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Exercise, Gut Microbiome, and Gastrointestinal Diseases: Therapeutic Impact and Molecular Mechanisms

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The benefits of regular physical activity (PA) on disease prevention and treatment outcomes have been recognized for centuries. However, only recently has interorgan communication triggered by the release of "myokines" from contracting skeletal muscles emerged as a putative mechanism by which exercise confers protection against numerous disease states. Cross-talk between active skeletal muscles and the gut microbiota reveal how regular PA boosts host immunity, facilitates a more diverse gut microbiome and functional metabolome, and plays a positive role in energy homeostasis and metabolic regulation. In contrast, and despite the large interindividual variation in the human gut microbiome, reduced microbial diversity has been implicated in several diseases of the gastrointestinal (GI) tract, systemic immune diseases, and cancers. Although prolonged, intense, weight-bearing exercise conducted in extreme conditions can increase intestinal permeability, compromising gut-barrier function and resulting in both upper and lower GI symptoms, these are transient and benign. Accordingly, the gut microbiome has become an attractive target for modulating many of the positive effects of regular PA on GI health and disease, although the precise dose of exercise required to induce favourable changes in the microbiome and enhance host immunity is currently unknown. Future efforts should concentrate on gaining a deeper understanding of the factors involved in exercise-gut interactions through the generation of functional 'omics readouts (ie, metatranscriptomics, metaproteomics, and metabolomics) that have the potential to identify functional traits of the microbiome that are linked to host health and disease states, and validating these interactions in experimental and preclinical systems. A greater understanding of how PA interacts with the GI tract and the microbiome may enable targeted therapeutic strategies to be developed for individuals and populations at risk for a variety of GI diseases.

Keywords: AMPK; Cross-Talk; Fecal Microbiota Transfer; Gastrointestinal Tract; Immunity; Inflammation; Ischemia; mTOR; Myokines; Physical Activity; Probiotics; Skeletal Muscle.

Epidemiologic and cross-sectional data provide overwhelming evidence to demonstrate that lifelong physical activity (PA, defined as voluntary bodily movement produced by skeletal muscles that requires energy expenditure) postpones the onset of numerous chronic metabolic conditions and noncommunicable diseases (NCDs) and is associated with an enhanced quality of life and extended health span.[1–6] In this regard, there has been belated recognition that "exercise is medicine" with the advancement and implementation of evidence-based approaches to elevate the status of PA in primary healthcare settings.[7–11] Many interdependent mechanisms underpin the health-promoting effects of PA although the precise molecular bases by which lifelong PA (ie, exercise training) promotes human health and reduces disease risk remain poorly understood.[12] Although the biochemical and metabolic adaptations to exercise training have been extensively investigated in skeletal muscle, heart, adipose tissue, and the vasculature,[13] only recently has there been appreciation that the gut microbiome plays a fundamental role in promoting some of the beneficial effects of regular PA on both general health, athletic performance, and anticancer immunity.[14–16] Murine models using a variety of exercise interventions reveal consistent changes in the gut microbiome associated with improved health outcomes and longevity.[17] Despite less than 5% overlap between human and mouse microbiota composition[18] and several interspecies differences,[19] such investigations provide opportunities for examining the mechanistic interactions between exercise and the gut microbiota that may be of direct translational value for discovering the functional processes underlying several human gastrointestinal (GI) disease states.[20,21]

The gut microbiome constantly interacts with the host immune system, producing a range of metabolites that exert both local (cell/tissue/organ) and systemic (whole-body) effects.[22] These interactions can trigger health or disease states by generating either harmful metabolites that

Abbreviations used in this paper: **AMPK, AMP-activated protein kinase; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; FMT, fecal microbiota transplantation; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IL, interleukin; MASLD, metabolic dysfunction-associated steatotic liver disease; MET, metabolic equivalent; mTOR, Akt/mammalian target of rapamycin; NK, natural killer; NCD, noncommunicable disease; PA, physical activity; RR, relative risk; SCFA, short-chain fatty acids; TNF-α, tumor necrosis factor alpha; VO_2max, maximal oxygen consumption.**

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provoke disorders (eg, inflammatory bowel disease [IBD]) or favorable metabolites (ie, short-chain fatty acids [SCFA]) that are health-promoting. For this reason, the role of the gut microbiome on its host has been the focus of intense research, with the gut microbiota now established as a powerful modulator of the efficacy of several treatments of GI diseases. There has been an emergence of clinical interventions targeting the microbiome to enhance health outcomes, particularly cancer,[23] from diagnosis and recurrence to prognosis as well as treatment effectiveness.[24] Here we discuss the role of PA and skeletal muscle metabolic cross-talk with other tissues and organs, especially the GI tract, with a focus on how exercise can modulate microbial diversity. We describe the effects of exercise on the GI tract concentrating on the role of bacteria and other microorganisms in this process. Finally, the role of exercise and the gut microbiome in the prevention of GI diseases will be discussed in anticipation of emerging treatments that target the microbiome to modulate these effects by understanding the complex and interdependent interactions between PA, diet, and GI function.

Metabolic Communication During Exercise

Skeletal Muscle Cross-Talk

The health-promoting effects of regular PA have traditionally been attributed to exercise-induced increases in whole-body cardiorespiratory fitness (VO_{2max}) evoked by extensive remodelling of the vascular system, especially the peripheral skeletal muscles subjected to exercise.[13] However, during the past 20 years, interorgan communication or "cross-talk" initiated by contracting skeletal muscles has emerged as a complementary mechanism through which PA confers protection against an array of disease states.[25] Although the hypothesis of a "general, humoral effect of exercise" was proposed more than 60 years ago,[26] the concept of skeletal muscle as an endocrine organ gained credibility just 2 decades ago when it was shown that the cytokine interleukin-6 (IL6) was released from skeletal muscle during exercise.[27] Since that time, cytokines and other peptides, which are released by contracting skeletal muscle fibers and exert autocrine, paracrine, or endocrine effects, have been classified as "myokines."[28,29] The list of bona fide myokines includes IL6, IL8, IL15, decorin, follistatin-like 1, fibroblast growth factor-21, irisin, chemokine CXC motif ligand-1 also known as keratinocyte-derived chemokine, mitochondrially encoded peptide-c and meteorin-like, although there are likely many more proteins secreted by contracting skeletal muscles.[25,29] Established roles for "adipokines" and "hepatokines" as exercise-stimulated signals that coordinate systemic metabolism in response to PA and inactivity have been reviewed previously.[25,30,31] The discovery of interorgan cross-talk offers a framework for understanding how PA transmits many of its beneficial effects on whole-body metabolic health (Figure 1).

