A Review of the Role of the Gut Microbiome in Personalized Sports Nutrition

Riley L. Hughes*

Department of Nutrition, University of California, Davis, Davis, CA, United States

The gut microbiome is a key factor in determining inter-individual variability in response to diet. Thus, far, research in this area has focused on metabolic health outcomes such as obesity and type 2 diabetes. However, understanding the role of the gut microbiome in determining response to diet may also lead to improved personalization of sports nutrition for athletic performance. The gut microbiome has been shown to modify the effect of both diet and exercise, making it relevant to the athlete’s pursuit of optimal performance. This area of research can benefit from recent developments in the general field of personalized nutrition and has the potential to expand our knowledge of the nexus between the gut microbiome, lifestyle, and individual physiology.

Keywords: gut microbiome, exercise, personalized nutrition, sports nutrition, performance, metabolism, athletes, optimization

INTRODUCTION

The gut microbiome has been implicated in the modulation of human health and metabolism (1, 2). This microbial “organ” has been linked to nutrition-related chronic diseases such as obesity and diabetes (3–6) and has also been shown to influence systemic functions including immunity (7, 8) and brain function (9, 10). The gut microbiome may influence health via mechanisms such as the production of metabolites (2, 11) [e.g., short-chain fatty acids (SCFAs)] that can influence a wide array of host systems and metabolic pathways (12, 13).

However, the gut microbiome is not a fixed trait, but instead responds to environmental stimuli and is a malleable part of the human supraorganism (14) (Figure 1). Much of microbiome research has focused on the effect of lifestyle factors, such as diet (15–17) and exercise (18, 19), on the gut microbiota. Variability in the composition and function of the gut microbiome (20, 21) has also fueled research on the relationship between features of the gut microbiota, such as diversity or the presence, absence, or amount of certain taxa, and host health. Precision nutrition studies are now investigating how to predict individual differences in glycemic response, triglycerides, cholesterol levels, and other indicators of health as a way to personalize nutrition recommendations and prevent diet-related chronic diseases such as obesity and type 2 diabetes. Our previous two-part review (22, 23) explored the effect of the gut microbiome on inter-individual variability in response to diet and how this may contribute to metabolic health.

Alternatively, we may consider the potential effect of the gut microbiome on measures of athletic performance. Successful performance in training, such as a time trial or rep max load, and general metabolic health are two distinct aspects of metabolic response that are not necessarily directly coupled (24). While nutrition is an important part of general health and well-being, it is also an important tool in an athlete’s arsenal to optimize performance (25).

Variability in the physiological response to training and nutrition has been attributed to factors such as age, sex, training history, initial training status, psychological factors, and the mode,
duration, intensity, and frequency of training (26). Genetics has also become a large topic of research in the area of variability in response to exercise training and potentially ergogenic dietary components (27–38). It is possible that variability in the gut microbiome may also influence gains in performance in response to training and nutrition. Despite the growing interest in the gut microbiome and personalized nutrition, very few studies have combined these fields with that of athletic performance. This is surprising as athletes are extremely motivated to capitalize on any advantage, however small, that could increase their performance. This review focuses on several topics related to the question of whether the gut microbiome may be used to predict performance response to dietary and/or training interventions. This includes topics such as (1) the effect of exercise on the gut microbiome, (2) the effect of dietary components or patterns relevant to athletic nutrition on the gut microbiome, and (3) the effect of the gut microbiome on performance response to diet and exercise. Each of these related topics will be discussed, as will gaps in the research and future directions.

METHODS
Numerous reviews have been published highlighting the effect of exercise on the gut microbiota (39–56). However, the primary focus of these reviews has been the implications for aspects of host health, such as the immune system and risk of chronic diseases. Only a few have discussed the implications for athletic performance (41, 48, 52). This review aims to provide a more in-depth discussion of the interactive effect between the gut microbiota and diet on athletic performance and highlight the need for further research in this area. A literature search in PubMed and Google Scholar, including combinations of key words “gut microbiota”, “exercise”, “performance”, “variability,” and “effect,” was used to identify relevant studies. References were also obtained from the above review articles.

The earliest study found was published in 2008 by Matsumoto et al. (57) but was followed by a host of studies aiming to identify the effects of exercise on the gut microbiota (19, 58–83). The majority of these studies have investigated the effect of exercise on the gut microbiota in rodents (57–75), though some have studied humans in intervention trials (18, 76–78, 84) and in cross-sectional or observational comparisons of athletes or active individuals and sedentary individuals (19, 79–83, 85, 86).

RESULTS
The Effect of Exercise on the Gut Microbiome
Microbiota Features Affected by Exercise
Table 1 summarizes the studies listed above and their findings of the effect of exercise on the gut microbiota.

Although there are similarities in microbial factors shown to be affected by exercise within the literature, directions of the effects are inconsistent, and some studies show contradictory results. For example, while some studies show a reduction in Firmicutes and/or an increase in Bacteroidetes as a result of exercise (58, 64, 66, 70, 73, 74, 81, 84), others show the opposite effect (19, 60–62, 68, 71, 81, 86), and others show no effect (69, 76, 82).

Findings on the effect of exercise on measures of diversity are also highly variable, some showing increases in α-diversity (19, 60, 64, 68, 70, 71, 75, 79, 86), some showing decreases (58, 59, 66), and others reporting no difference (18, 59, 63, 65, 69, 76–78, 82, 83). Brandt et al. (73) also found that exercise attenuated the decrease in α-diversity that occurred when mice were fed a high-fat diet.

Bacterial taxa commonly shown to respond to exercise training include Lactobacillus (typically increased) (58, 60, 62, 68), Bifidobacterium (typically increased) (58, 62, 76, 82), Proteobacteria (typically decreased) (58, 65, 66, 68, 76), Akkermansia (typically increased) (19, 75, 76, 79, 82), Streptococcus (variable effects) (61, 68, 69), Clostridium (variable effects) (58, 62, 63, 67, 77), Turicibacter (typically decreased) (59, 64), and Rikenellaceae (typically decreased) (63, 66, 69) as well as measures of α- and β-diversity (variable effects) (19, 58, 60, 64, 66, 68, 70, 76, 80).

