Physical Activity, Gut Microbiota and Gut-Brain Axis

Subjects: Sport Sciences

Contributor: Stefania Cataldi , Luca Poli , Fatma Neşe Şahin , Antonino Patti , Luigi Santacroce , Antonino Bianco , Gianpiero Greco , Barbara Ghinassi , Angela Di Baldassarre , Francesco Fischetti

Physical activity (PA) can impact significantly the gut microbiota composition and diversity, and could also produce modifications in the gut microbiota that can mediate and induce mental health benefits. The PA favors bacterial strains that can promote physical performance and that can induce beneficial changes in the brain.

cognitive functions anxiety depression microbiome overweight elderly athletes sports fitness overtraining

1.Introduction

In recent years, research on the interaction between gut microbiota (GM) and health has expanded considerably. High-throughput sequencing has favored and facilitated research on GM in multiple aspects [1]. Indeed, humans have specific microbial profiles at the oral, skin, reproductive organ, gastrointestinal and fecal levels [2],[3]. In particular, the human gastrointestinal (GI) tract has a microbial diversity of up to 100 trillion microorganisms, predominantly bacteria but also archaea, viruses, and parasites. The GM encodes more than three million genes that produce hundreds of metabolites [4]. Only recently, the effect of the physical activity (PA) on the GM has been more thoroughly investigated, although considerable difficulties persist in structuring research protocols capable of limiting the various confounding elements as much as possible. Most evidence shows that a sedentary lifestyle is associated with a higher incidence of chronic diseases [5],[6],[7], on which PA can play a preventive and therapeutic role through different mechanisms. Recently, the potential effects produced on GM have been proposed as another modality through which PA can perform beneficial functions on host health [8].

Although there is no gold standard for gut health, and its definition remains uncertain [9],[10],[11], the interaction between host PA can favor the growth of beneficial bacteria and gut cells that maintain the integrity of the intestinal surface, which acts as the first defense against pathogens. In return, the selected bacteria synthesize molecules capable of modifying the metabolism and immune functions of the host [12]. Furthermore, disruption of the gut barrier is considered one of the mechanisms of major depression and other cognitive and behavioral alterations, with the gut–brain axis (GBA) playing a role in mediating these processes [13]. In this context, PA seems able to influence this two-way communication interaction through the GBA [14].

2.Physical Activity and Gut Microbiota in Preclinic Studies

It is now quite clear that, in animal models, exercise initiates significant changes in the GM. In agreement with Kang et al. [15], Denou et al. [16] found an increased bacterial diversity in diet-induced obesity (DIO) mice fed an high fat diet (HFD) following forced treadmill running (FTR). In contrast to Kang et al. [15], using a high-intensity interval training (HIIT) protocol did not result in a reduction in body mass, suggesting the possibility of different bacterial changes based on the exercise modality used. Ribeiro et al. [17] highlighted that the use of a medium-low intensity exercise (50% of maximal velocity) induces insignificant changes in the GM to counteract the effects of a prolonged HFD. It has been found [18] that forced exercise (FWR) results in a significant up-regulation of the Ruminococcus gnavus species, a bacterium capable of degrading the intestinal mucosa and thus penetrating its inner and outer layers, exposing intestinal epithelial cells to immunogenic bacterial proteins and thus exacerbating intestinal inflammation [19]. However, the regulation of mucin, the glycoprotein that makes up intestinal muscle, and the bacterial dynamics involved in relation to exercise have been little investigated. Of note is the increase in the Anaerotruncus genus, a butyrate-producing bacterial group that colonizes the outer layer of the colonic mucosa and is phylogenetically related to Fecalibacterium prausnitzii, a known butyrate producer in humans [20],[21]. These bacteria often feed on lactate, acetate, or other intermediates produced by other bacterial strains, and so it is possible that the activity-induced changes in so-called lactate producers (e.g., lactobacilli) and butyrate producers (e.g., Anaerotruncus) are related by a cross-feeding phenomenon. The period of life in which exercise is carried out would also appear to be important, thus representing age as a determining factor in the regulation of the GM. Using germ-free (GF) mice, an early sensitive period has been identified during which the absence of an intact GM reflects physiological consequences such as the exaggerated activity of the hypothalamic-pituitary-adrenal (HPA) axis that can only be partly normalized by the introduction of Bifidobacteria infantis if administered during the early period of life [22]. This evidence reveals that the framework of GM during development can strongly influence the health of the host throughout life. Furthermore, just as physiological systems during development are remarkably malleable and sensitive to change, likewise the GM is more plastic in the early stages of life [23],[24] and, consequently, the microbial ecosystem present during the early period of life may be more sensitive to environmental changes due in part to its lower stability and diversity than in adulthood. Mika et al. [25] hypothesize and note that exercise undertaken during early life (EL) may have a greater impact on GM than that undertaken in adulthood, corroborated recently by another study [26]. They also observe a lower species richness in juvenile than in adult rats. A similar condition was observed in humans by Yatsunenko et al. [27], supporting the idea that it is precisely this condition of the young GM that encourages greater changes within it, unlike in the adult GM where the greater microbial complexity may make it more resistant to changes induced by environmental factors. Li et al. [28] note that HFDs can induce an increase in circulating Lipopolysaccharide (LPS) levels which are related to the onset of osteoarthritis [29]. PA (VWR) seems able to remodel the GM by increasing its diversity and consequently reducing LPS levels in the blood and synovial fluid. Yuan et al. [30] find out negative effects of excessive exercise on the GM showing a reduced α-diversity and β-diversity compared with the control group.