Recently, important links between skeletal muscle and the gut microbiota have been uncovered, revealing how exercise facilitates a more diverse gut microbiome and functional metabolome, casting new light on the interconnectivity between these 2 organs in health and disease states.[32] Exercise training alters both the bacterial community structure and numerous taxa that are associated with improved host health.[33] However, these exercise-induced changes are not universal with only moderate to high-intensity exercise undertaken more than 3 times per week for longer than 8 weeks being consistently associated with either alterations in bacterial community and/or community structure.[34] In that analysis, the health status of the cohort under investigation created variability and potential confounders in results,[34] with a rather liberal definition of "healthy" that included individuals with no defined exclusion criteria in terms of chronic illness.

Contemporary investigations show that the gut microbiota exerts multiple effects on skeletal muscle bioenergetics[35] and have revealed how the gut bacteria respond to an exercise challenge with reciprocal roles in fuel availability, muscle function, and endurance capacity.[16,36] The notion of cross-talk between the gut microbiota and contracting skeletal muscle emerged from studies in rodents showing increases in several species of SCFAs (acetate, butyrate, propionate, and conjugated linoleic acid) after endurance training.[37–39] Although early studies demonstrated that SCFAs were absorbed in both the small and large intestine by similar mechanisms, it is now accepted that there exist species differences in SCFA producers as well as different transporter isoforms expressed in enterocytes along the intestine.[40] SCFAs have a protective effect on the host by reducing inflammation through transcriptional inhibition of cytokines and inflammatory proteins. Among the SCFAs, butyrate has received considerable attention for its beneficial effects on both cellular energy metabolism and intestinal homeostasis: butyrate is the primary fuel for colonocytes, increasing colonic epithelial cell proliferation, promoting gut barrier integrity, and regulating host gene expression and immunity.[41]

Compelling evidence for the existence of a "muscle-gut axis" came from the study of Lahiri et al[42] who compared the skeletal muscle of germ-free mice that lacked a gut microbiota to the skeletal muscle of pathogen-free mice with an intact functional gut microbiota. In contrast to pathogen-free mice, skeletal muscle from the germ-free animals displayed significant atrophy and reduced muscle strength, underpinned by a decreased expression of insulin-like growth factor-1 along with reduced transcription of genes associated with skeletal muscle growth and mitochondrial function. Treating germ-free mice with a cocktail of SCFAs resulted in a reduced expression of *Atrogin-1* and an increased expression of myoblast determination protein-1, and partially reversed the functional impairments to muscle. These data support a role for the gut microbiota in regulating skeletal muscle mass and function, although whether this is a direct effect or immune-mediated remains to be determined. The influence of the microbiota-derived SCFA on hosts includes proliferation, differentiation, and aspects of metabolism, with most of these functions acting via gene expression, with butyrate modulating the expression of >20% of genes in humans.[43]

