

**HUMAN CLINICAL DATA**

Based on current literature, it is not clear whether dysbiosis is a cause or a result of IBD[[13](#_ENREF_13)]; however, some conclusions could be drawn from certain scientific findings: Disease activity is mostly focused on bowel segments where the fecal stream is slower and bacterial populations are higher[[2](#_ENREF_2)]. Mutations in genes affecting the functions of intestinal Paneth cells (*e.g.,* *NOD2*), which defend the small intestine against bacteria, are risk factors for IBD[[2](#_ENREF_2)]; moreover, exposure to antibiotics in early life is linked to IBD later in life[[13](#_ENREF_13)]. Antibiotics are, however, effective in certain conditions involving IBD, such as in inflammation of the ileoanal pouch after colectomy indicated by IBD-related complications[41]. Surgical fecal diversion is beneficial in the treatment of CD, as bowel segments excluded from the fecal stream tend to show remission[[2](#_ENREF_2)]; furthermore, probiotics and fecal transfer are a therapeutic option for inducing and maintaining IBD remission[[13](#_ENREF_13)]. These findings suggest that there exists a causal component to the microbiotic patterns associated with IBD, despite the inconsistencies between observed microbiotic changes as reported by different studies[13].

Regarding the probable protective effect of exercise in IBD, it is thought to stem from anti-inflammatory actions[6]. These include the secretion of myokines by skeletal muscles, such as myostatin, irisin, IL-15, brain-derived neurotrophic factor, myonectin, decorin, and secreted protein acidic and rich in cysteine, mediators with autocrine, paracrine, and endocrine anti-inflammatory actions[[42](#_ENREF_42)]; moreover, in obese humans, exercise has been found to alter the gut microbiome and reduce endotoxemia, as measured by the levels of the endogenous protein lipopolysaccharide binding protein[[11](#_ENREF_11)], thus suggesting another probable anti-inflammatory effect for physical activity. Exercise training has also been found to reduce the levels of NLR Family Pyrin Domain Containing 3 and caspase 1, proteins that participate in the inflammasome activation pathway, in obese children[14].

Several mechanisms have been proposed by which exercise may influence gut microbiota. These include crosstalk between muscles and the gut microbiota through the 5’ adenosine monophosphate-activated protein kinase and fasting-induced adipose factor pathways as well a reduction of fecal bile acids, an increase in production of short-chain fatty acids, an increase in gut luminal immunoglobulin A, a reduction in luminal transit time, and the activation of the stress hypothalamic-pituitary-adrenal axis, effects found to be produced by exercise[[43-46](#_ENREF_43)].

The functions of a healthy microbiome include metabolic functions, such as the production of anti-inflammatory short-chain fatty acids, vitamin K, and biotin, protective effects, such as induction of secretions that attack pathogenic bacteria, triggering of mucosal proliferation through the Toll-like receptor pathway, inhibition of adhesion of pathogenic bacteria, and trafficking of neutrophils, as well as trophic functions, *i.e.* protecting the intestinal mucosa from immune-mediated damage[[46-48](#_ENREF_46)]. Part of the pathogenesis of IBD is thought to include a loss of these effects, probably caused by a damaging shift to the microbial composition in the gut[1]. These include reductions in Bacteroidetes, *Clostridium leptum*, *Prevotella*, *Bifidobacterium*, and *Roseburia* as well as increases in Proteobacteria, as mentioned above. All of these alterations are restored by exercise interventions in animal and human studies (Table 1), suggesting a plausible mechanism for the beneficial effect of exercise in IBD.

Current exercise guidelines from the American Heart Association for adults aged 18 years to 65 years of age recommend moderate-intensity aerobic exercise for at least 30 min, 5 d a week or vigorous-intensity exercise physical activity for 20 min, 3 d a week[49]. No specific guidelines exist for patients with IBD, however, evidence suggests that mild-to-moderate exercise harbors multiple benefits for patients with at least mild IBD, and excessive exercise could pose hazards for patients’ health[[41](#_ENREF_41)]; therefore, physicians should be cautious when prescribing exercise for patients with IBD, being on the lookout for exercise addiction[[41](#_ENREF_41)].