However, in some studies, changes in taxa are dependent on other factors such as changes in weight, body fat, and blood glucose (64, 76). This suggests that the associated metabolic effects of the exercise regime may be the proximal cause, while exercise is the ultimate cause. Related variables, SCFA production and butyrate-producing taxa, have been consistently shown to increase in response to exercise (18, 57, 79) and have also been positively correlated to changes in lean muscle mass, also suggesting that SCFAs may play an important role
### TABLE 1 | Summary of effect of exercise on the gut microbiome.

| References | Subjects | Type of exercise | Diet | Microbiota method | Microbial diversity | Firmicutes (phylum) | Bacteroidetes (phylum) | Lactobacillaceae (family) | Bifidobacteriaceae (family) | Other microbiota factors |
|------------|----------|-----------------|------|-------------------|---------------------|---------------------|-----------------------|----------------------|------------------------|-------------------------|
| **Rodent studies** | | | | | | | | | | |
| Allen et al. (59) | Mice (C57BL/6J, 6 wk, male) | Voluntary wheel running (VWR) vs. forced treadmill running (FTR) for 6 wk | Commercial diet | Composition (16S) | ↓ in VWR (Chao1) \(\rightarrow\) (Shannon) | ↓ Turicibacter in VWR | | | | |
| Lambert et al. (62) | Mice (diabetic db/db C57BL/KsJ-leprdb/leprdb and normal db/+, 8 wk, male) | Treadmill vs. sedentary | Chow diet | Composition (qPCR) | ↑ Firmicutes, Clostridium | ↓ Bacteroides, Prevotella | ↑ Lactobacillus (not after adjustment for body weight and blood glucose) | ↑ Bifidobacterium in exercised normal vs. sedentary normal | ↓ Bifidobacterium in exercised diabetic |
| Lamoureux et al. (63) | Mice (C57BL/6, 6–10 wks, 11 male and 31 female) | Voluntary exercise (VE) vs. moderate forced exercise (treadmill) (FE) for 8 wk | Normal diet | Composition (16S) | ↔ α-diversity (species richness) or β-diversity (weighted and unweighted UniFrac, Bray-Curtis) | Random forest predicted voluntary exercise with 97% accuracy using Bacteroides, Lactobacillus, Akkermansia, Lachnospiraceae; predicted forced exercise with 86% accuracy using Bacteroides, Clostridiales, and Lactobacillales | ↑ Butyrivibrio, Prevotella, Akkermansia in exercise/non-surgery mice | ↑ Erysipelotrichaceae, Sphingobacteriales, Akkermansia in control/sham mice | ↑ Corynebacterium, Staphylococcus, Enterobacteriaceae in control/sham mice | ↑ Phenylobacterium and Roseateles in exercise/MI mice |
| Liu et al. (75) | Mice (C57BL/6J, 4 wk, male; myocardial infarction (MI), sham, or no-surgery) | Treadmill for 4 wk | None | Composition (16S) | ↑ α-diversity (Shannon, PD_whole_tree) | | | | ↑ Entrobacteriaceae in exercised diabetic vs. sedentary diabetic |
| Brandt et al. (73) | Mice (C57BL/6N, 8–10 wk, male, loxP insertions in Ppargc1a gene) | Voluntary wheel running (VWR) for 16 wk | Standard rodent chow (CCON) vs. High-fat diet (HFD) vs. HFD + resveratrol | Composition (16S) | ↓ α-diversity in HFD mice vs. CCON | ↑ β-diversity in HFD mice vs. HFD | ↓ Actinobacteria in HFD plus exercise vs. HFD | ↓ Erysipelotrichaceae, Veuminicobic in HFD plus exercise vs. HFD | ↑ Allotypes in HFD plus exercise vs. HFD |
| Campbell et al. (87) | Mice (C57BL/6NT, 8 wk, male) | Voluntary wheel running for 12 wk | Normal diet vs. High-fat diet (HFD) | Composition (TRFLP, 16S) | ↑ Allobaculum, Clostridiales, Faecalibacterium prausnitzii | | | | |

(Continued)
| References | Subjects | Type of exercise | Type of study | Diet | Microbiota method | Microbial diversity | Firmicutes (phylum) | Bacteroidetes (phylum) | Lactobacillaceae (family) | Bifidobacteriaceae (family) | Other microbiota factors |
|------------|----------|------------------|---------------|------|-------------------|---------------------|---------------------|-----------------------|--------------------------|--------------------------|--------------------------|
| Evans et al. (64) | Mice (C57BL/6J, 6 wk, male) | Voluntary wheel running for 12 wk | Intervention | Low-fat vs. High-fat diet | Composition (16S, qPCR, TRFLP) | † α-diversity (Shannon) with high-fat diet and exercise | ↓ Firmicutes (16S), Turicibacteriaceae, Erysipelotrichaceae (qPCR) | ↑ Bacteroidetes (16S), Bacteroides (qPCR) | ↓ Lactobacillaceae (qPCR) | † Actinobacteria (16S), Bifidobacteriaceae (qPCR) | † butyrate-producing taxa |
| McCabe et al. (74) | Mice (C57BL/6J, 6 wk, male) | Voluntary wheel running for 14 wk | Intervention | Low-fat vs. High-fat diet | Composition (16S) | ↓ Firmicutes/Bacteroides in HF-exercise | ↓ Firmicutes/Bacteroides in HF-exercise | ↓ Bacteroidetes | ↓ Bacteroidetes | ↓ Tenericutes |
| Kang et al. (61) | Mice (C57BL/6J, 8 wk, male) | Motorized wheel running for 16 wk | Intervention | Normal diet vs. High-fat diet | Composition (16S) | ↑ Firmicutes, Lachnospiraceae ↓ Streptococcaceae | ↑ Bacteroidetes/Bacteroides | ↓ Firmicutes/Bacteroides in HF-exercise | ↓ Firmicutes/Bacteroides in HF-exercise | ↑ KEGG-annotated metabolism genes |
| Denou et al. (73) | Mice (C57BL/6J, 8 wk, male) | High-intensity interval training (HIIT) on treadmill for 6 wk | Intervention | Chow diet vs. High-fat diet | Composition (16S) and function (PICRUSt) | † α-diversity (Shannon) | ↑ Bacteroidetes/Firmicutes | ↑ Bacteroidetes | ↑ Bacteroidetes/Firmicutes | ↓ Bacteroidetes |
| Choi et al. (60) | Mice (C56BL/6NT, 11–13 mo, male) | Voluntary wheel running for 5 wk | Intervention | Polychlorinated biphenyls (PCBs) | Composition (16S) | ↑ abundance | ↑ Firmicutes (mostly Lactobacillales) | ↑ Bacteroidetes | ↑ Lactobacillales | ↓ Tenericutes (Erysipelotrichaceae) | ↑ Proteobacteria (prevented PCB-induced decrease) |
| Liu et al. (65) | Rats (ovariectomized [OVX] high capacity [HCR] and low capacity [LCR] runners, 27 wk, females) | Voluntary wheel running for 11 wk | Intervention | Chow diet | Composition (16S) | † β-diversity (Chao1) | ↑ Firmicutes in HCR ↓ Firmicutes in LCR | ↓ Proteobacteria, Cyanobacteria in HCR | ↓ Proteobacteria, Cyanobacteria in LCR | ↓ Proteobacteria, Cyanobacteria in HCR |
| Mikaelsson et al. (50) | Rats (F344, day 24 vs. day 70, male) | Voluntary wheel running for 6 wk | Intervention | Standard diet | Composition (16S) | ↓ α-diversity (Shannon entropy, species richness) in young rats | ↑ Firmicutes in young rats Blautia, Anaerostipes in young rats ↑ Turicibacter in adult rats | ↑ Bacteroidetes in young rats | ↑ Euryarchaeota (Methanosphaera) in young rats | ↓ Proteobacteria (Desulfuviobrios) in young rats ↓ Rikenellaceae in young rats ↑ Rikenellaceae in adult rats Bacteroides, Bifidobacterium, Ruminococcus, Rikenellaceae, Parabacteroides, Christensenellaceae, Methanosaeta predict time point in young rats | (Continued)
TABLE 1  | Continued