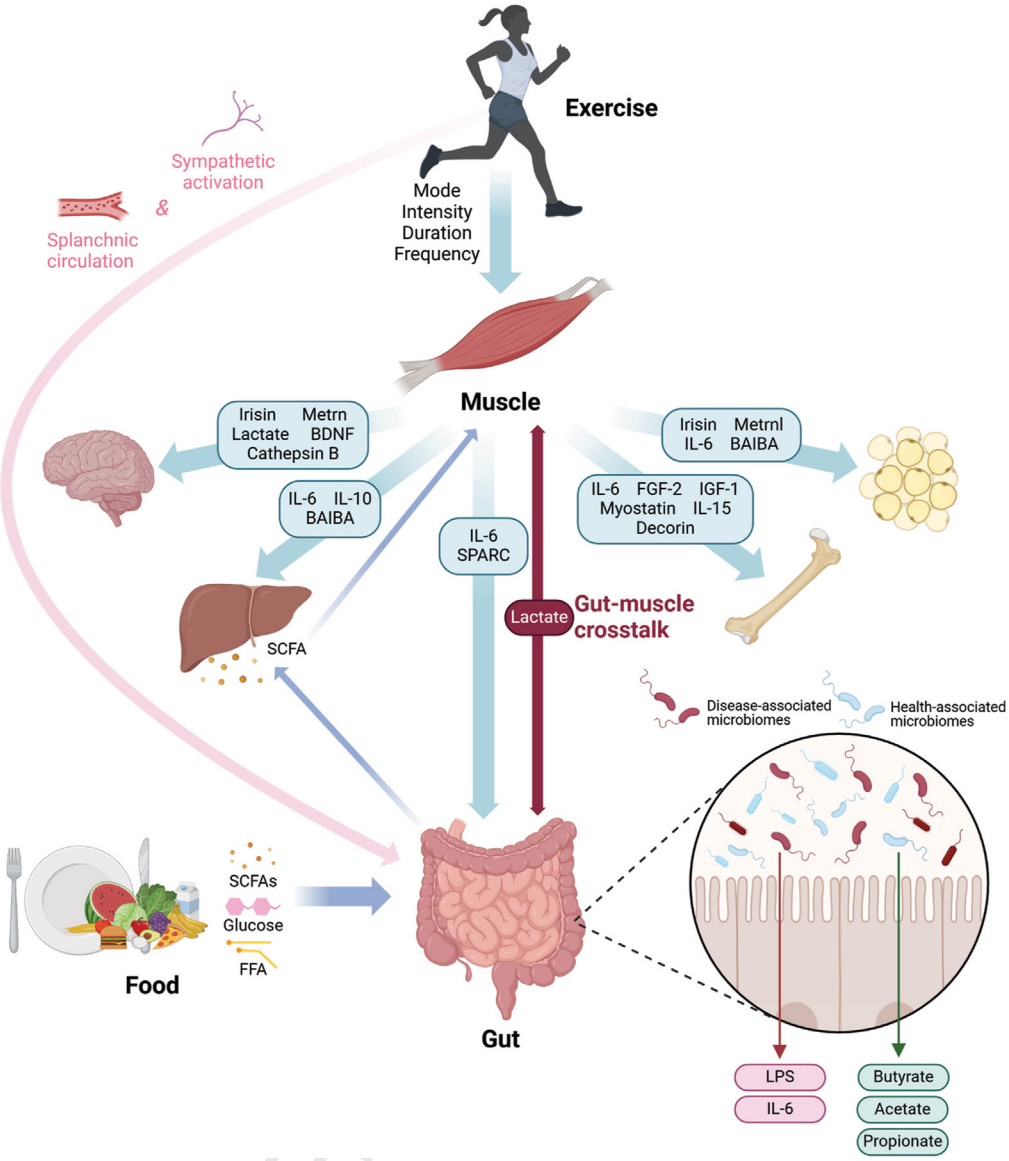

Figure 1. Skeletal muscle cross-talk. Regular PA has both acute and chronic effects on multiple organ systems. In response to contractile stimuli, skeletal muscles secrete a range of molecules that "communicate" with other tissues and organs including adipose tissue, liver, brain, gut, bone, and the GI tract. While the majority of myokines are released from skeletal muscle in response to an acute bout of exercise, adipokines and hepatokines exert their biological function in response to repeated exercise stimuli through changes in whole-body metabolism. The release of cytokines and other mediators, alongside neurologic and vascular changes induced by exercise, modulate the intestinal barrier and gut function. Such changes are highly individual and are modified by the prevailing exercise challenge (mode, intensity, duration, and environmental conditions), an individual's habitual diet, and the microbiome. Exercise training is associated with increased microbial diversity and abundance of bacterial species, increasing SCFAs, whereas reduced microbial diversity in human intestines has been implicated in several GI diseases and CRC, with the microbiome exacerbating inflammation or other disease processes with immunomodulatory functions. BAIBA, β-aminoisobutyric acid; BDNF, brain-derived neurotrophic factor; FFA, free fatty acids; FGF-2, fibroblast growth factor-2; IGF-1, insulin-like growth factor 1; LPS, lipopolysaccardides; Metrnl, meteorin-like; SPARC, secreted protein acidic rich in cysteine. Created in BioRender. Belhaj M. (2025) https://BioRender.com/s64m052. Q21

The first evidence demonstrating that exercise training in humans was associated with increased microbial diversity and abundance of bacterial species came from cross-sectional studies on well-trained athletic populations. Clarke et al[44] reported that professional rugby players had higher alpha diversity and a greater relative abundance of the health-associated genus *Akkermansia* compared with high- and low-body mass index (BMI) sedentary controls. Subsequent observational studies revealed that trained states were associated with a higher alpha diversity, an enrichment of beneficial taxa, and a higher abundance of fecal SCFAs.[16] In these investigations, VO_{2max} accounted for up to a quarter of the variation in taxonomic richness after allowing for all other factors including diet,[45] with higher

levels of fitness associated with a greater degree of both alpha and beta diversity.[44–47] These observations suggest that a high level of cardiorespiratory fitness is related to certain bacterial species and metabolite production, which have been implicated in several diseases states including reduced cancer risk.[23] Indeed, a recent study reported greater gut microbiome diversity and differential abundances between colorectal cancer (CRC) survivors who were physical active compared with those who were inactive,[48] with active patients having enriched abundance of multiple dominant genera including *Faecalibacterium* and *Blautia* and less dominant genera including *Succiniclasticum* and *Succinivibrio*. At the phylum level, active patients had lower Actinobacteria abundance. These findings are consistent with studies showing higher abundances of *Succinivibrio, Faecalibacterium prausnitztii, Roseburia hominis,* and *Akkermansia muciniphila* in healthy individuals and athletes.[44,45,47] *Faecalibacterium* and *Succinivibrio* have been linked to health-promoting attributes including decreased risk for CRC.[49]

Further evidence of a muscle-gut axis comes from the work of Scheiman et al.[50] Using 16S rRNA profiling, these workers reported a higher abundance of *Veillonella* in 15 runners who completed the 2015 Boston marathon compared with a group of 10 healthy but sedentary controls. *Veillonella* species metabolize lactate into the SCFAs acetate and propionate via the methylmalonyl-CoA pathway and, although many other microbes have the capacity to use lactate, they do not possess the full pathway to convert lactate to propionate. Using intracolonic infusion, a strain of *Veillonella atypica* was isolated from stool samples of the runners and when this strain was inoculated into mice, treadmill running time to exhaustion was significantly increased. These findings are intriguing as they highlight that the microbiome may be a critical component of endurance performance but raise the question of how this performance-facilitating organism came to be more prevalent among endurance-trained athletes in the first place.

In contrast, reduced microbial diversity has been implicated in many GI diseases[51,52] although direct causation remains to be determined. In severe liver disease and IBD, antibiotics are frequently prescribed, leading to periods of significantly reduced microbial diversity, potentially driving ongoing disease pathogenesis. Such microbial effects are also strongly associated with sarcopenia, defined as a loss of skeletal muscle mass, which is often seen in parallel with these diseases and is closely related to levels of PA.[53,54] This "dysbiosis" affects host metabolism and the functionality and pathophysiology of several peripheral organs with exercise a potential intervention to perturb gut microbiota composition and re-establish gut symbiosis. There is a large variation in the outcomes of exercise on the microbiome across studies[38,55,56] due to the complexity of the interaction with individual microbiome variation, different participant cohorts, the exercise dose (ie, the intensity, duration, and frequency) and other variables (diet, cultural, and geographical demographics).[57] For example, the relative abundance of *Prevotella* is associated with endurance-based exercise programs,[58] whereas in athletes who undertake more intense power-based training, there is marked intestinal inflammation and greater abundance of bacteria involved in inflammatory processes such as *Haemophilus, Rothia*, *Mucispirillum*, and *Ruminococcus gnavus*.[59,60] Although the optimal dose of exercise to induce favourable changes in the gut microbiota is unknown, it is likely to be specific to an individual's prevailing health status and background diet. Results from a recent investigation demonstrate that exercise training–induced alterations to gut microbiota composition and function were dependent on the body composition of participants. Allen et al[61] reported that short-term endurance exercise training increased fecal concentrations of SCFAs in lean individuals (BMI <25 kg/m^2) but not those with obesity (BMI >30 25 kg/m^2), an observation that was independent of diet. Of note, the exercise-induced changes to the microbiota, VO_{2max}, and body composition were rapidly lost in both cohorts when the training stimulus was terminated, suggesting that shifts in the metabolic capacity of the gut microbiota were strongly associated with the prevailing fitness levels, were transient, and were highly dependent on a regular exercise stimulus. Clearly, regular PA is necessary to produce favorable long-term modifications in the gut microbiota composition, largely through immune-metabolic pathways associated with anti-inflammatory effects.[61–63] Further studies are required to understand the mechanisms that regulate changes in the composition and functions of the microbiome caused by PA along with their related effects.[33]