3.Physical Activity and Gut Microbiota in Human Studies

Clarke et al. [31] performed the first study on athletes and greater richness and α-diversity were observed in the athletes than in the control groups, in agreement with Mörkl et al. [32]. Microbial diversity is positively associated

with protein intake, suggesting that exercise and diet are drivers of gut bacterial diversity. In the athletes' group, an increase in butyrate-producer phylum (Firmicutes) and genus (F.prausnitzii) was observed [20],[21]. Furthermore, athletes and LBG show increased Akkermansiaceae family and Akkermansia genus, associated with metabolic disorders [33]. Castellanos et al. [34], using data collected through their previous observational study [35] identified bacterial taxa considered to be 'key' microorganisms for the structure of the GM since the pathogenicity of certain bacteria is not always and only related to their abundance but also to other factors such as interactions with other microorganisms. No changes were found after three weeks of HIIT protocol, indicating that short-term HIIT protocol does not impact the fecal bacterial community and that progress in the cardiorespiratory fitness (CRF) does not lead to modification of GM in the short term [36], similarly to Moitinho-Silva [37]. Durk et al. [38] supporting other similar work in both animal models and humans [39],[32],[18], found that the PA can be a factor that positively affect the human GM. Bycura et al. [40] in contrast to Quiroga et al. [41], where aerobic and resistance exercises were analyzed separately, observed that only aerobic activity causes an initial significant change within the GM that subsequently decreases until it becomes irrelevant. Petersen et al. [42], found a significant correlation between the presence of the genus Prevotella, with concomitant upregulation of brain chain amino acids (BCAAs), and the time spent training (>11 h/week) in both professionals and amateurs. A decrease in Bacteroides and, among 30 cyclists, an increase in the genus Akkermansia was noted, as already observed [31]. It was also observed that the increased presence of Prevotella correlates with certain carbohydrate and amino acids (AAs) metabolic pathways, including the biosynthesis of BCAAs [43]. Morishima et al. [44] found that in endurance runners, some bacteria associated with gut inflammation (Haemophilus, Rothia, and Ruminococcus ganvus) were more abundant. Counterintuitively, Fecalibacterium, known as a beneficial butyrate producer, was also more abundant in the endurance runners (ER) group. This could be explained by the fact that an abnormal intestinal environment prompts the Fecalibacterium to produce succinate, a risk factor for diarrhea and loose stools [45], and not butyrate. This suggests that prolonged high-intensity exercise may lead to a form of dysbiosis in the athlete. One study [46] attempted to assess whether endurance activity can modulate GM in elderly men and whether these changes are associated with specific cardiometabolic conditions in the host. While genus Oscillospira, associated with reduced BMI [47],[48], increases, species Clostridioides difficile decreases. Furthermore, changes in these taxa were correlated with changes in several cardio-metabolic risk factors such as systolic and diastolic blood pressure. Researchers found that after six months of combined training, seven high-intensity and eight moderate-intensity exercises [49], Oscillospira, Bifidobacterium, and Anaerostipes, health-related genus [50],[51], were increased. Quiroga et al. [41] found that a combined endurance and strength training can alter GM composition and function in obese subjects by significantly reducing the phylum Proteobacteria, corroborating the results obtained by Munukka et al. [52] and the class Gammaproteobacteria. These results suggest the presence of a negative bacterial profile related to the state of obesity that can be positively modified by PA.