| References | Subjects | Type of exercise | Type of study | Diet | Microbiota method | Microbial diversity | Firmicutes (phylum) | Bacteroidetes (phylum) | Lactobacillaceae (family) | Bifidobacteriaceae (family) | Other microbiota factors |
|------------|----------|-----------------|---------------|------|-------------------|-------------------|---------------------|----------------------|------------------------|--------------------------|-------------------------|
| Matsumoto et al. (57) | Rats (Wistar, 7 wk, male) | Voluntary wheel running for 5 wk | Intervention | Casein-sucrose diet | Composition (PCR-TGGE) | ↓ α-diversity (band richness) | ↓ Firmicutes in ABA vs. Exercise and Ad lib; in Exercise vs. Ad lib | ↑ Bacteroidetes in ABA vs. Exercise and Ad lib | ↑ Lactobacillus in Exercise vs. Ad lib | ↓ Actinobacteria in ABA; ↑ Proteobacteria in ABA vs. Exercise and Ad lib | Differential clustering between exercise and controls; ↑ butyrate-producing taxa |
| Queipo-Otun et al. (58) | Rats (Sprague Dawley, 5 wk, male) | Voluntary wheel running for 6 d | Intervention | Activity based anorexia (ABA, 1 h food intake w/ exercise), ABA control (sedentary), Exercise (ad lib w/ exercise), Ad lib (ad lib sedentary) | Composition (PCR-DGGE, qPCR) | ↓ α-diversity (band richness) | ↓ Firmicutes in ABA vs. Exercise and Ad lib; in ABA | ↑ B. Coccoides - E. rectale group in Exercise vs. Ad lib | ↓ Clostridium, Enterooccus in Exercise vs. Ad lib | ↓ Actinobacteria in ABA; ↑ Proteobacteria in ABA vs. Exercise and Ad lib | ↑ α-diversity (band richness) |
| Welly et al. (69) | Rats (obesity prone OP-CD, 4 wk, male) | Voluntary wheel running | Intervention | High-fat diet (HFD; groups: sedentary, w/ exercise, weight matched to exercise) | Composition (qPCR) | ↔ α-diversity (species richness) | ↑ Streptococcaceae in Exercise | ↔ Firmicutes/ Bacteroidetes ratio | ↓ S24–7 in Exercise | ↓ Actinobacteria in Exercise and Ad lib; ↑ Bifidobacterium in Exercise | ↓ Riikenellaceae in Exercise |
| Feng et al. (71) | Rats (high capacity HCR and low capacity LCR runniers, surgery or sham) | Treadmill for 6 wk | Intervention | None | Composition (16S) | ↑ α-diversity (Shannon) in LCR rats | ↑ Firmicutes in HCR rats | ↓ Bacteroidetes in HCR rats | | | |
| Petriz et al. (68) | Rats (Zucker obese, Zucker (spontaneously hypertensive), and Wistar (non-obese, control), 20 wk, male/female?) | Forced treadmill running for 4 wk | Intervention | Not reported | Composition (16S) | ↑ α-diversity (Shannon, rarefaction) | ↑ Firmicutes in non-obese Wistar | ↓ Bacteroidetes in non-obese Wistar; ↑ Allobaculum in hypertensive | | ↓ Proteobacteria; ↑ Proteobacteria in hypertensive |
| Batacan et al. (72) | Rats (Wistar, 12 wk, male) | Control (CTL), sedentary (SED), light-intensity trained (LIT), and high-intensity interval trained (HIIT) for 12 wk | Intervention | Standard chow (SC) versus high-fat high-fructose (HF) diet | Composition (16S) | ↔ α-diversity between activity groups regardless of diet (Chao1, observed species, Shannon, Simpson, | ↓ Firmicutes in LIT-SC | ↑ Clostridiaceae in LIT-SC | ↓ Lachnospiraceae in LIT-SC | ↑ Actinobacteria in LIT-SC | ↑ Tenericutes, Prevotella excrementihominis, Erysipelotrichaceae in LIT-SC (Erysipelotrichacea higher in HF-fed rats); ↑ Turicibacteraceae in SC; ↑ polysaccharide degraders and SCFA producers with exercise in both SC and HF (effects weaker in HF) |

(Continued)
| References       | Subjects                                                                 | Type of exercise                                                                 | Diet                          | Microbiota method                                      | Microbial diversity | Firmicutes (phylum) | Bacteroidetes (phylum) | Lactobacillaceae (family) | Bifidobacteriaceae (family) | Other microbiota factors |
|------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------|---------------------|---------------------|-----------------------|---------------------------|---------------------------|--------------------------|
| Human intervention studies                                                                 |
| Allen et al. (18) | Humans (32 previously sedentary subjects, 18 lean, 14 obese)             | Endurance exercise for 6 wk progressed from moderate to vigorous, followed by 6 wk sedentary | Intervention                     | Habitual diet                                          |                     |                     |                       |                           |                           |                          |
|                        |                                                                           |                                    |                                | Composition (16S) and function (qPCR of select functional genes) | ↔ α-diversity (Chao1) | ↔ β-diversity (after exercise/ washout (weighted and/ or unweighted UniFrac) |                       |                           |                           |                          |
| Munukka et al. (76) | Humans (19 overweight, sedentary women)                                  | Endurance exercise (bike erg) for 6 wk                                           | Intervention                   | None                                                   | ↔ α-diversity (not reported) | ↔ Firmicutes        | ↔ Bacteroidetes                                    |                           |                          |
|                        |                                                                           |                                    |                                | Composition and function (16S, metagenomics)            |                     |                     |                       |                           |                           |                          |
| Morita et al. (84)  | Humans (32 Japanese sedentary adult women, >65 years old)                 | Aerobic exercise (AE) or trunk muscle training (TM) for 12 wk                      | Intervention                   | Habitual diet                                          | ↔ α-diversity (Shannon, observed OTUs) | ↓ Clostridium difficile during exercise |                       |                           |                           |                          |
|                        |                                                                           |                                    |                                | Composition (TRFLP)                                    |                     |                     |                       |                           |                           |                          |
| Cronin et al. (78)  | Humans (74 healthy Irish adults)                                          | Mixed aerobic exercise and resistance exercise training program for 8 wk           | Intervention                   | Whey Protein + Exercise (EP) vs. Exercise (E) (metagenomics) vs. Whey Protein (P) | ↔ α-diversity from baseline but higher in EP vs. P group |                       |                       |                       |                           |                          |