Diseases of the GI Tract and Effects of Exercise on GI Symptoms

Acute exercise has diverse effects on the GI tract (Figure 2) that can broadly be divided into upper (ie, heartburn, belching, regurgitation, and epigastric pain) or lower GI symptoms (ie, nausea, diarrhea, blood loss, flatulence, urgency, and abdominal pain). Exercise affects both motility and absorptive properties of the GI tract, with acute exercise slowing transit times in the upper GI tract due to increased sympathetic nervous activity.[64] There is also a reduced absorptive capacity during exercise,[65,66] with increased nutrient load to the caecum and colon driving symptoms in the lower GI tract.[67] The altered nutrient environment also interacts with the resident microbiome as a potential modifier of such symptoms. Upper GI symptoms are more common than lower GI symptoms with prolonged (>90 min) weight-bearing exercise (ie, running) associated with a greater number and severity of symptoms.[68,69] GI problems are especially common in athletes training for and competing in endurance events with 30%–50% of athletes reporting 1 or more GI symptoms.[70] However, most GI symptoms are mild, transient, and of no risk to long-term health.

Ischemia and inflammation

Changes in splanchnic blood flow underpin many of the adverse clinical effects of exercise on GI function[71,72] during which splanchnic ischemia leads to gut barrier

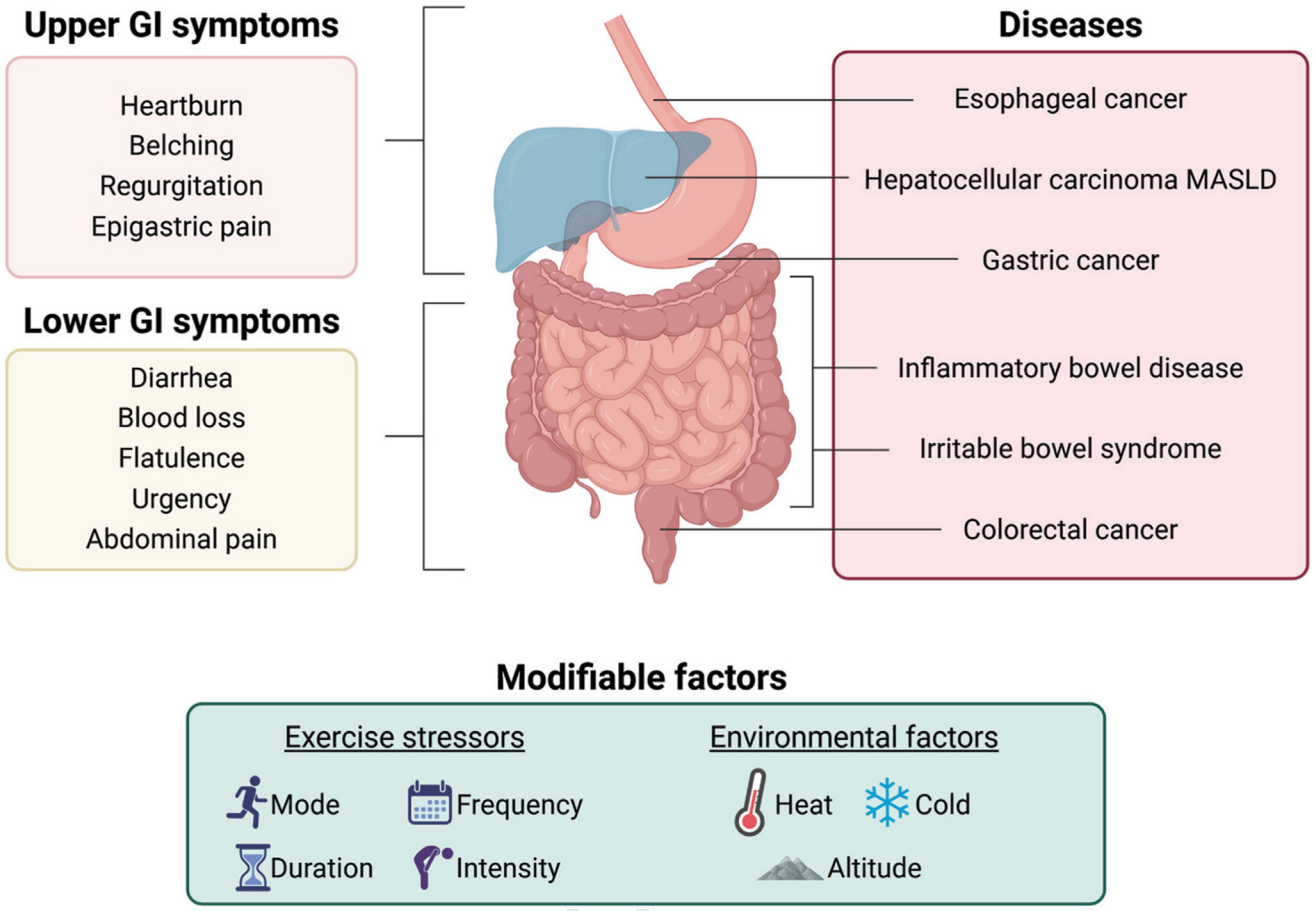

Figure 2. Clinical symptoms associated with "excessive" exercise challenges along with the protective effects of exercise training on GI diseases. Acute bouts of exercise can induce both upper and lower GI symptoms (*left*) depending on the prevailing exercise and environmental factors (*middle*, *lower*). Exercise training is associated with favorable outcomes for a number of GI diseases (*right*). Created in BioRender. Belhaj M. (2025) https://BioRender.com/s64m052.