4.Physical Activity, Gut Microbiota and Cognitive Ability

According to Gubert et al. [53], considering the concomitant intestinal dysbiosis present in several neurodegenerative diseases and the impact that PA or exercise can have on the intestinal microbiome and neuronal degeneration, a triangulation between these aspects seems plausible to assess whether PA can

contribute to the modulation of neurodegeneration through GM. Kang et al. [15] showed that mice subjected to a 16-week training protocol reported an improvement in memory associated with the increase in the Firmicutes:Bacteroidetes ratio induced by exercise. One hour per day of exercise can increase the relative abundance of the family Lachnospiraceae, which is negatively correlated with anxiogenic behavior and is capable of producing butyrate (SCFA), a molecule that over-regulates Brain-Derived Neurotrophic Factor (BDNF) expression in the hippocampus and frontal cortex, supporting the survival of existing neurons and stimulating the formation of new neurons and synapses [54]. Thus, according to the authors, this association between induced changes in certain GM phyla and families and memory improvement could be used as a biomarker for exercise-induced effects at a cognitive level. Experimental data have shown that GM modifications induced by an aerobic activity, specifically characterized by an increase in certain bacteria (e.g., *Lactobacillus plantarum* and *Streptococcus thermophile*), are capable of inducing the synthesis of serotonin, a molecule that protects against symptoms of anxiety and depression [55]. Abraham et al. [56] extrapolated findings that seem to indicate the ability of exercise to improve cognitive function and some markers of Alzheimer's disease (AD); using transgenic mice (APP/PS1) subjected to a 20-week treadmill exercise protocol, they note a significant improvement in the Morris Maze Test, which assesses spatial memory, and a reduction in β-amyloid plaques, one of the main aspects involved in AD [57], supporting what was previously observed by Lin et al. [58]. Near these plaques, an increase in microglia, important for brain development by providing structural and metabolic support to neurons and involved in neuroplasticity and regulation of neural repair [59], is found, underlining the neuroprotective effect of exercise. This appears to be associated with the abundance of some bacterial strains (Eubacteria, Roseburia) and the reduction of others, so these results suggest that the cognitive effects of exercise may be mediated through GM alteration, reducing the levels of microbes involved in disease exacerbation and promoting the abundance of those bacteria capable of producing SCFAs that appear beneficial.

5.Conclusion

A PA performed voluntarily appears to attenuate intestinal inflammation, in contrast to a forced activity that instead increases this condition in animal models. Vigorous endurance exercise can negatively affect the GM framework in humans; furthermore, only aerobic activities can alter the GM structure, probably because of the positive correlation between CRF and microbial diversity. PA can stimulate bacterial community richness by altering SCFAs-producing species, as well as favoring the colonization of health and athletic performance-promoting strains (e.g., A. muciniphila and Veillonella). PA seems able to regulate cognitive conditions (e.g., anxiety and depression) and functionality (e.g., Alzheimer's and Parkinson's Disease) through modifications of microbial composition and subsequently the production of certain protective molecules, to date in animal models.

References

1. Guojun Wu; Naisi Zhao; Chenhong Zhang; Yan Y. Lam; Liping Zhao; Guild-based analysis for understanding gut microbiome in human health and diseases. *Genome Medicine* **2021**, *13*, 1-12,

10.1186/s13073-021-00840-y.