Clinical data studying the association of IBD with exercise suggest that sedentary occupations confer a higher risk for IBD than more physically demanding occupations, as found in a retrospective study of German employees[[50](#_ENREF_50)]; moreover, both CD and UC have been associated with low physical activity during childhood[[51](#_ENREF_51)]. Exercise has been reported to decrease the risk of relapse in patients with IBD in remission[52]. Mild-to-moderate exercise is beneficial in patients with at least mild IBD[41]. A recent study reported that prolonged moderate-intensity walking did not appear to increase blood cytokine levels in patients with IBD more than it did in healthy controls, and fecal calprotectin levels were found to be comparable between patients who walked and patients who did not walk, suggesting that exercise does not cause exacerbation of IBD[[53](#_ENREF_53)].

**CONCLUSION**

The findings of the present review imply that there exists a promising field of research regarding exercise-induced changes of the microbiome in IBD. What needs to be elucidated is whether the microbiome is a passive “bystander” in the systemic effects induced by physical activity, *i.e.* observing and reacting to activity-related systemic metabolic and endocrine signals by altering its composition, or whether it is a necessary physiological intermediate in the restoration of immune tolerance and normal gastrointestinal function in the context of IBD. Further research should also focus on disease determinants, such as age, sex, type, localization, histology, refractory phenotype, disease activity, molecular markers, and performance status, which could affect the disease’s response to certain types of physical exercise.Besides, considering that there is not only one optimal microbiota composition for the IBD patients, more studies are also needed to reveal how microorganisms interact with each other and with their host to identify different healthy microbiota schemes and an optimal, potentially personalized, dose of exercise for these patients. Lastly, an interesting field might exist for the microbiome as an index predictive or indicative of exercise-induced amelioration of IBD clinical symptoms, as part of current research on the molecular epidemiology of IBD.

**REFERENCES**

1 **Guan Q**. A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease. *J Immunol Res* 2019; **2019**: 7247238 [PMID: 31886308 DOI: 10.1155/2019/7247238]

2 **Glassner KL**, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. *J Allergy Clin Immunol* 2020; **145**: 16-27 [PMID: 31910984 DOI: 10.1016/j.jaci.2019.11.003]

3 **Furey TS**, Sethupathy P, Sheikh SZ. Redefining the IBDs using genome-scale molecular phenotyping. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 296-311 [PMID: 30787446 DOI: 10.1038/s41575-019-0118-x]

4 **Chen P**, Zhou G, Lin J, Li L, Zeng Z, Chen M, Zhang S. Serum Biomarkers for Inflammatory Bowel Disease. *Front Med (Lausanne)* 2020; **7**: 123 [PMID: 32391365 DOI: 10.3389/fmed.2020.00123]

5 **Veltkamp C**, Tonkonogy SL, De Jong YP, Albright C, Grenther WB, Balish E, Terhorst C, Sartor RB. Continuous stimulation by normal luminal bacteria is essential for the development and perpetuation of colitis in Tg(epsilon26) mice. *Gastroenterology* 2001; **120**: 900-913 [PMID: 11231944 DOI: 10.1053/gast.2001.22547]

6 **Ticinesi A**, Lauretani F, Tana C, Nouvenne A, Ridolo E, Meschi T. Exercise and immune system as modulators of intestinal microbiome: implications for the gut-muscle axis hypothesis. *Exerc Immunol Rev* 2019; **25**: 84-95 [PMID: 30753131]

7 **Mancin L**, Rollo I, Mota JF, Piccini F, Carletti M, Susto GA, Valle G, Paoli A. Optimizing Microbiota Profiles for Athletes. *Exerc Sport Sci Rev* 2021; **49**: 42-49 [PMID: 33044333 DOI: 10.1249/JES.0000000000000236]