disorders.[73–75] Such exercise-induced ischemia leads to systemic endotoxemia and an associated inflammatory response.[76–79] Historically intestinal damage has been measured after exercise through fecal blood loss[80] and more recently with intestinal-fatty acid binding protein[75,81] and calprotectin.[75] In healthy individuals intestinal permeability is related to the prevailing exercise-intensity with intense exercise (>80% of VO_{2max}) resulting in greater increases in small intestinal permeability compared with exercise undertaken at 40%–60% of VO_{2max}. However, increases in permeability do not always result in a higher prevalence of GI symptoms and increased intestinal permeability.[82] A study of endurance-trained athletes performing 1 hour of intense cycling at 80% of VO_{2max} reported little effect on barrier function or self-reported GI symptoms,[83] suggesting there is considerable variability in the effect of both the relative exercise intensity and mode on gut damage, with well-trained individuals experiencing fewer GI disturbances compared with exercise-naïve subjects. Indeed, the GI tract is highly adaptable: gastric emptying as well as stomach comfort can be "trained" and perceptions of fullness decreases in athletes practicing a variety of nutritional strategies before and during exercise.[84,85]

Endotoxemia is suggestive of barrier dysfunction or damage, with either bacteria or their products translocating across the epithelial lining of the GI tract. Evidence of such dysfunction during PA is confounded by the different modes and intensities of exercise, the fitness level of subjects studied, and the various measures of gut damage used in investigations. This, in part, explains the wide range of outcomes reported, although one should also consider that the resident microbiome is another variable in exercise-induced barrier stress. For example, a high protein diet (1.5 g/kg body mass), commonly consumed by athletes training for strength/power events, may contribute to dysbiosis (eg, increased *Escherichia coli* lipopolysaccharide) and Q8 amplify intestinal damage and symptoms. As exercise intensity and duration increases, there is considerable evidence for increases in indices of intestinal injury, permeability, and endotoxemia, together with impairment of gastric emptying, slowing of small intestinal transit, and malabsorption.[86] The addition of heat stress and running mode exacerbates markers of GI disturbance, with an exercise duration of ~2 hours at a moderate (60% of VO_{2max}) intensity seemingly the "threshold" at which significant GI perturbations occur.[86]

The Potential Role of the Gut Microbiome as a Mechanism to Reduce GI Symptoms During Exercise

A potential role for the microbiome in modulating the effects of PA is through dietary interventions. Carbohydrate ingestion immediately before or during exercise attenuates GI symptoms and markers of intestinal damage[87–89] and, while this effect may be independent of the microbiome, increased carbohydrate availability may temper the dysbiosis reported by many athletes.[86,90] Other diets, including a gluten-free diet, have been investigated in an attempt to reduce GI symptoms, but appear ineffective.[91] To support the splanchnic circulation and reduce intestinal damage during exercise, the nitric oxide precursors and amino acid supplements L-arginine and L-citrulline supplements have been investigated, although their efficacy is equivocal.[92,93] Although these dietary interventions are likely to have moderate effects on the microbiome, it remains speculative whether they would exert any effect on exercise capacity, or the mechanism of such an effect.

Direct attempts to modulate the microbiome to preserve permeability and attenuate other exercise-induced barrier damage have been largely ineffective, including combinations comprising 6 (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Enterococcus faecium*, *Lactobacillus acidophilus*, *L. brevis*, and *Lactococcus lactis)* and 9 probiotic strains *(L acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Lactobacillus fermentum*, *Lactobacillus casei*, *Bifidobacterium breve*, *B lactis*, *B bifidum*, and *Streptococcus thermophilus)*.[94,95] In a recent double-blind placebo-controlled trial, probiotic supplementation (*L acidophilus* and *Bifidobacterium longum)* administered for 5 weeks to amateur runners reduced GI symptoms and was associated with less dysbiosis.[96] In a double-blind, crossover study 16 runners were randomized to 4 weeks of daily supplementation with a probiotic cocktail containing *Pediococcus acidilactici* bacteria and *L plantarum* or placebo. Treadmill running tests (90 minutes at 65%–70% of VO_{2max} or until fatigue/GI symptoms developed, undertaken in 27°C) were performed before and after supplementation. GI symptoms, gut permeability-associated parameters (intestinal-fatty acid binding protein, lipopolysaccharide-binding protein, zonulin, and cytokines), and intestinal microbial content were not altered by the probiotic supplementation.[97] *L casei* supplementation for 7 days before 2 hours of running at 60% of VO_{2max} in extreme (34°C) heat did not alter resting circulatory endotoxin concentration or plasma cytokine profile compared with a placebo, although there was a trend for higher plasma endotoxin and tumor necrosis factor alpha (TNF-α) concentrations after exercise in the probiotic-supplemented group,[98] suggesting that changes to the microbiome may influence barrier function during PA, although not always favorably. Although probiotic supplementation has traditionally focused on gut health, in recent years, the clinical applications of probiotics have broadened to allergic, metabolic, inflammatory, GI, and respiratory conditions. Probiotic supplementation could yield small beneficial effects in promoting health in trained individuals, likely by reducing the risk of respiratory and GI illness during intensified periods of training and competition but precise compositions and dosage regimes remain to be determined. Such benefits would most likely be mediated by changes in gut microbiota and enhanced mucosal barrier integrity in the GI and respiratory tracts.[99]

The Potential Role of Exercise-Microbiome Cross-Talk in GI Diseases

Exercise undertaken according to the American College of Sports Medicine guidelines[100] is associated with improved health outcomes in numerous NCDs, including many nonmalignant conditions of the GI tract and also several cancers. Perhaps the most obvious GI condition linked with regular PA is metabolic dysfunction-associated steatotic liver disease (MASLD), with exercise recommended as a primary treatment across many international guidelines.[101] Although MASLD is intimately related to lack of PA, obesity, and a poor diet, not all sedentary people with obesity develop fatty infiltration of the liver. The gut microbiome is related to this complex interplay with a "gut-liver axis" of diet, genetics, and inflammation being potential drivers of the fibrosis and risk of hepatocellular carcinoma. Treatment strategies for these conditions should consider combining regular exercise with microbiome modulation to impact MASLD[102] because exercise can reverse gut "dysbiosis" in MASLD patients.[103]