2. Karimé González; Jorge Fuentes; José Luis Márquez; Physical Inactivity, Sedentary Behavior and Chronic Diseases. *Korean Journal of Family Medicine* **2017**, *38*, 111-115, 10.4082/kjfm.2017.38.3.111.
3. Frank W. Booth; Matthew J. Laye; Simon J. Lees; R. Scott Rector; John P. Thyfault; Reduced physical activity and risk of chronic disease: the biology behind the consequences. *Graefe's Archive for Clinical and Experimental Ophthalmology* **2007**, *102*, 381-390, 10.1007/s00421-007-0606-5.
4. Renqing Zhao; W. Bu; Y. Chen; X. Chen; The Dose-Response Associations of Sedentary Time with Chronic Diseases and the Risk for All-Cause Mortality Affected by Different Health Status: A Systematic Review and Meta-Analysis. *The journal of nutrition, health & aging* **2019**, *24*, 63-70, 10.1007/s12603-019-1298-3.
5. Emanuele Rinninella; Pauline Raoul; Marco Cintoni; Francesco Franceschi; Giacinto Abele Donato Miggiano; Antonio Gasbarrini; Maria Cristina Mele; What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms* **2019**, *7*, 14, 10.3390/microorganisms7010014.
6. Nicholas D. Youngblut; Georg H. Reischer; William Walters; Nathalie Schuster; Chris Walzer; Gabrielle Stalder; Ruth E. Ley; Andreas H. Farnleitner; Host diet and evolutionary history explain different aspects of gut microbiome diversity among vertebrate clades. *Nature Communications* **2019**, *10*, 1-15, 10.1038/s41467-019-10191-3.
7. Allison Clark; Núria Mach; Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes. *Journal of the International Society of Sports Nutrition* **2016**, *13*, 1-21, 10.1186/s12970-016-0155-6.
8. Daniela Campaniello; Maria Rosaria Corbo; Milena Sinigaglia; Barbara Speranza; Angela Racioppo; Clelia Altieri; Antonio Bevilacqua; How Diet and Physical Activity Modulate Gut Microbiota: Evidence, and Perspectives. *Nutrients* **2022**, *14*, 2456, 10.3390/nu14122456.
9. Wenjing Yang; Yingzi Cong; Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. *Cellular & Molecular Immunology* **2021**, *18*, 866-877, 10.1038/s41423-021-00661-4.
10. Yanna Liu; Fenghua Xu; Shuang Liu; Gang Liu; Xiaohan Yang; Wenting Gao; Kai Fan; Henan Zhao; Jianmei Ma; Significance of gastrointestinal tract in the therapeutic mechanisms of exercise in depression: Synchronism between brain and intestine through GBA. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **2020**, *103*, 109971, 10.1016/j.pnpbp.2020.109971.

11. Alyssa Dalton; Christine Mermier; Micah Zuhl; Exercise influence on the microbiome–gut–brain axis. *Gut Microbes* **2019**, *10*, 555-568, 10.1080/19490976.2018.1562268.
12. Wenjing Yang; Yingzi Cong; Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. *Cellular & Molecular Immunology* **2021**, *18*, 866-877, 10.1038/s41423-021-00661-4.
13. Yanna Liu; Fenghua Xu; Shuang Liu; Gang Liu; Xiaohan Yang; Wenting Gao; Kai Fan; Henan Zhao; Jianmei Ma; Significance of gastrointestinal tract in the therapeutic mechanisms of exercise in depression: Synchronism between brain and intestine through GBA. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **2020**, *103*, 109971, 10.1016/j.pnpbp.2020.109971.
14. Alyssa Dalton; Christine Mermier; Micah Zuhl; Exercise influence on the microbiome–gut–brain axis. *Gut Microbes* **2019**, *10*, 555-568, 10.1080/19490976.2018.1562268.
15. Silvia S Kang; Patricio R Jeraldo; Aishe Kurti; Margret E Berg Miller; Marc D Cook; Keith Whitlock; Nigel Goldenfeld; Jeffrey A Woods; Bryan A White; Nicholas Chia; et al.John D Fryer Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. *Molecular Neurodegeneration* **2014**, *9*, 36-36, 10.1186/1750-1326-9-36.
16. Emmanuel Denou; Katarina Marcinko; Michael G. Surette; Gregory Steinberg; Jonathan D. Schertzer; High-intensity exercise training increases the diversity and metabolic capacity of the mouse distal gut microbiota during diet-induced obesity. *American Journal of Physiology-Endocrinology and Metabolism* **2016**, *310*, E982-E993, 10.1152/ajpendo.00537.2015.
17. Filipe M. Ribeiro; Camila F. A. Ribeiro; Ana Cláudia M. G.; Alinne P. Castro; Jeeser A. Almeida; Octavio L. Franco; Bernardo A. Petriz; Limited Effects of Low-to-Moderate Aerobic Exercise on the Gut Microbiota of Mice Subjected to a High-Fat Diet. *Nutrients* **2019**, *11*, 149, 10.3390/nu11010149.
18. Jacob Allen; Margret E. Berg Miller; Brandt D. Pence; Keith Whitlock; Vandana Nehra; H. Rex Gaskins; Bryan A. White; John D. Fryer; Jeffrey A. Woods; Voluntary and forced exercise differentially alters the gut microbiome in C57BL/6J mice. *Journal of Applied Physiology* **2015**, *118*, 1059-1066, 10.1152/japplphysiol.01077.2014.
19. Louise E. Tailford; C. David Owen; John Walshaw; Emmanuelle H. Crost; Jemma Hardy-Goddard; Gwenaelle Le Gall; Willem M. de Vos; Garry L. Taylor; Nathalie Juge; Discovery of intramolecular trans-sialidases in human gut microbiota suggests novel mechanisms of mucosal adaptation. *Nature Communications* **2015**, *6*, 7624, 10.1038/ncomms8624.
20. Petra Louis; Harry J. Flint; Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. *FEMS Microbiology Letters* **2009**, *294*, 1-8, 10.1111/j.1574-6968.2009.01514.x.