8 **Carbajo-Pescador S**, Porras D, García-Mediavilla MV, Martínez-Flórez S, Juarez-Fernández M, Cuevas MJ, Mauriz JL, González-Gallego J, Nistal E, Sánchez-Campos S. Beneficial effects of exercise on gut microbiota functionality and barrier integrity, and gut-liver crosstalk in an *in vivo* model of early obesity and non-alcoholic fatty liver disease. *Dis Model Mech* 2019; **12**: dmm039206 [PMID: 30971408 DOI: 10.1242/dmm.039206]

9 **Lambert JE**, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise training modifies gut microbiota in normal and diabetic mice. *Appl Physiol Nutr Metab* 2015; **40**: 749-752 [PMID: 25962839 DOI: 10.1139/apnm-2014-0452]

10 **Clarke SF**, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, Hayes P, O'Reilly M, Jeffery IB, Wood-Martin R, Kerins DM, Quigley E, Ross RP, O'Toole PW, Molloy MG, Falvey E, Shanahan F, Cotter PD. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut* 2014; **63**: 1913-1920 [PMID: 25021423 DOI: 10.1136/gutjnl-2013-306541]

11 **Motiani KK**, Collado MC, Eskelinen JJ, Virtanen KA, LÖyttyniemi E, Salminen S, Nuutila P, Kalliokoski KK, Hannukainen JC. Exercise Training Modulates Gut Microbiota Profile and Improves Endotoxemia. *Med Sci Sports Exerc* 2020; **52**: 94-104 [PMID: 31425383 DOI: 10.1249/MSS.0000000000002112]

12 **Mohr AE**, Jäger R, Carpenter KC, Kerksick CM, Purpura M, Townsend JR, West NP, Black K, Gleeson M, Pyne DB, Wells SD, Arent SM, Kreider RB, Campbell BI, Bannock L, Scheiman J, Wissent CJ, Pane M, Kalman DS, Pugh JN, Ortega-Santos CP, Ter Haar JA, Arciero PJ, Antonio J. The athletic gut microbiota. *J Int Soc Sports Nutr* 2020; **17**: 24 [PMID: 32398103 DOI: 10.1186/s12970-020-00353-w]

13 **Stange EF**, Schroeder BO. Microbiota and mucosal defense in IBD: an update. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 963-976 [PMID: 31603356 DOI: 10.1080/17474124.2019.1671822]

14 **Quiroga R**, Nistal E, Estébanez B, Porras D, Juárez-Fernández M, Martínez-Flórez S, García-Mediavilla MV, de Paz JA, González-Gallego J, Sánchez-Campos S, Cuevas MJ. Exercise training modulates the gut microbiota profile and impairs inflammatory signaling pathways in obese children. *Exp Mol Med* 2020; **52**: 1048-1061 [PMID: 32624568 DOI: 10.1038/s12276-020-0459-0]

15 **Pedersini P**, Turroni S, Villafañe JH. Gut microbiota and physical activity: Is there an evidence-based link? *Sci Total Environ* 2020; **727**: 138648 [PMID: 32498183 DOI: 10.1016/j.scitotenv.2020.138648]

16 **Rettedal EA**, Cree JME, Adams SE, MacRae C, Skidmore PML, Cameron-Smith D, Gant N, Blenkiron C, Merry TL. Short-term high-intensity interval training exercise does not affect gut bacterial community diversity or composition of lean and overweight men. *Exp Physiol* 2020; **105**: 1268-1279 [PMID: 32478429 DOI: 10.1113/EP088744]

17 **Maillard F**, Vazeille E, Sauvanet P, Sirvent P, Combaret L, Sourdrille A, Chavanelle V, Bonnet R, Otero YF, Delcros G, Barnich N, Boisseau N. High intensity interval training promotes total and visceral fat mass loss in obese Zucker rats without modulating gut microbiota. *PLoS One* 2019; **14**: e0214660 [PMID: 30964881 DOI: 10.1371/journal.pone.0214660]