IBD has 2 major phenotypic forms: Crohn's disease and ulcerative colitis, with rising worldwide incidence. Although the precise etiology of IBD is unknown, several factors arising from adipose tissue and skeletal muscle have been implicated including cytokines, adipokines, and myokines.[104] In a high-fat–fed murine model of colitis, moderate-intensity exercise (voluntary wheel running) significantly decreased macroscopic and microscopic colitis, increased colonic blood flow, and attenuated plasma TNF-α, IL6, monocyte chemoattractant protein-1, IL1β, and leptin levels. In contrast, in sedentary mice fed the same diet, colonic lesions were aggravated, colonic tissue weight increased, and the plasma TNF-α, IL6, monocyte chemoattractant protein-1, IL1β and leptin levels significantly increased.[105] In children with IBD, intense exercise did not alter symptomatic outcomes or changes in serum inflammatory cytokines when compared with age-matched controls.[106] However, a recent systematic review of 637 patients (34% males) and pooled evidence from 6 randomized clinical trials found exercise improved disease activity but not disease-specific quality of life compared with controls.[107] Given that IBD is triggered by an abnormal immune response to the resident microbiota,[108] any effects of exercise on IBD likely impact the microbiome, although a systematic review of the systemic inflammatory response in exercise-based intervention studies in IBD patients reported no consistent effect.[109] A combination of exercise and psychological interventions in a group of patients with Crohn's disease led to positive changes in their intestinal microbiome with accompanying reductions in systemic markers of inflammation.[110]

A recent meta-analysis concluded there was a reduced risk of developing IBD in individuals who undertook regular high- vs low-intensity PA.[111] However, early results from the IBD-FITT study (ClinicalTrials.gov NCT04816812), a RCT of 12 weeks of aerobic exercise in people with IBD,[112] show improvements in quality of life and other health-related outcomes, without any effect on disease activity.[113] These contrasting results suggest strong individual variation, with differences in the timing of the commencement of exercise training in relation to disease activity likely to be important. Fatigue, a major symptom in IBD patients, is associated with muscle deconditioning, with a small study showing patients with Crohn's disease exhibit impaired postexercise recovery, measured based on slower rates of muscle phosphocreatine resynthesis.[114] Although the links between PA, the microbiome, and disease outcomes in IBD remain unclear, sarcopenia is associated with poor clinical outcomes independent of IBD activity and, therefore, muscle health should be assessed in all IBD patients at routine intervals.[54]

In patients with irritable bowel syndrome (IBS), a disease without an easily measurable inflammatory response, symptoms are reduced after exercise training[115,116] and associated with exercise-induced improvements in gut motility along with favorable psychological changes. The first-line therapy for IBS is the low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP) diet,[117] which modulates its effect through direct dietary impact on the microbiome. As such, the benefit of exercise on IBS and other motility-related GI conditions may be mediated, in part, through the microbiome. A recent trial reporting fewer IBS symptoms after exercise training[118] also found that exercise reduced cell-free mitochondrial DNA in the plasma of the control (non-IBS) group.[118,119] Because mitochondrial DNA is a damage-associated molecular pattern that is bidirectionally associated with dysbiosis,[120] the results from that study suggest that PA can modify cellular damage–associated molecular patterns in healthy patients but not in IBS patients, which may be due to different microbial ecologies in those with IBS. A recent Cochrane review reported moderate positive outcomes of regular PA on IBS symptoms without clear improvement in quality of life,[121] again suggesting strong individual variation in such effects. Putative mechanisms that link the microbiome to effects of PA on IBS patients include changes to transit time, greater SCFA production, improvement in the intestinal barrier, as well as modulation of the immune response.[122]

Exercise and GI Cancer Prevention: Molecular Mechanisms Related to the Microbiome

The protective effect of regular, moderate to vigorous PA against cancer risk is well established with evidence from epidemiologic studies, randomized controlled trials, and meta-analyses from cohort investigations showing that regular exercise reduces the risk of between 7 and 13 different cancers and cancer mortality, including less frequent recurrence and fewer/less severe adverse effects.[123–128] Regular PA is inversely related to the risk of cancer at the proximal (relative risk [RR], 0.76; 95% confidence intervals [CI], 0.70–0.83) and distal colon (RR, 0.77; 95% CI, 0.71–0.83), although there is limited evidence for any positive effects of PA on reducing risk of rectal cancers (RR, 0.98; 95% CI, 0.88–1.08), indicating that different mechanisms are operating in the development of colon and rectal cancer.[129] The RR for gastroesophageal cancer is 0.82 (CI, 0.74–0.90).[130] The cancer for which regular PA confers the greatest protective effect is CRC,[131–133] with moderate levels of PA associated with a 25% reduction of CRCs and greater amounts of PA linked to a greater (40%) reduction in risk.[134,135] Even colorectal polyps can be reduced in number by increasing levels of PA.[132,136] After a year-long exercise training intervention in previously sedentary men who completed a minimum of 250 min/week of moderate- to vigorous-intensity exercise and whose VO_{2max} increased by >5%, there was a significant decrease in colon crypt proliferation and associated biomarkers (crypt height, number, and relative position of Ki67+ cells in stained cells in colon mucosal crypts) compared with nonexercising control subjects.[132] In an analyses of 48 studies that included 40,674 colon cancer/CRC cases, a graded inverse dose-response association was observed between PA and colon cancer for both sexes. This dose-response effect of physical activity on colon cancer risk was especially strong when patients performed activities of >4.5 metabolic equivalents (MET) vs <4.5 MET (where 1 MET is the resting metabolic rate equivalent to 3.5 mL O_2/kg/min).[135] Of note, adjusting for potential cofounding factors including age, diet, and obesity does not diminish the observed associations between levels of PA and colon cancer occurrence.[132] Exercise training has also been shown to reduce the risk of gastric cancer with individuals who are more physically active having a 19% lower incidence.[137] A similar prognostic effect was seen for esophageal cancer.[138,139] Given the range of similar risk reduction it appears likely that there is at least a degree of mechanistic crossover in the benefits in PA across GI cancers, with the mechanisms underpinning such effects being multifactorial. Here we focus on those mechanisms potentially related to muscle-microbiome cross-talk.