(Continued)
| References | Subjects | Type of exercise | Type of study | Diet | Microbiota method | Microbial diversity | Firmicutes (phylum) | Bacteroidetes (phylum) | Lactobacillaceae (family) | Bifidobacteriaceae (family) | Other microbiota factors |
|------------|----------|------------------|---------------|------|-------------------|---------------------|---------------------|---------------------|------------------------|------------------------|-------------------------|
| Bressa et al. (82) | Humans [40 premenopausal Caucasian women; 19 active (ACT), 21 sedentary (SED)] | General physical activity (measured for 1 wk) | Cross-sectional | Habitual diet | Composition (16S, qPCR) | ↔ α-diversity (Chao1, Observed, Shannon) ↔ β-diversity (unweighted or weighted UniFrac) Observed # species, Shannon, Simpson indices (+) ∼ minimum time per sedentary bout (work days) | ↑ Firmicutes (trending) ↔ F/B ratio | ↓ Bacteroidetes (trending) ↔ F/B ratio | † Bildobacterium in ACT women | † Haemophilus, Paraprevotella, Coprococcus, Ruminococcaceae unclassified ↑ in ACT women (16S) ↓ Desulfod vibriionaceae unclassified, Turicibacter, Bacteroidiaceae, Odoribacteriaceae, Ruminococcaceae unclassified ↓ Ruminococcus in ACT women (16S) ↑ Faecalibacterium prausnitzii, Roseburia hominis, Akkermansia muciniphila in ACT women (qPCR) Random forest using microbiota predicted pre- and post-STRESS samples with 100% accuracy |
| Karl et al. (86) | Humans (73 Norwegian soldiers, 26 provided pre- and post-stool samples) | 4-day cross-country ski-march (STRESS) | Cross-sectional | Rations with or without protein- or carbohydrate-based supplements | Composition (16S) | ↑ α-diversity post-STRESS (Shannon) | ↑ Firmicutes | ↓ Bacteroidetes |
| Shukla et al. (81) | Humans (10 myalgic Cycling (max test) Chronic fatigue syndrome (ME/CFS) patients, 10 healthy controls) | Cross-sectional | Habitual diet | Composition (16S) in blood and stool | ↑ Firmicutes in ME/CFS patients after exercise ↓ Firmicutes in healthy controls after exercise ↑ Firmicutes in ME/CFS patients after exercise ↓ Bacteroidetes in healthy controls after exercise |

(Continued)
| References | Subjects | Type of exercise | Type of study | Diet | Microbiota method | Microbial diversity | Firmicutes (phylum) | Bacteroidetes (phylum) | Lactobacillaceae (family) | Bilobobacteriaceae (family) | Other microbiota factors |
|------------|----------|-----------------|--------------|------|-------------------|---------------------|---------------------|----------------------|------------------------|------------------------|------------------------|
| Barton et al. (79) | Humans (40 professional rugby players, 46 controls) | Rugby | Cross-sectional | None | Function (metagenomics) | ↑ α-diversity in athletes vs. high-BMI controls (Shannon, Simpson) or all controls (Phylogenetic diversity, Chao1, Observed species) | ↑ Akkermansia pathways in athletes vs. high-BMI controls | ↑ pathways (amino acid and antibiotic biosynthesis, carbohydrate metabolism) in athletes |
| Clarke et al. (19) | Humans (40 professional rugby players, 46 controls) | Rugby | Cross-sectional | Habitual diet | Composition (16S) | ↑ α-diversity in athletes vs. high-BMI controls (Shannon, Simpson) or all controls (Phylogenetic diversity, Chao1, Observed species) | ↑ Akkermansia in low-BMI athletes vs. high-BMI controls |
| O’Donovan et al. (83) | Humans (37 professional Irish athletes) | 16 different sports across varying sports classification groups (SCGs) | Cross-sectional | Habitual diet | Composition and function (metagenomics) ↔ α-diversity (Shannon and Simpson) between SCGs | ↑ Bacteroides caccae ~ SCGs with high static/high dynamic components | ↑ Bilobobacterium animalis ~ SCGs with low static/high dynamic components | ↑ Streptococcus suis, Clostrium botale, Lactobacillus phage Lf66, Anaerostipes hadrus, flavin biosynthesis and fermentation pathways ~ SCGs with moderate dynamic component | ↑ Lactobacillus acidophilus, Prevotella intermedia, Faecalibacterium prausnitzii ~ SCGs with low static/high dynamic components | ↑ folate and amino acid biosynthesis pathways ~ SCGs with high static/high dynamic components | ↑ Nucleotide biosynthesis ~ SCGs with high static/low dynamic components | No species associated with SCGs with high static/low dynamic components or high dynamic/moderate static components |

(Continued)
in mediating the effects of exercise and the gut microbiome on host response (18). Table 2 summarizes additional effects of exercise on microbial metabolites, host health, and dietary interactions.

**Potential Causes of Discrepancies Between Studies**

Potential reasons for the disparate results of these studies include study design factors as well as analytic methods (Figure 2). Study design factors include the choice of model (e.g., humans, mice, rats), the strain of mouse/rat (e.g., C57BL/6J, Zucker, Wistar, Sprague Dawley, etc.) (87), choice of diet (72), health or disease status (75, 81), age (66), gender, and the mode, duration, and intensity of training (59, 63, 72, 83, 84) as well as analytic methods such as DNA extraction and PCR primer biases (88–90), choice of microbiome sequencing methods (e.g., 16S rRNA gene sequencing, qPCR, metagenomics, etc.) (64), bioinformatic pipelines (90), and choice of diversity metrics (e.g., Shannon, Chao1, Simpson, etc.). For example, mouse models often use forced treadmill running or voluntary wheel running as modes of training. However, forced treadmill exercise often uses aversive motivation, such as shocks, which could induce negative stress responses (91–93) that may also affect intestinal permeability and the gut microbiome (59, 94, 95). In humans, exercise or sport is a broad term that can apply to a wide range of modes, durations, and intensities of activity. O'Donovan et al. (83) attempted to determine differential effects of different modes of exercise on the gut metagenome by doing a cross-sectional analysis of professional athletes from different sports with varying degrees of static and dynamic components. In this analysis, O'Donovan et al. found some differences in bacterial taxa and metabolites between sports classification groups (SCGs) that did not correlate with any other metadata (e.g., diet, sex, etc.) (83).