18 **Valeriani F**, Gallè F, Cattaruzza MS, Antinozzi M, Gianfranceschi G, Postiglione N, Romano Spica V, Liguori G. Are nutrition and physical activity associated with gut microbiota? A pilot study on a sample of healthy young adults. *Ann Ig* 2020; **32**: 521-527 [PMID: 32744583 DOI: 10.7416/ai.2020.2372]

19 **Campbell SC**, Wisniewski PJ, Noji M, McGuinness LR, Häggblom MM, Lightfoot SA, Joseph LB, Kerkhof LJ. The Effect of Diet and Exercise on Intestinal Integrity and Microbial Diversity in Mice. *PLoS One* 2016; **11**: e0150502 [PMID: 26954359 DOI: 10.1371/journal.pone.0150502]

20 **Denou E**, Marcinko K, Surette MG, Steinberg GR, Schertzer JD. High-intensity exercise training increases the diversity and metabolic capacity of the mouse distal gut microbiota during diet-induced obesity. *Am J Physiol Endocrinol Metab* 2016; **310**: E982-E993 [PMID: 27117007 DOI: 10.1152/ajpendo.00537.2015]

21 **Lloyd-Price J**, Abu-Ali G, Huttenhower C. The healthy human microbiome. *Genome Med* 2016; **8**: 51 [PMID: 27122046 DOI: 10.1186/s13073-016-0307-y]

22 **Thursby E**, Juge N. Introduction to the human gut microbiota. *Biochem J* 2017; **474**: 1823-1836 [PMID: 28512250 DOI: 10.1042/BCJ20160510]

23 **Castellanos N**, Diez GG, Antúnez-Almagro C, Bailén M, Bressa C, González Soltero R, Pérez M, Larrosa M. A Critical Mutualism - Competition Interplay Underlies the Loss of Microbial Diversity in Sedentary Lifestyle. *Front Microbiol* 2019; **10**: 3142 [PMID: 32038575 DOI: 10.3389/fmicb.2019.03142]

24 **Bressa C**, Bailén-Andrino M, Pérez-Santiago J, González-Soltero R, Pérez M, Montalvo-Lominchar MG, Maté-Muñoz JL, Domínguez R, Moreno D, Larrosa M. Differences in gut microbiota profile between women with active lifestyle and sedentary women. *PLoS One* 2017; **12**: e0171352 [PMID: 28187199 DOI: 10.1371/journal.pone.0171352]

25 **Morita E**, Yokoyama H, Imai D, Takeda R, Ota A, Kawai E, Hisada T, Emoto M, Suzuki Y, Okazaki K. Aerobic Exercise Training with Brisk Walking Increases Intestinal Bacteroides in Healthy Elderly Women. *Nutrients* 2019; **11** [PMID: 30999699 DOI: 10.3390/nu11040868]

26 **Munukka E**, Ahtiainen JP, Puigbó P, Jalkanen S, Pahkala K, Keskitalo A, Kujala UM, Pietilä S, Hollmén M, Elo L, Huovinen P, D'Auria G, Pekkala S. Six-Week Endurance Exercise Alters Gut Metagenome That Is not Reflected in Systemic Metabolism in Over-weight Women. *Front Microbiol* 2018; **9**: 2323 [PMID: 30337914 DOI: 10.3389/fmicb.2018.02323]

27 **Taniguchi H**, Tanisawa K, Sun X, Kubo T, Hoshino Y, Hosokawa M, Takeyama H, Higuchi M. Effects of short-term endurance exercise on gut microbiota in elderly men. *Physiol Rep* 2018; **6**: e13935 [PMID: 30536648 DOI: 10.14814/phy2.13935]

28 **Hampton-Marcell JT**, Eshoo TW, Cook MD, Gilbert JA, Horswill CA, Poretsky R. Comparative Analysis of Gut Microbiota Following Changes in Training Volume Among Swimmers. *Int J Sports Med* 2020; **41**: 292-299 [PMID: 31975357 DOI: 10.1055/a-1079-5450]