Over recent years, the use of immunotherapy in cancer treatment has highlighted the critical role of the immune system in cancer pathogenesis. The microbiome is intimately involved in the development of the immune system, especially in the GI tract.[140,141] Exercise induces a biphasic response in lymphocytes and mobilizes vascular, pulmonary, hepatic, and splenic white blood cells into the peripheral circulation. This initial lymphocytosis affects mainly natural killer (NK) cells, which increase several-fold above resting levels, with their mobilization proportional to the relative intensity of exercise. This response underpins adrenaline-stimulation of β2-adrenergic receptors on the surface of lymphocytes leading to endothelial detachment and the subsequent recirculation of lymphocytes into the bloodstream. Blood lymphocyte count decrease 1–2 hours after exercise cessation with transient lymphopenia not

uncommon, although NK and T-cell counts return to baseline within 24 hours.[142] The precise mechanisms by which exercise-stimulated catecholamine signalling drive immune cell mobilization, redistribution, and function are not known, nor is the relationship by which this could be modified by changes in the microbiome.[143]

The immune-stimulating effects resulting from an acute bout of exercise persist for several hours and the use of exercise-stimulated T cells to augment the volume of cells that could be used for adoptive transfer into lymphopenic patients has been discussed elsewhere.[15] However, it is the chronic effects of the progressive accumulation of frequent acute challenges that are likely to play regulatory roles in tumor growth kinetics and tumor metabolism, through their effects of immune function in general, and on antitumor immune function specifically.[15] In rodents, a program of voluntary wheel running for 2 months was linked to improved antitumorigenic function through an increase in splenic NK cell cytoxic function, an effect that persisted 3 weeks after the training intervention ceased.[144] A similar immune response has been reported in humans with Lynch syndrome (a hereditary condition with a high lifetime risk of CRCs and endometrial cancers), where chronic (12 months) exercise training decreased inflammatory markers (prostaglandin E) in colon and blood and increased the colonic mucosa levels of NK and CD8+ T cells in the exercise-trained patients.[145] These findings have important implications for cancer interventions in patients with Lynch syndrome because they demonstrate the beneficial biological effects of exercise in the immune system of a target organ in patients at risk for cancer. Given the relationship between mucosal immunity and the microbiome,[146] it is conceivable that such an effect may be mediated through intestinal microbiota.

While PA modulates pathways regulating local and systemic inflammation and oxidative stress,[126] exercise-induced activation/suppression of pathways that sense and regulate energy availability, cellular metabolism, tumor development, proliferation, metastasis, and cytoskeleton organization are also important in conferring the protective effect of PA. These pathways include the AMP-activated protein kinase (AMPK) and the Akt/mammalian target of rapamycin (mTOR) pathways. The targets of these signalling nodes include many transcription factors, coactivators, and repressors[13] with all of these pathways potentially modified by alternations in the gut microbiome. Indeed, a growing body of evidence supports the beneficial effects of AMPK on gut health, such as enhancing intestinal absorption, improving barrier function, suppressing colorectal carcinogenesis, and reducing intestinal inflammation and metabolic-related disease states. Conversely, AMPK is inhibited under conditions of obesity and diabetes, both of which are correlated with impaired intestinal barrier function.[147]

The AMPK pathway is activated in tumors in response to an acute bout of PA, although exercise training may inhibit carcinogenesis by suppressing the activation of the mTOR signaling network in carcinomas, an effect mediated through effects of PA on circulating growth factors and hormones that regulate the mTOR network that are distinct from those affecting mTOR activity in contracting skeletal muscle.[148] Although this premise has some mechanistic basis, no studies have fully elucidated the direct effects of mTOR signalling on tumor growth in humans.[149] Tumors have altered cellular metabolism that favors aerobic glycolysis to support the high energy turnover and rapid cell proliferation. Accordingly, intratumoral metabolism will be impacted by whole-body PA, with results from preclinical studies suggesting that tumors with intrinsically high metabolism are susceptible to exercise-induced energy depletion. Such shifts in metabolism induced by exercise modulate the metabolic reprogramming that occurs during carcinogenesis to support cell growth and proliferation, and suggest that carcinogenesis can be inhibited or enhanced by effects on intermediary metabolism linked to PA and dependent on exercise intensity and duration. A recent example in CRC patients provided mechanistic insights into PA impact on tumor growth. In large CRC datasets, RPS4X expression (related to "stemness"), which is associated with metastases and poor outcomes, is down-regulated with exercise.[150] Given the relationship between the microbiome and stem cell regulation in the intestine, it is feasible that exercise may influence CRC risk via this pathway. This makes CRC a potential early candidate for combining microbiome modulation with PA in improving clinical outcomes.

Another potential mechanism for the beneficial effects of regular exercise on CRC risk and tumor growth is the training-induced increase in SCFA production. CRC patients typically present with a compromised gut microbiota characterized by a reduced abundance of butyrate-producing taxa, including *Roseburia* and *Lachnospiraceae. Results from in vitro* studies demonstrate that butyrate differentially regulates gene expression in healthy vs cancerous cells.[151] In healthy epithelial cells, butyrate is rapidly metabolized via the mitochondrial TCA cycle, causing in the accumulation of cytosolic citrate and acetyl CoA, thus increasing the acetylation of histones by histone acetyltransferases. This epigenetic modification increases expression of genes involved in cell proliferation and cell turnover, strengthening the intestinal barrier. However, in CRC cells, mitochondrial dysfunction results in the accumulation of butyrate in the cytosol. This free butyrate inhibits histone deacetylases, resulting in the epigenetic suppression of proliferation and promotion of cell death pathways that may lead to a reduction in tumor size and reduces the chance of metastasis.[151]

Human Microbiome Research: Current Perspectives and Directions for Future Research

The benefits of regular PA in preventing and/or treating numerous NCDs have been known for centuries. However, the precise mechanisms by which exercise training defends and protects the body against a range of lifestyle-induced diseases have not been elucidated. The discovery that contracting skeletal muscle is an endocrine organ acting as the primary metabolic communicator for interorgan

communication provides a plausible mechanism by which exercise training boosts immunity at both the whole-body and local (tissue) level. Although regular PA facilitates a more diverse gut microbiome and functional metabolome with direct and variable effects on GI disease outcomes, the precise dose of exercise necessary to induce favorable changes in the gut microbiome and enhance host immunity is unknown. Although "excessive" PA can have detrimental effects on intestinal barrier integrity, these are transient and benign. The gut microbiome, therefore, is an attractive target for modulating many of the positive effects of exercise on GI health and disease with the links between certain GI microbiota and the disease states of peripheral tissues/organs making microbial modulation a potentially potent immunotherapeutic therapy.