In addition to differences in how results are obtained or measured, there is also a great deal of heterogeneity in what results are measured, or reported, that make it difficult to determine the full extent of variability in response between studies. In order to gain better insight into the potential effects and pathways by which exercise exerts its effect on the gut microbiome, it would be beneficial for studies to report effects on at least a certain standard set of microbiota variables that have already been shown to be relevant by multiple studies such as *Firmicutes, Bacteroidetes, Lactobacillus, Bifidobacterium, Akkermansia, Clostridium*, and *Proteobacteria* as well as diversity (though a standard metric has yet to be determined), butyrate-producing taxa (96), and SCFA production, even if the result is no change/difference. Munukka et al. (76) reported a lack of consistent effects due to inter-individual variability in response of the gut microbiota to exercise. This too is an important finding that should be reported and explored to determine factors that contribute to this variability in response and whether these differences in microbial response translate to differences in physiological response. These reporting standards would allow for better comparison between studies and potentially enable researchers to determine how different methods impact the results and elucidate factors that may contribute to variability in response.
| References          | SCFAs                                                                 | Other metabolites                                                                 | Host health                                                                 | GI tract physiology                                                                 | Diet interactions                                      |
|---------------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------|
| **Rodent studies**  |                                                                       |                                                                                   |                                                                              |                                                                                 |                                                        |
| Allen et al. (59)   |                                                                       |                                                                                   | ↑ glucose in exercised normal vs. sedentary normal                             | ↓ gastrointestinal inflammation in VWR, ↑ in FTR                                  |                                                        |
| Lambert et al. (62) |                                                                       |                                                                                   | ↔ glucose in exercised diabetic vs. sedentary diabetic                         |                                                                                  |                                                        |
| Liu et al. (75)     |                                                                       | ↑ Left ventricular ejection fraction (EF), fractional shortening (FS), cardiac output (CO), and stroke volume (SV) FS, EF, CO, SV, and left ventricular end systolic diameter (LVESD) correlated with gut microbiota taxa | ↑ Left ventricular ejection fraction (EF), fractional shortening (FS), cardiac output (CO), and stroke volume (SV) FS, EF, CO, SV, and left ventricular end systolic diameter (LVESD) correlated with gut microbiota taxa | ↑ Left ventricular ejection fraction (EF), fractional shortening (FS), cardiac output (CO), and stroke volume (SV) FS, EF, CO, SV, and left ventricular end systolic diameter (LVESD) correlated with gut microbiota taxa |                                                        |
| Brandt et al. (73)  |                                                                       |                                                                                   | ↑ body weight in HFD vs. CON, HFD plus resveratrol                            | ↓ body weight in HFD vs. HFD plus exercise                                       |                                                        |
|                     |                                                                       |                                                                                   | ↔ body weight in HFD vs. HFD plus exercise                                       | ↓ body weight in HFD vs. HFD plus exercise                                       |                                                        |
|                     |                                                                       |                                                                                   | ↓ body fat %, subcutaneous, and visceral adipose tissue in HFD and HFD plus exercise vs. CON | ↑ serum amyloid A (SAA) in all HFD groups vs. CON                                  |                                                        |
|                     |                                                                       |                                                                                   | ↑ body fat %, subcutaneous, and visceral adipose tissue in HFD and HFD plus exercise vs. CON | ↑ serum amyloid A (SAA) in all HFD groups vs. CON                                  |                                                        |
| Campbell et al. (67)|                                                                       | Body fat %: High-fat sedentary > High-fat exercise > low-fat sedentary > low-fat exercise | Body fat %: High-fat sedentary > High-fat exercise > low-fat sedentary > low-fat exercise | ↓ inflammatory infiltrate, COX-2, and high-fat diet-induced morphological changes in exercise |                                                        |
| McCabe et al. (74) |                                                                       | ↑ Bone volume fraction with exercise (~Firmicutes/Bacteroides (−), Clostridia (−), Lachnospiraceae (−), Actinobacteria (+)) | ↑ Bone volume fraction with exercise (~Firmicutes/Bacteroides (−), Clostridia (−), Lachnospiraceae (−), Actinobacteria (+)) | ↓ Trabecular bond volume with high-fat diet                                         |                                                        |
|                     |                                                                       |                                                                                   | ↑ Trabecular bond volume with high-fat diet                                         | ↓ Trabecular bond volume with high-fat diet                                         |                                                        |
| Kang et al. (61)    |                                                                       |                                                                                   | ↑ Marrow adiposity with high-fat diet                                             | Body weight, fat pad mass, fasting glucose with exercise and low-fat diet           |                                                        |
|                     |                                                                       |                                                                                   | ↑ Marrow adiposity with high-fat diet                                             | Body weight, fat pad mass, fasting glucose with exercise and low-fat diet           |                                                        |
| Denou et al. (70)   |                                                                       | High-fat diet with exercise vs. high-fat diet:                                    | High-fat diet with exercise vs. high-fat diet:                                    | ↑ cognitive abilities                                                               |                                                        |
|                     |                                                                       |                                                                                   | ↔ high-fat diet-induced anxiety                                                  | ↑ cognitive abilities                                                               |                                                        |
| Liu et al. (65)     | ↓ non-esterified fatty acids (NEFAs) and triglycerides in LOR rats    | ↑ non-esterified fatty acids (NEFAs) and triglycerides in HCR rats                 | ↑ non-esterified fatty acids (NEFAs) and triglycerides in HCR rats                 |                                                                                   |                                                        |
|                     | and triglycerides in LOR rats                                        |                                                                                   |                                                                                   |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↓ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ body weight, fat mass, feed efficiency in LCR rats                              |                                                                                   |                                                        |
| Mika et al. (60)    |                                                                       |                                                                                   | ↓ weight in adult rats                                                             |                                                                                   |                                                        |
|                     |                                                                       |                                                                                   | ↑ weight, lean mass in young rats                                                 |                                                                                   |                                                        |
| Matsumoto et al. (57)| ↑ cecal n-butyrate                                                      |                                                                                   |                                                                                   |                                                                                   | ↑ cecum size/weight                                      |
| Queipo-Ortuno et al.|                                                                       |                                                                                   |                                                                                   |                                                                                   |                                                        |
| (58)                |                                                                       |                                                                                   |                                                                                   |                                                                                   |                                                        |

(Continued)
TABLE 2  |  Continued

| References | SCFAs | Other metabolites | Host health | GI tract physiology | Diet interactions |
|------------|-------|-------------------|-------------|---------------------|------------------|
| Welly et al. (69) | ↓ leptin [~Lactobacillus (+), Bifidobacterium (+)] | ↓ total cholesterol, adiposity, inflammation in Exercise and weight-matched sedentary | ↑ total energy expenditure in Exercise and weight-matched sedentary | ↓ RQ, insulin resistance, LDL, liver mass in Exercise | ↑ mitochondrial function in brown adipose in Exercise |
| Feng et al. (71) | Exercise improved preoperative cognitive impairment in LCR rats | | |
| Petriz et al. (68) | ↑ velocity | ↓ lactate [~Clostridiaceae (–), Bacteroidiaceae (–), Oscillospira (+), Ruminococcus (–)] | |
| Batacan et al. (72) | Samples grouped by diet (not activity group) | |