21. Peter J. Turnbaugh; Fredrik Bäckhed; Lucinda Fulton; Jeffrey I. Gordon; Diet-Induced Obesity Is Linked to Marked but Reversible Alterations in the Mouse Distal Gut Microbiome. *Cell Host & Microbe* **2008**, *3*, 213-223, 10.1016/j.chom.2008.02.015.
22. Nobuyuki Sudo; Yoichi Chida; Yuji Aiba; Junko Sonoda; Naomi Oyama; Xiao-Nian Yu; Chiharu Kubo; Yasuhiro Koga; Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *The Journal of Physiology* **2004**, *558*, 263-275, 10.1113/jphysiol.2004.063388.
23. R Wall; R.P Ross; C.A Ryan; S Hussey; B Murphy; G.F Fitzgerald; C Stanton; Role of Gut Microbiota in Early Infant Development. *Clinical medicine. Pediatrics* **2009**, *3*, 45-54, 10.4137/cmped.s2008.
24. Jeremy E. Koenig; Aymé Spor; Nicholas Scalfone; Ashwana D. Fricker; Jesse Stombaugh; Rob Knight; Largus T. Angenent; Ruth E. Ley; Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences* **2010**, *108*, 4578-4585, 10.1073/pnas.1000081107.
25. Agnieszka Mika; Will Van Treuren; Antonio González; Jonathan J. Herrera; Rob Knight; Monika Fleshner; Exercise Is More Effective at Altering Gut Microbial Composition and Producing Stable Changes in Lean Mass in Juvenile versus Adult Male F344 Rats. *PLOS ONE* **2015**, *10*, e0125889, 10.1371/journal.pone.0125889.
26. Monica P. McNamara; Jennifer M. Singleton; Marcell D. Cadney; Paul M. Ruegger; James Borneman; Theodore Garland; Early-life effects of juvenile Western diet and exercise on adult gut microbiome composition in mice. *Journal of Experimental Biology* **2021**, *224*, 222-234, 10.1242/jeb.239699.
27. Tanya Yatsunenko; Federico E. Rey; Mark Manary; Indi Trehan; Maria Gloria Dominguez-Bello; Monica Contreras; Magda Magris; Glida Hidalgo; Robert N. Baldassano; Andrey Anokhin; et al.Andrew C. HeathBarbara WarnerJens ReederJustin KuczynskiJ. Gregory CaporasoCatherine A. LozuponeChristian LauberJose Carlos ClementeDan KnightsRob KnightJeffrey I. Gordon Human gut microbiome viewed across age and geography. *Nature Cell Biology* **2012**, *486*, 222-227, 10.1038/nature11053.
28. Kefeng Li; Anli Liu; Wenhao Zong; Lulu Dai; Yang Liu; Renping Luo; Shulin Ge; Guijun Dong; Moderate exercise ameliorates osteoarthritis by reducing lipopolysaccharides from gut microbiota in mice. *Saudi Journal of Biological Sciences* **2020**, *28*, 40-49, 10.1016/j.sjbs.2020.08.027.
29. Zeyu Huang; Virginia Byers Kraus; Does lipopolysaccharide-mediated inflammation have a role in OA?. *Nature Reviews Rheumatology* **2015**, *12*, 123-129, 10.1038/nrrheum.2015.158.
30. Xin Yuan; Shijie Xu; Haiyang Huang; Jian Liang; Yayun Wu; Chujie Li; Huiqi Yuan; Xuejie Zhao; Xiaoping Lai; Shaozhen Hou; et al. Influence of excessive exercise on immunity, metabolism, and

gut microbial diversity in an overtraining mice model. *Scandinavian Journal of Medicine & Science in Sports* **2018**, *28*, 1541-1551, 10.1111/sms.13060.