29 **Zhao X**, Zhang Z, Hu B, Huang W, Yuan C, Zou L. Response of Gut Microbiota to Metabolite Changes Induced by Endurance Exercise. *Front Microbiol* 2018; **9**: 765 [PMID: 29731746 DOI: 10.3389/fmicb.2018.00765]

30 **Keohane DM**, Woods T, O'Connor P, Underwood S, Cronin O, Whiston R, O'Sullivan O, Cotter P, Shanahan F, Molloy MGM. Four men in a boat: Ultra-endurance exercise alters the gut microbiome. *J Sci Med Sport* 2019; **22**: 1059-1064 [PMID: 31053425 DOI: 10.1016/j.jsams.2019.04.004]

31 **Liang R**, Zhang S, Peng X, Yang W, Xu Y, Wu P, Chen J, Cai Y, Zhou J. Characteristics of the gut microbiota in professional martial arts athletes: A comparison between different competition levels. *PLoS One* 2019; **14**: e0226240 [PMID: 31881037 DOI: 10.1371/journal.pone.0226240]

32 **Cook MD**, Allen JM, Pence BD, Wallig MA, Gaskins HR, White BA, Woods JA. Exercise and gut immune function: evidence of alterations in colon immune cell homeostasis and microbiome characteristics with exercise training. *Immunol Cell Biol* 2016; **94**: 158-163 [PMID: 26626721 DOI: 10.1038/icb.2015.108]

33 **Mach N**, Fuster-Botella D. Endurance exercise and gut microbiota: A review. *J Sport Health Sci* 2017; **6**: 179-197 [PMID: 30356594 DOI: 10.1016/j.jshs.2016.05.001]

34 **Weingarden AR**, Vaughn BP. Intestinal microbiota, fecal microbiota transplantation, and inflammatory bowel disease. *Gut Microbes* 2017; **8**: 238-252 [PMID: 28609251 DOI: 10.1080/19490976.2017.1290757]

35 **Tan P**, Li X, Shen J, Feng Q. Fecal Microbiota Transplantation for the Treatment of Inflammatory Bowel Disease: An Update. *Front Pharmacol* 2020; **11**: 574533 [PMID: 33041818 DOI: 10.3389/fphar.2020.574533]

36 **Allen JM**, Mailing LJ, Cohrs J, Salmonson C, Fryer JD, Nehra V, Hale VL, Kashyap P, White BA, Woods JA. Exercise training-induced modification of the gut microbiota persists after microbiota colonization and attenuates the response to chemically-induced colitis in gnotobiotic mice. *Gut Microbes* 2018; **9**: 115-130 [PMID: 28862530 DOI: 10.1080/19490976.2017.1372077]

37 **Cook MD**, Martin SA, Williams C, Whitlock K, Wallig MA, Pence BD, Woods JA. Forced treadmill exercise training exacerbates inflammation and causes mortality while voluntary wheel training is protective in a mouse model of colitis. *Brain Behav Immun* 2013; **33**: 46-56 [PMID: 23707215 DOI: 10.1016/j.bbi.2013.05.005]

38 **Allen JM**, Berg Miller ME, Pence BD, Whitlock K, Nehra V, Gaskins HR, White BA, Fryer JD, Woods JA. Voluntary and forced exercise differentially alters the gut microbiome in C57BL/6J mice. *J Appl Physiol (1985)* 2015; **118**: 1059-1066 [PMID: 25678701 DOI: 10.1152/japplphysiol.01077.2014]

39 **Cho J**, Kim D, Kang H. Exercise Preconditioning Attenuates the Response to Experimental Colitis and Modifies Composition of Gut Microbiota in Wild-Type Mice. *Life (Basel)* 2020; **10** [PMID: 32937846 DOI: 10.3390/Life10090200]

40 **Estaki M**, Morck DW, Ghosh S, Quin C, Pither J, Barnett JA, Gill SK, Gibson DL. Physical Activity Shapes the Intestinal Microbiome and Immunity of Healthy Mice but Has No Protective Effects against Colitis in MUC2-/- Mice. *mSystems* 2020; **5** [PMID: 33024049 DOI: 10.1128/mSystems.00515-20]