**Human intervention studies**

| Allen et al. (18) | ↑ SCFAs in lean | ↓ body fat % | ∆Butyrate and butyrate-producers ~ ∆lean mass | |
| Munukka et al. (76) | ↑ max power, VO_{2\text{max}}, glucose | ↓ lactate, HDL, LDL, large VLDL | ↔ weight, blood pressure, weight circumference, BMI, fat mass/% | |
| Taniguchi et al. (77) | ↑ VO_{2\text{peak}}, [~C. difficile (–)], HDL [~Oscillospira (+)], total cholesterol [~C. difficile (–)] during exercise | ↓ CAVI [~C. difficile (–)], intrahepatic fat %, HbA1c [~Oscillospira (+)], ~C. difficile (–)] during exercise | ↔ body fat % [~Oscillospira (–), visceral fat area, SBP, AST, ALT [~C. difficile (–)], LDL [~C. difficile (–)] | Oscillospira ~ changes in light-colored vegetable, seaweed, and rice consumption |
| Cronin et al. (78) | ↑ VO_{2\text{max}}, lean mass in E and EP groups | ↓ resting heart rate, % body fat, total fat mass, truck fat mass in E and EP groups | ↔ pro-inflammatory markers | |

**Human cross-sectional studies**

| Bressa et al. (82) | ↑ cysteine aminopeptidase in ACT women [~Bacteroides (–)] | ↔ BMI, weight, adiposity and muscle parameters Turicibacter (~) ~ BMI Bacteriaceae (–) ~ % body fat Odoribacter (–), Haemophilus (–) ~ adiposity index, estimated visceral fat, % body fat Faecalibacterium (–) ~ muscle mass index, appendicular muscle mass index Coprococcus (+), Lachnospiraceae unclassified (~) ~ appendicular muscle mass index | Turicibacter ~ dairy products, cereals Bifidobacterium ~ protein intake % Odoribacter ~ fiber, fat intake % Lachnospiraceae unclassified 1 & 2 ~ fat intake % |
| Karl et al. (86) | Random forest using stool metabolites predicted pre- and post-STRESS samples with 84% accuracy | ↑ intestinal permeability (IP) Pre-STRESS Actinobacteria | |

(Continued)
TABLE 2  | Continued

| References       | SCFAs in athletes | Other metabolites                                                                 | Host health                                                                 | GI tract physiology                                                                 | Diet interactions |
|------------------|------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------|
| Barton et al. (79) | ↑ SCFAs in athletes | 81% of stool metabolites decreased during STRESS                                    | and changes in serum IL-6 and stool cysteine accounted for 84% of variability in change in IP |                                                                                      |                  |
|                  |                  | 478 plasma metabolites significantly changed during STRESS, including metabolites partially or fully derived from microbial metabolism |                                                                            |                                                                                      |                  |
|                  |                  | In athletes:                                                                       |                                                                            |                                                                                      |                  |
|                  |                  | ↑ TMA, TMAO, L-carnitine, dimethylglycine, O-acetyl carnitine, proline betaine, creatine, acetoacetate, 3-hydroxy-isovaleric acid, acetone, N-methyl nicotinate, N-methyl nicotinamide, phenylacetylglutamine (PAG), 3-methyl histidine, lysine, and methylamine | Propionite ~ protein                                                              |                  |
|                  |                  | ↓ glycerate, allantoin, succinate, glycerine, tyrosine                              |                                                                            |                                                                                      |                  |
| Clarke et al. (19) |                  | 21 metabolites significantly different between SCGs (4 with significant pairwise differences: succinic acid, cis-aconitate, lactate, and creatinine) | Diversity ~ protein intake and creatine kinase                                |                                                                                      |                  |
|                  |                  | ↑ cis-aconitate, succinic acid in SCG with moderate static/high dynamic vs. low static/high dynamic |                                                                            |                                                                                      |                  |
|                  |                  | ↑ fecal creatinine in SCG with low static/high dynamic vs. high static/low dynamic and moderate/high static and high dynamic |                                                                            |                                                                                      |                  |
|                  |                  | ↓ lactate in SCG with low static/high dynamic vs. moderate/high static and high dynamic |                                                                            |                                                                                      |                  |

ABA, activity-based anorexia; ACT, active [designated group in Bressa et al. (82)]; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAVI, cardio-ankle vascular index; CO, cardiac output; CON, control; E, Exercise [designated group in Cronin et al. (78)]; EF, left ventricular ejection fraction; EP, Whey protein + Exercise [designated group in Cronin et al. (78)]; FS, fractional shortening; FTR, forced treadmill running; HCR, high-capacity running; HDL, high-density lipoprotein; HFD, high-fat diet; LCR, low-capacity running; IP, intestinal permeability; LDL, low-density lipoprotein; LVEDD, left ventricular end systolic diameter; NEFA, non-esterified fatty acid; PAG, phenylacetylglutamine; RER, respiratory exchange ratio; RQ, respiratory quotient; SAA, serum amyloid A; SBP, systolic blood pressure; SCFA, short-chain fatty acid; SV, stroke volume; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; TRFLP, VLDDL, very low-density lipoprotein; VO2max, maximal (O2) oxygen uptake; VO2peak, highest value of VO2 achieved during high-intensity exercise test.

Effect of Dietary Components Relevant to Exercise Nutrition on the Gut Microbiome Confounding Effects of Diet

Diet is also a major factor that influences and shapes the gut microbiome (15–17). Kang et al. report that diet and exercise both cause shifts in the gut microbiome but that these changes are orthogonal (61). However, some of the studies above reported that dietary factors influenced the gut microbiota independently of, or in combination with, exercise. Dietary factors found in the studies presented here to associate with gut microbiome differences or changes include dairy products (82), light-colored vegetables (77), seaweed (77), rice (77), cereals (82), sucrose (76), fiber (76, 79, 82), protein intake (19, 79, 82), fat intake (82), and total food intake (65, 76) (Figure 3). Some differences or changes in the gut microbiota that seem to be associated with exercise may therefore be due to differences or changes in dietary intake, especially plants and carbohydrates, rather than exercise itself. There is therefore a need for studies investigating the link between the gut microbiome and exercise that control and standardize the dietary intake of participants.