31. Siobhan Clarke; Eileen F Murphy; Orla O'Sullivan; Alice Lucey; Margaret Humphreys; Aileen Hogan; Paula Hayes; Maeve O'Reilly; Ian Jeffery; Ruth Wood-Martin; et al.David M KerinsEamonn QuigleyReynolds RossPaul W O'TooleMichael G MolloyEanna FalveyFergus ShanahanPaul Cotter Exercise and associated dietary extremes impact on gut microbial diversity. *Gut* **2014**, *63*, 1913-1920, 10.1136/gutjnl-2013-306541.
32. Sabrina Mörkl; Sonja Lackner; Wolfram Müller; Gregor Gorkiewicz; Karl Kashofer; Andreas Oberascher; Annamaria Painold; Anna Holl; Peter Holzer; Andreas Meinitzer; et al.Harald ManggeSandra Holasek Gut microbiota and body composition in anorexia nervosa inpatients in comparison to athletes, overweight, obese, and normal weight controls. *International Journal of Eating Disorders* **2017**, *50*, 1421-1431, 10.1002/eat.22801.
33. Amandine Everard; Clara Belzer; Lucie Geurts; Janneke P. Ouwerkerk; Céline Druart; Laure B. Bindels; Yves Guiot; Muriel Derrien; Giulio G. Muccioli; Nathalie M. Delzenne; et al.Willem M. de VosPatrice D. Cani Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proceedings of the National Academy of Sciences* **2013**, *110*, 9066-9071, 10.1073/pnas.1219451110.
34. Nazareth Castellanos; Gustavo G. Diez; Carmen Antúnez-Almagro; Carlo Bressa; María Bailén; Rocío González-Soltero; Margarita Pérez; Mar Larrosa; Key Bacteria in the Gut Microbiota Network for the Transition between Sedentary and Active Lifestyle. *Microorganisms* **2020**, *8*, 785, 10.3390/microorganisms8050785.
35. Nazareth Castellanos; Gustavo G. Diez; Carmen Antúnez-Almagro; Maria Bailen; Carlo Bressa; Rocío González Soltero; Margarita Pérez; Mar Larrosa; A Critical Mutualism – Competition Interplay Underlies the Loss of Microbial Diversity in Sedentary Lifestyle. *Frontiers in Microbiology* **2020**, *10*, 3142, 10.3389/fmicb.2019.03142.
36. Elizabeth A. Rettedal; Julia M. E. Cree; Shannon E. Adams; Caitlin MacRae; Paula M. L. Skidmore; David Cameron-Smith; Nicholas Gant; Cherie Blenkiron; Troy L. Merry; Short-term high-intensity interval training exercise does not affect gut bacterial community diversity or composition of lean and overweight men. *Experimental Physiology* **2020**, *105*, 1268-1279, 10.1113/ep088744.
37. Lucas Moitinho-Silva; Michelle Wegener; Sandra May; Florian Schrinner; Awais Akhtar; Teide J. Boysen; Eva Schaeffer; Clint Hansen; Timo Schmidt; Malte C. Rühlemann; et al.Matthias HübenthalPhilipp RauschMustafa T. KondakciWalter MaetzlerStephan WeidingerMatthias LaudesPhilip SüßDominik SchulteRalf JunkerFelix SommerBurkhard WeisserCorinna BangAndre Franke Short-term physical exercise impacts on the human holobiont obtained by a randomised intervention study. *BMC Microbiology* **2021**, *21*, 1-14, 10.1186/s12866-021-02214-1.