41 **Cheifetz AS**, Gianotti R, Luber R, Gibson PR. Complementary and Alternative Medicines Used by Patients With Inflammatory Bowel Diseases. *Gastroenterology* 2017; **152**: 415-429.e15 [PMID: 27743873 DOI: 10.1053/j.gastro.2016.10.004]

42 **Bilski J**, Mazur-Bialy A, Brzozowski B, Magierowski M, Zahradnik-Bilska J, Wójcik D, Magierowska K, Kwiecien S, Mach T, Brzozowski T. Can exercise affect the course of inflammatory bowel disease? Experimental and clinical evidence. *Pharmacol Rep* 2016; **68**: 827-836 [PMID: 27255494 DOI: 10.1016/j.pharep.2016.04.009]

43 **Codella R**, Luzi L, Terruzzi I. Exercise has the guts: How physical activity may positively modulate gut microbiota in chronic and immune-based diseases. *Dig Liver Dis* 2018; **50**: 331-341 [PMID: 29233686 DOI: 10.1016/j.dld.2017.11.016]

44 **Sohail MU**, Yassine HM, Sohail A, Al Thani AA. Impact of Physical Exercise on Gut Microbiome, Inflammation, and the Pathobiology of Metabolic Disorders. *Rev Diabet Stud* 2019; **15**: 35-48 [PMID: 31380886 DOI: 10.1900/RDS.2019.15.35]

45 **Donati Zeppa S**, Agostini D, Gervasi M, Annibalini G, Amatori S, Ferrini F, Sisti D, Piccoli G, Barbieri E, Sestili P, Stocchi V. Mutual Interactions among Exercise, Sport Supplements and Microbiota. *Nutrients* 2019; **12** [PMID: 31861755 DOI: 10.3390/nu12010017]

46 **Cerdá B**, Pérez M, Pérez-Santiago JD, Tornero-Aguilera JF, González-Soltero R, Larrosa M. Gut Microbiota Modification: Another Piece in the Puzzle of the Benefits of Physical Exercise in Health? *Front Physiol* 2016; **7**: 51 [PMID: 26924990 DOI: 10.3389/fphys.2016.00051]

47 **Monda V**, Villano I, Messina A, Valenzano A, Esposito T, Moscatelli F, Viggiano A, Cibelli G, Chieffi S, Monda M, Messina G. Exercise Modifies the Gut Microbiota with Positive Health Effects. *Oxid Med Cell Longev* 2017; **2017**: 3831972 [PMID: 28357027 DOI: 10.1155/2017/3831972]

48 **Laing B**, Barnett MPG, Marlow G, Nasef NA, Ferguson LR. An update on the role of gut microbiota in chronic inflammatory diseases, and potential therapeutic targets. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 969-983 [PMID: 30052094 DOI: 10.1080/17474124.2018.1505497]

49 **Engels M**, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. *Clin Exp Gastroenterol* 2018; **11**: 1-11 [PMID: 29317842 DOI: 10.2147/CEG.S120816]

50 **Sonnenberg A**. Occupational distribution of inflammatory bowel disease among German employees. *Gut* 1990; **31**: 1037-1040 [PMID: 2210450 DOI: 10.1136/gut.31.9.1037]

51 **Hlavaty T**, Toth J, Koller T, Krajcovicova A, Oravcova S, Zelinkova Z, Huorka M. Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of inflammatory bowel disease: A Slovak case-control study. *United European Gastroenterol J* 2013; **1**: 109-119 [PMID: 24917948 DOI: 10.1177/2050640613478011]

52 **Jones PD**, Kappelman MD, Martin CF, Chen W, Sandler RS, Long MD. Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. *Inflamm Bowel Dis* 2015; **21**: 1063-1071 [PMID: 25723616 DOI: 10.1097/MIB.0000000000000333]

53 **Lamers CR**, de Roos NM, Bongers CCWG, Ten Haaf DSM, Hartman YAW, Witteman BJM, Hopman MTE. Repeated prolonged moderate-intensity walking exercise does not appear to have harmful effects on inflammatory markers in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2021; **56**: 30-37 [PMID: 33211989 DOI: 10.1080/00365521.2020.1845791]**Footnotes**