Current evidence indicates that a certain level of hormesis is necessary to perturb the human gut microbiota, with exercise interventions lasting a minimum of 2–3 months needed to produce consistent changes across alpha and beta diversity and most genera,[34] although some of the observable modifications in gut microbiota occur 2–4 weeks after the onset of an appropriate exercise stimulus.[34] As noted previously,[61] the beneficial effects of exercise training on the gut microbiota are rapidly reversed after several weeks of inactivity in both lean and obese individuals, a similar time-course of loss of adaptation observed in patients with celiac disease.[152] In athletes with a prolonged history of exercise training, the alpha-diversity and global composition of the gut microbiome remain unaffected by 3 weeks of reduced exercise,[153] suggesting that changes in exercise volume have less of an impact on individuals with a background of regular PA. However, the duration (months or years) of regular PA required to establish "steady-state" homeostasis in the gut microbiome that persists in the face of the removal of an exercise stimulus is unknown.

There remain many challenges facing microbiome science with several fundamental questions still remaining. For example, much of the observed interindividual differences in the gut microbiome can be attributed to the fact that some parts of the total microbiome remain poorly characterized, with their biological significance largely unknown. Nevertheless, an emerging area with potential clinical significance to improve host health are a number of microbial interventions, including fecal microbiota transfer (FMT). A recent study examined the effects of FMT from exercised-trained mice to germ-free animals.[154] Fecal samples from sedentary and trained animals were gavaged into germ-free mice. After receiving fecal samples from trained donor mice, recipient mice had elevated levels of AMPK and insulin-like growth factor-1 in skeletal muscle along with improved whole-body glycemia and insulin sensitivity, effects that were mediated, in part, by the anti-inflammatory properties of bile acid deconjugation. This study concluded that FMT mimics the health-promoting effects of exercise by inducing critical exercise-inducible signal transduction pathways in skeletal muscle, thereby improving metabolic health through the "muscle and gut axis."[154] Other studies in murine models of obesity also demonstrate that the beneficial effects of both exercise and diet are transmissible via FMT.[155] In humans, FMT involves the infusion of feces from a healthy donor to the GI tract of a recipient patient with the aim of treating diseases associated with alteration of gut microbiota. Although the results from several rodent studies reveal positive outcomes of FMT from both exercise- or diet-manipulated donor animals to germ-free mice on several health markers,[154,155] data from FMT in humans is lacking for the majority of GI-related disease states. Indeed, consistent with a European consensus conference on FMT in clinical practice,[156] *Clostridium difficile* infection is the only indication where market authorization for FMT has been achieved.

There are several exciting clinical opportunities in microbiome science with the recent application of a host of molecular techniques offering the potential for a greater understanding of the multiplicity and complexity of networks involved in exercise responses and on the mechanisms by which muscle "communicates" with the GI tract to mediate many of the beneficial effects of PA. While the structural characteristics of the gut microbiota have been described through the application of 16S rRNA amplicon sequencing,[157] next-generation sequencing techniques and the creation and integration of functional 'omics readouts (ie, metatranscriptomics, metaproteomics, and metabolomics) will provide more accurate assessment of health and disease states and provide a basis for functional and experimental validation. This is essential as up to 85% of the variance within the human microbiome from population-based studies is still unaccounted.[57] For example, in a longitudinal study of Q18 patients with Crohn's disease (n = 303) and ulcerative colitis (n = 228), most of the compositional variance of the gut microbiota remained unexplained.[158]

Resetting gut microbiome-derived signals of "unhealthy" ageing through personalized or subpopulation-level microbiome-associated interventions is a promising area of research that will be informed by large shotgun metagenomics-based studies and data analytics coupled with preclinical experimental models. Resulting microbiome-based therapeutics for the elderly will need a combination of therapies, including dietary intervention with microbial restoration of lost strains.[159] The identification of microbial profiles in middle-age that confer increased disease risk later in life (eg, biomarkers for colon cancer) present a formidable clinical challenge that will be confounded by the loss of dietary diversity with age, along with the associated decrease of microbiota diversity accompanied by increased risk of inflammation.[160] Levels of habitual PA also decrease with age[161] and are associated with sarcopenia and loss of function.[160] The influence of these lifestyle factors on modifying microbiome composition and controlling for them in large-scale human studies presents a huge challenge when trying to unravel the mechanisms underpinning the therapeutic effects of PA and diet interventions on the gut microbiota, and will require integration of large multicenter cohorts, advanced 'omics technologies and sophisticated experimental validations of the mechanistic associations identified.

Increasing evidence demonstrates the association of specific taxa in the development of certain GI diseases

including many cancers; altering the composition of the gut microbiota to improve the efficacy of anticancer drugs may be a feasible intervention in the future. Interindividual differences in patients' treatment-naïve gut microbiome may play a role in the efficacy of the hosts response to certain therapies, analogous to "low vs high responders" to exercise training interventions. Another exciting area for future research is gaining a better understanding of the relationship between gut microbiota, skeletal muscle mass, and physical function[162] particularly during ageing, which is associated with reduced microbiota biodiversity, increased interindividual variability, lower representation of butyrate-producing bacteria, and over-representation of pathobionts.[163] Reduced muscle mass has been associated with distinct microbiota composition and reduced fermentive capacity in mice, with the administration of probiotics and butyrate to mouse models of muscle wasting, associated with improved muscle mass.[162] Especially promising are the results from preclinical data showing that colonization of mice with gut microbiota from exercise-trained mice attenuated the response to chemically induced colitis, reduced colon shortening, attenuated mucus depletion, and augmented expression of cytokines involved in tissue regeneration.[164] As such, future efforts should concentrate on gaining a deeper understanding of the factors involved in exercise-gut interactions through the application of advanced techniques to measure both the microbiome and the systemic effects of exercise in a variety of diseased populations. It is hoped that future therapies to treat a range of GI-related disorders, including cancers, will be based on a growing recognition that regular PA can positively modify the human gut microbiome, boost immunity, and decrease the incidence, progression, and personal burden of these NCDs. As such, it is recommended that regular PA be incorporated into standard clinical treatment protocols for individuals with several GI-related diseases.

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Conflicts of interest
The authors disclose the following: Samuel C. Forster is a consultant to BiomeBank Australia and has acted as an advisor to Microbiotica. Edward M. Giles is an advisor to AbbVie and Janssen; and has received speaker fees from Takeda, Janssen, Nutricia, Aspen Nutritionals, AbbVie, Evolution Health, and H&H Group. The remaining author discloses no conflicts

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