Effects of Supplements and Dietary Patterns on the Gut Microbiome

Although studies have shown some dietary interactions with the gut microbiome in athletes, it is unclear the extent to which the gut microbiome might be affected by supplements or dietary patterns commonly used by athletes, and the potential effects of this on the host. A review by Kärlund et al. (97) comprehensively discusses the topic of protein supplementation in athletes and the potential unknown effects on the gut microbiome. Excess protein may be fermented in the large intestine by various species from the genera Clostridium, Bacteroides, and others from the
Proteobacteria phylum (98, 99), resulting in end products such as ammonia, amines, phenols, and sulfides as well as some SCFAs that may have systemic and metabolic effects on the host (100, 101). Different protein types have been shown to have differential effects on the gut microbiome (102–104) and plant-based vs. animal-based diets have also been shown to induce differences in the gut microbiome composition in humans (16). Additionally, different protein types have been assessed in the context of the anabolic response to exercise (105). However, there are no studies evaluating the impact of different types of protein supplements or whole-food protein sources on the gut microbiome and amino acid fermentation in athletes (97). As protein and protein supplements are widely advertised and recommended to athletes, this is an important gap in the research that should be addressed. Future research should also be sure to compare the effects of different protein sources as both isolated supplements as well as in their whole-food form as the matrix of the whole food has been shown to play an important role in the anabolic response to exercise and may alter effects based on factors such as the type and amount of fat (106, 107). Additionally, it would be interesting to know whether supplementation of plant-based proteins with amino acids such as leucine, lysine, and methionine, which is a strategy that has been shown by a couple studies to augment the anabolic effect of plant proteins (105), alters the effect of these proteins on the gut microbiome.

Carbohydrate is a primary fuel source for exercise and is therefore also a primary focus of athletes’ dietary intake (108, 109). In addition to whole food forms of carbohydrates, such as bread, pasta, fruit, and potatoes, there is also a wide array of carbohydrate supplements that may be used before, during, or after exercise to enhance performance and recovery (110). The effects of whole food carbohydrates on the gut microbiome differs widely as a function of fiber content and type (111–113), though generally fiber tends to increase SCFA producing bacteria such as Bacteroidetes and Actinobacteria and decrease Firmicutes (114). However, the effects of frequent use of carbohydrate supplements, which are typically high in sugar and low in microbiota-accessible carbohydrates, on the gut microbiome is unknown. It is may therefore be of interest to develop carbohydrate supplements that also target the gut microbiome.

Though carbohydrates and protein are made the primary focus of athlete nutrition, fat is also an important fuel source during prolonged exercise and the popularity of high-fat diets such as the ketogenic diet has prompted athletes and scientists to investigate its potential for sports performance (115). However, evidence suggests that a high-fat diet does not improve exercise performance more than or as much as a high-carbohydrate diet (116). Additionally, the lack of microbiota-accessible carbohydrates on the ketogenic diet makes it questionable whether or how it would benefit the gut microbiome, though there has been little research in this area and none of it has been in athletes (117, 118).

Caffeine is also a widely used ergogenic aid among athletes. Coffee, one of the primary dietary sources of caffeine, has been linked to increases in Bifidobacterium and protection against high-fat diet-induced decreases in Lactobacillus, though these effects may be due to other bioactive compounds present in coffee such as chlorogenic acid (119). The effect of these aspects of
dietary intake on the gut microbiome in athletes is only one half of the story. The other is the effect of the gut microbiome on the overall response, in terms of performance and training adaptation, of the athlete.

**Personalized Sports Nutrition and the Potential Effect of the Gut Microbiome on Response to Diet and Exercise**

The Gut Microbiome in Personalized Sports Nutrition

As discussed in Hughes et al. (22, 23), the gut microbiome is a potential predictor of response to diet. However, that review focused on predictors of response relevant to general health and prevention of chronic disease. Here, the evidence that the gut microbiome may be a predictor of athletic performance is reviewed. Personalized sports nutrition has incorporated the type of sport or activity, the training status of the individual, the athlete's goals, the time of the competitive season, and the athlete's food preferences (120, 121) as well as biological traits such as genetic polymorphisms, RNA expression, and epigenetic modifications (28–30, 34–38) in the attempt to optimize athletic performance and response to training programs.

The gut microbiome should be incorporated into this system as it modulates metabolism of diet and dietary supplements, and therefore has the potential to contribute to variability in response. Inter-individual variability among athletes in response to dietary supplements, such as caffeine and antioxidants, has been attributed to genetic polymorphisms and baseline antioxidant concentrations (35, 122). However, the gut microbiome has been identified as an important factor in the bioavailability and metabolism of antioxidants (123–125) and may be involved in caffeine metabolism via mechanisms such as modulation of the expression of the N-acetyltransferase 2 (NAT2) gene (126). Variability in the gut microbiome has been linked to variability in serum carotenoid concentrations (127), which suggests that the gut microbiome does indeed play a role in modulating antioxidant metabolism. In short, the gut microbiome may affect the metabolism of dietary components, supplements, and dietary patterns marketed to and used by athletes, but this is an area of research that has not yet been adequately explored.

**The Effect of the Gut Microbiome on Performance**

Though the gut microbiome has been shown to modulate metabolism of relevant dietary components, as discussed above, the implications of this for performance are still unclear.

Mostly cross-sectional, studies have examined the correlation between measures of fitness, such as VO$_{2\text{max}}$ and VO$_{2\text{peak}}$, and the gut microbiota (18, 77, 85, 128–130) (Table 3). Butyrate-producing bacteria have been shown in both Allen et al. (18) and Estaki et al. (129) to correlate positively with VO$_{2\text{max}}$ and VO$_{2\text{peak}}$, respectively. **Bacteroides** and the **Firmicutes/Bacteroidetes** ratio have also been shown to correlate with VO$_{2\text{max}}$ (85, 128, 130), although studies have shown contrasting results. Durk et al. (128) found the **Firmicutes/Bacteroidetes** ratio to correlate positively with VO$_{2\text{max}}$. Conversely, Yu et al. (85) found a lower F/B ratio in elderly adults with higher exercise capacity and Yang et al. (130) found that the high VO$_{2\text{max}}$ group had lower **Eubacterium rectale-Clostridium cocoides** (Erec), which are members of the **Firmicutes** phylum, and higher **Bacteroides**. Yu et al. (85) also identified several other taxa that were correlated with VO$_{2\text{peak}}$ in their elderly population such as **Lactobacillales**, **Blautia**, **Ruminococcus**, **E. coli**, and **Alcaligenaceae**. Taniguchi et al. (77) found an inverse correlation between **Clostridium difficile** and changes in VO$_{2\text{peak}}$ in elderly Japanese men during a cycling intervention.