**Conflict-of-interest statement:** Authors have nothing to disclose.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** February 26, 2021

**First decision:** April 18, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Greece

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ogino S, Shankar U **S-Editor:** Liu M **L-Editor:**Filipodia**P-Editor:**

**Table 1 Effect of exercise on the gut microbiome**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study subject** | **Sample type** | **Exercise protocol** | **Exercise *vs* controls** | **Notes** |
| Lambert *et al[*[9](#_ENREF_9)] | Mouse, type 2 diabetic, (C57BL/KsJ-leprdb/leprdb) | Cecal matter | Treadmill, 5 d/wk, 66 min/d, 2.87 m/min | ↑ Clostridium leptum | ↑ Bifidobacterium with exercise in non-diabetic mice |
| ↑ Lactobacillus |
| ↓ Total bacteria |
| ↓ Bacteroides |
| ↓ Bifidobacterium |  |
| ↓ Methanobrevibacter |
| ↓ Prevotella |
| Campbell *et al*[[19](#_ENREF_19)] | Mouse C57BL/6NTac, male | Fecal matter from the distal colon | Free running wheel | ↑ Allobaculum | Normal-diet, not observed in a high-fat diet, except for Faecalibacterium prausnitzi |
| ↑ Clostridiales |
| ↑ Faecalibacterium prausnitzi |
| Denou *et al*[[20](#_ENREF_20)] | Mouse, C57 BL/6, high-fat diet, obese | Feces from anal area, then full intestinal sampling | Treadmill, 6 wk total, 3 d/wk,  1 h/d, 17 m/min at 5% grade for 2 min + 2 min rest, increase by 1 m/min every week | ↑ Bacteroidetes/Firmicutes ratio in the cecum | - |
| ↑ Bacteroidetes/Firmicutes ratio in the rectum |
| Carbajo-Pescador *et al*[[8](#_ENREF_8)] | Juvenile male Wistar rats on early obesity and non-alcoholic fatty liver disease onset | Fecal matter | Treadmill, 11 wk total, 60 min/d combined aerobic and  resistance training (10-min  running; eight 2-min  progressive incline run from 10°-25° at 20-25 cm/s /1 min rest;  30 min aerobic exercise) | ↑ Parabacteroides |  |
| ↑ Bacteroides |
| ↑ Flavobacterium genera |
| ↓ Blautia |
| ↓ Dysgonomonas |
| ↓ Porphyromonas |
| Clarke *et al*[[10](#_ENREF_10)] | Human, rugby player, male | Fecal matter, self-collected | Rugby training, capacity determined by EPIC-Norfolk questionnaire | ↑ Akkermansia (than high-BMI controls) | - |
| ↓ Bacteroides (than low-BMI controls) |
| ↓ Lactobacillus (than low-BMI controls) |
| Bressa *et al*[[24](#_ENREF_24)] | Human, female, premenopausal, BMI 20-25 kg/m2 | Fecal matter, self-collected | No forced exercise, physical activity level gauged by accelerometers | ↑ Akkermansia muciniphila | - |
| ↑ Faecalibacterium prausnitzii |
| ↑ Roseburia hominis |
| Munukka *et al*[[26](#_ENREF_26)] | Human, female, sedentary, BMI > 27.5 kg/m2 | Fecal matter, self-collected | Ergometer,  Weeks 1-2: at 60 rpm, low intensity, 3 d/wk, 40 min/d | ↑ Akkermansia | - |
| ↑ Anaerofilum |
| ↑ Bifidobacteriaceae |
| ↑ Dorea |
| ↑ Verrucomicrobiaceae |
| Weeks 3-4: 3 d/wk, 50 min/d, every other session 3 10-min intervals of moderate-intensity cycling, the rest low intensity |
| ↓ Desulfovibrionaceae |
| ↓ Enterobacteriaceae |
| ↓ Odoribacter |
| ↓ Porphyromonadaceae |
| ↓ Proteobacteria |
| ↓ Streptococcus |