38. Ryan P. Durk; Esperanza Castillo; Leticia Márquez-Magaña; Gregory J. Grosicki; Nicole D. Bolter; C. Matthew Lee; James R. Bagley; Gut Microbiota Composition Is Related to Cardiorespiratory Fitness in Healthy Young Adults. *International Journal of Sport Nutrition and Exercise Metabolism* **2019**, *29*, 249-253, 10.1123/ijsnem.2018-0024.

39. Mehrbod Estaki; Jason Pither; Peter Baumeister; Jonathan P. Little; Sandeep K. Gill; Sanjoy Ghosh; Zahra Ahmadi-Vand; Katelyn R. Marsden; Deanna L. Gibson; Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. *Microbiome* **2016**, *4*, 1-13, 10.1186/s40168-016-0189-7.

40. Dierdra Bycura; Anthony Santos; Arron Shiffer; Shari Kyman; Kyle Winfree; Jay Sutliffe; Talima Pearson; Derek Sonderegger; Emily Cope; J Greg Caporaso; et al. Impact Of Different Exercise Modalities On The Human Gut Microbiome. *Medicine & Science in Sports & Exercise* **2021**, *53*, 230-230, 10.1249/01.mss.0000761700.42507.2b.

41. Rocío Quiroga; Esther Nistal; Brisamar Estébanez; David Porras; María Juárez-Fernández; Susana Martínez-Flórez; María Victoria García-Mediavilla; José A. de Paz; Javier González-Gallego; Sonia Sánchez-Campos; et al.María J. Cuevas Exercise training modulates the gut microbiota profile and impairs inflammatory signaling pathways in obese children. *Experimental & Molecular Medicine* **2020**, *52*, 1048-1061, 10.1038/s12276-020-0459-0.

42. Lauren M. Petersen; Eddy J. Bautista; Hoan Nguyen; Blake M. Hanson; Lei Chen; Sai H. Lek; Erica Sodergren; George M. Weinstock; Community characteristics of the gut microbiomes of competitive cyclists. *Microbiome* **2017**, *5*, 1-13, 10.1186/s40168-017-0320-4.

43. Vittoria Cella; Silvia Migliaccio; Antonio Paoli; Microbiota intestinale ed esercizio fisico: nuova possibile area di intervento?. *L'Endocrinologo* **2020**, *21*, 338-343, 10.1007/s40619-020-00777-1.

44. So Morishima; Wataru Aoi; Aki Kawamura; Takahiro Kawase; Tomohisa Takagi; Yuji Naito; Takamitsu Tsukahara; Ryo Inoue; Intensive, prolonged exercise seemingly causes gut dysbiosis in female endurance runners. *Journal of Clinical Biochemistry and Nutrition* **2021**, *68*, 253-258, 1 0.3164/jcbn.20-131.

45. Takamitsu Tsukahara; Kazunari Ushida; Succinate accumulation in pig large intestine during antibiotic-associated diarrhea and the constitution of succinate-producing flora.. *The Journal of General and Applied Microbiology* **2002**, *48*, 143-154, 10.2323/jgam.48.143.

46. Hirokazu Taniguchi; Kumpei Tanisawa; Xiaomin Sun; Takafumi Kubo; Yuri Hoshino; Masahito Hosokawa; Haruko Takeyama; Mitsuru Higuchi; Effects of short-term endurance exercise on gut microbiota in elderly men.. *Physiological Reports* **2018**, *6*, e13935, 10.14814/phy2.13935.

47. Sebastian Tims; Catherine Derom; D.M.A.E. Jonkers; Robert Vlietinck; Wim H Saris; Michiel Kleerebezem; Willem M De Vos; Erwin G Zoetendal; Microbiota conservation and BMI signatures in adult monozygotic twins. *The ISME Journal* **2012**, *7*, 707-717, 10.1038/ismej.2012.146.

48. Julia K. Goodrich; Jillian L. Waters; Angela C. Poole; Jessica L. Sutter; Omry Koren; Ran Blekhman; Michelle Beaumont; William Van Treuren; Rob Knight; Jordana T. Bell; et al.Timothy D. SpectorAndrew G. ClarkRuth E. Ley Human Genetics Shape the Gut Microbiome. *Cell* **2014**, *159*, 789-799, 10.1016/j.cell.2014.09.053.