| Weeks 5-6: 3 d/wk, 60 min/d, four 10-min moderate intensity intervals, the rest low intensity |
| Taniguchi *et al*[[27](#_ENREF_27)] | Human, male, age > 60 yr, healthy | Fecal matter, self-collected | Cycling,  Weeks 1-2: 3 d/wk, 30 min/d, 60% of VO2peak (week 1), 70% of VO2peak (week 2) | ↓ Clostridium difficile | - |
| ↑ Oscillospora |
| Weeks 3-5:  3 d/wk, 45 min/d, 70% of VO2max (week 3), 75% of VO2max (weeks 4-5) |
| Zhao *et* *al*[[29](#_ENREF_29)] | Human, marathon runners | Fecal matter, self-collected | The 2016 Chongqing half marathon, before and after the race | ↑ Acidobacteria | Post- *vs* pre-running |
| ↑ Lentisphaerae |
| Castellanos *et al*[[23](#_ENREF_23)] | Human | Fecal matter, self-collected | No forced exercise, physical activity level gauged by accelerometers | ↑ Blautia | - |
| ↑ Coprococcus |
| ↑ Eubacterium |
| ↓ Bacteroides |
| ↓ Parabacteroides |
| Keohane *et al*[[30](#_ENREF_30)] | Human, male, athlete | Fecal matter, self-collected | Rowing race, 33 d 22 h, 151.8 km per day | ↑ Roseburia hominis | Post-ultra-endurance exercise |
| ↑ Subdoligranulum |
| Liang *et al*[[31](#_ENREF_31)] | Human, martial arts athlete | Fecal matter, self-collected | Martial arts, athletes, divided into higher- and lower-level based on General Administration of Sport of  China criteria | ↑ Bilophila | Higher- *vs* lower-level athletes |
| ↑ Oscillibacter |
| ↑ Parabacteroides |
| ↑ Phascolarctobacterium |
| ↓ Allisonella |
| ↓ Citrobacter |
| ↓ Megasphaera |
| Morita *et al*[[25](#_ENREF_25)] | Human, female, age > 65 yr, sedentary | Fecal matter, self-collected | Trunk strengthening training, 12 wk, 1 h/wk: 5-10 min of warm-up + 45 min of targeted resistance training of trunk muscles + 5 – 10 cool-down and at-home exercise daily | ↑ Bacteroides | After 12 wk of aerobic training |
| Hampton-Marcell *et al*[[28](#_ENREF_28)] | Human, age 18-24 yr, swimmers | Cotton swab sample | Self-reporting of daily swimming distance and duration during daily practice | ↑ Coprococcus | Before *vs* after reduction of training volume |
| ↑ Faecalibacterium |
| Quiroga *et al*[[14](#_ENREF_14)] | Human, age 7-12 yr, obese | Fecal matter, self-collected | Strength and endurance training | ↑ Blautia | After a 12-wk strength and endurance training program |
| ↑ Dialister |
| 12 wk, 2 d/wk: |
| Warm-up on an ergometer for 7 min, low-medium load, 60 rpm | ↑ Roseburia |
| Third minute onwards, a sprint of 30s at 3’30”, 4’30”, 5’30”, and 6’30” |
| Strength exercises for five muscle groups, initially 3 sets of 12 repetitions at 30% 1RM, up to 3 sets of 8 repetitions at 70% 1RM |
| Cool-down at an elliptical cardiovascular device, 7 min, 50 rpm, 4 min low-medium load + 3 min high load |
| Rettedal *et al*[[16](#_ENREF_16)] | Human, male, age 20-45 yr | Fecal matter, self-collected | 9 sessions of high-intensity interval training on non-consecutive days over 3 wk:  60 s cycling at VO2peak  75 s rest | No significant changes in composition | Before and after high-intensity interval training |
| 8 intervals initially, up to 12 intervals by the end of the protocol |

BMI: Body mass index.