49. Kristine M. Erlandson; Jay Liu; Rachel Johnson; Stephanie Dillon; Catherine M. Jankowski; Miranda Kroehl; Charles E. Robertson; Daniel N. Frank; Yunus Tuncil; Janine Higgins; et al.Bruce HamakerCara C. Wilson An exercise intervention alters stool microbiota and metabolites among older, sedentary adults. *Therapeutic Advances in Infectious Disease* **2021**, *8*, 125-137, 10.1177/20499361211027067.

50. Andreas Schwiertz; Georgina Hold; Sylvia H. Duncan; Bärbel Gruhl; Matthew D. Collins; Paul A. Lawson; Harry J. Flint; Michael Blaut; Anaerostipes caccae gen. nov., sp. nov., a New Saccharolytic, Acetate-utilising, Butyrate-producing Bacterium from Human Faeces. *Systematic and Applied Microbiology* **2002**, *25*, 46-51, 10.1078/0723-2020-00096.

51. Mohsen Mazidi; Niloofar Shekoohi; Adrian Covic; Dimitri P. Mikhailidis; Maciej Banach; Adverse Impact of *Desulfovibrio* spp. and Beneficial Role of *Anaerostipes* spp. on Renal Function: Insights from a Mendelian Randomization Analysis. *Nutrients* **2020**, *12*, 2216, 10.3390/nu12082216.

52. Eveliina Munukka; Juha P. Ahtiainen; Pere Puigbó; Sirpa Jalkanen; Katja Pahkala; Anniina Keskitalo; Urho Kujala; Sami Pietilä; Maija Hollmén; Laura Elo; et al.Pentti HuovinenGiuseppe D'AuriaSatu Pekkala Six-Week Endurance Exercise Alters Gut Metagenome That Is not Reflected in Systemic Metabolism in Over-weight Women. *Frontiers in Microbiology* **2018**, *9*, 2323, 10.3389/fmicb.2018.02323.

53. Carolina Gubert; Geraldine Kong; Thibault Renoir; Anthony J. Hannan; Exercise, diet and stress as modulators of gut microbiota: Implications for neurodegenerative diseases. *Neurobiology of Disease* **2020**, *134*, 104621, 10.1016/j.nbd.2019.104621.

54. T. Huang; Kristian Traberg Larsen; Mathias Ried-Larsen; Niels Christian Møller; Lars Bo Andersen; The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scandinavian Journal of Medicine & Science in Sports* **2013**, *24*, 1-10, 10.1111/sms.12069.

55. Laura Micheli; Manuela Ceccarelli; Giorgio D’Andrea; Felice Tirone; Depression and adult neurogenesis: Positive effects of the antidepressant fluoxetine and of physical exercise. *Brain Research Bulletin* **2018**, *143*, 181-193, 10.1016/j.brainresbull.2018.09.002.

56. Dora Abraham; Janos Feher; Gian Luca Scuderi; Dora Szabo; Arpad Dobolyi; Melinda Cservenak; Janos Juhasz; Balazs Ligeti; Sandor Pongor; Mari Carmen Gomez-Cabrera; et al.Jose VinaMitsuru HiguchiKatsuhiro SuzukiIstvan BoldoghZsolt Radak Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: Role of microbiome. *Experimental Gerontology* **2019**, *115*, 122-131, 10.1016/j.exger.2018.12.005.

57. M. Paul Murphy; Harry LeVine; Alzheimer's Disease and the Amyloid-β Peptide. *Journal of Alzheimer's Disease* **2010**, *19*, 311-323, 10.3233/JAD-2010-1221.
58. Tzu-Wei Lin; Yao-Hsiang Shih; Shean-Jen Chen; Chi-Hsiang Lien; Chia-Yuan Chang; Tung-Yi Huang; Shun-Hua Chen; Chauying J. Jen; Yu-Min Kuo; Running exercise delays neurodegeneration in amygdala and hippocampus of Alzheimer’s disease (APP/PS1) transgenic mice. *Neurobiology of Learning and Memory* **2015**, *118*, 189-197, 10.1016/j.nlm.2014.12.005.
59. Ting Shen; Yumei Yue; Tingting He; Cong Huang; Boyi Qu; Wen Lv; Hsin-Yi Lai; The Association Between the Gut Microbiota and Parkinson's Disease, a Meta-Analysis. *Frontiers in Aging Neuroscience* **2021**, *13*, 145-156, 10.3389/fnagi.2021.636545.