Few studies have directly investigated the effect of the gut microbiome on athletic performance (Table 4). Hsu et al. (131) and Huang et al. (132) both used germ free (GF) mice (C57BL/6Narl) and compared these to mice colonized with bacteria to determine potential effects of the presence of the microbiome as well as specific bacteria on physical performance. Specific pathogen free (SPF) mice were found to have the highest exercise capacity and germ-free mice the lowest (131, 132). Mice colonized with individual bacterial taxa showed improvements in exercise capacity compared to their GF counterparts (131), though not all bacteria showed the same degree of impact (132). Hsu et al. (131), compared germ free (GF) mice, gnotobiotic mice colonized with **Bacteroides fragilis** (BF), and specific pathogen free (SPF) mice in a test of endurance swimming. In a similar study, Huang et al. (132) compared germ-free mice to gnotobiotic mice monocolonized with either **Eubacterium rectale**, **Clostridium cocoides**, or **Lactobacillus plantarum** TWK10 on performance in a swim-to-exhaustion test. In Hsu et al. (131), swim-to-exhaustion time was significantly different among all groups, with SPF mice having the greatest endurance, followed by BF mice, with GF mice having the least endurance capacity. In Huang et al. (132), gnotobiotic mice colonized with **E. rectale** showed significantly higher performance, both with and without aerobic training, than the GF mice as well as the mice colonized with **C. cocoides** and **L. plantarum**.

The potential mechanisms of these effects differed between the two studies. Differences in endurance capacity in Hsu et al. were accompanied by differences in antioxidant enzyme systems, with SPF mice showing greater serum and hepatic antioxidant enzyme activity, and physiological metrics, such as weight of muscle and brown adipose tissue (131). The gut microbiome modulates adipose tissue thermogenic pathways, including browning of white adipose and activity of brown adipose, via potential mechanisms such as bile acids and the endocannabinoid system (143). The gut microbiome may also modulate skeletal muscle anabolism and function via SCFA production and alteration of the availability of intramuscular fuels (55). Mice colonized with **E. rectale** and **C. cocoides** in Huang et al. showed higher lactate levels and higher glucose levels while mice colonized with **E. rectale** showed a lower creatine kinase (CK), a marker of muscular stress, and higher wheel running distance compared to both GF mice and the other gnotobiotic mice (132).

It is worth noting, however, in Huang et al. (132) that **L. plantarum** and **C. cocoides** did not colonize stably in the mice, fecal analysis showed no significant increases of these microbes, while **E. rectale** did colonize and increase over time. Therefore, it is unclear whether the ergogenic effect was due to the presence of **E. rectale** specifically, or simply due to the
The gut microbiome may influence performance. They also indicate that a more diverse microbiome may be more beneficial as SPF mice performed better than monocolonized BF mice (131). While Huang et al. (132) suggests that individual taxa such as E. rectale may be partially responsible for performance effects,
| References       | Subjects                                                                                                                                                                                                 | Type of exercise                  | Microbiota analysis/supplementation method | Performance metric(s)                                                                                           | Performance results                                                                                                                                                                                                                     | Host health results                                                                                     |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Hsu et al. (131) | Mice (C57BL/6JNarl, specific pathogen free (SPF), germ free (GF), gnotobiotic Bacteroides fragilis (BF); 12 wk, male)                                                                                       | Endurance swimming                | N/A                                        | Swim-to-exhaustion time                                                                                       | Swim-to-exhaustion time SPF > BF, and GF. Antioxidant systems: glutathione peroxidase (GPx) and catalase (CAT) SPF > GF and BF; superoxide dismutase (SOD) activity SPF and GF > BF. | Levels of antioxidant enzyme activity GPx, SOD, and CAT: SPF > BF > GF % weight of liver, muscle, brown adipose tissue and epididymal fat pad SPF > BF & GF. |
| Huang et al. (132)| Mice (C57BL/6JNarl; germ free (GF); maintained germ free or colonized with Eubacterium rectale, Clostridium coccoides, or Lactobacillus plantarum TWK10; 6 wk, male)                                      | Endurance swimming                | N/A                                        | Swim-to-exhaustion time                                                                                       | Swim-to-exhaustion time in specific pathogen free (SPF) > GF mice both before and after training (time increased in both SPF and GF mice after training). After training, swim-to-exhaustion time in E. rectale-colonized mice > GF. | E. rectale and C. coccoides mice showed higher lactate level vs. GF and L. plantarum. Ammonia level increased in GF group. Creatine kinase (CK) lower in E. rectale vs. C. coccoides (no difference between GF and L. plantarum) Glucose levels higher in E. rectale and C. coccoides vs. GF and L. plantarum. GLUT4 higher in E. rectale vs. GF and L. plantarum. Hepatic glycogen higher in GF vs. SPF, E. rectale, L. plantarum, and C. coccoides Basal metabolic rate (BMR) higher in L. plantarum and C. coccoides mice vs. GF and E. rectale. Wheel running distance higher in gnotobiotic mice (E. rectale -> L. plantarum and C. coccoides -> GF). Growth curve higher in GF and E. rectale vs. L. plantarum and C. coccoides. | Probiotic supplementation decreased body weight, serum lactate, ammonia, urea, nitrogen, albumin, CK, creatinine, triacylglycerol (TAG), and glucose and increased relative muscle weight, number of type I muscle fibers in gastrocnemius muscle. Blood glucose levels higher in TWK10 group vs. placebo after exercise. No significant differences in lactate, ammonia, free fatty acids (FFAs), or CK. |
| Chen et al. (133)| Mice (ICR, specific pathogen free (SPF), 6 wk, male)                                                                                                                                                      | Grip strength and endurance swimming | N/A Probiotic supplementation (Lactobacillus plantarum TWK10—dose-response in mice) | Grip strength and swim-to-exhaustion time                                                                      | Probiotic supplementation increased grip strength and endurance swimming time after exercise.                                                                                             | Probiotic supplementation decreased body weight, serum lactate, ammonia, urea, nitrogen, albumin, CK, creatinine, triacylglycerol (TAG), and glucose and increased relative muscle weight, number of type I muscle fibers in gastrocnemius muscle. Blood glucose levels higher in TWK10 group vs. placebo after exercise. No significant differences in lactate, ammonia, free fatty acids (FFAs), or CK. |
| Huang et al. (134)| Humans (16 male runners)                                                                                                                                                                                  | Running (treadmill test)           | N/A Probiotic supplementation (1 x 10^{11} CFU Lactobacillus plantarum TWK10) | Run time-to-fatigue                                                                                             | Probiotic supplementation increased run time-to-fatigue but not VO_{2max}                                                                                                           | Blood glucose levels higher in TWK10 group vs. placebo after exercise. No significant differences in lactate, ammonia, free fatty acids (FFAs), or CK. |
| Huang et al. (132)| Humans (54 healthy adults with no prior training; 27 men, 27 women)                                                                                                                                   | Running (treadmill test)           | N/A Probiotic supplementation (Lactobacillus plantarum TWK10 - placebo, low dose 3 x 10^{10} CFU, high dose 9 x 10^{10} CFU) | Run time-to-fatigue                                                                                             | Probiotic supplementation increased time to exhaustion in both TWK10 groups but was significantly higher in the high-dose compared to low-dose group. | Lactate accumulation and ammonia production improved in the TWK10 groups during exercise and recovery phase. Blood glucose higher in high-dose group during exercise. Decrease in body fat and increase in muscle mass in high-dose group. |

(Continued)
| References          | Subjects | Type of exercise                | Microbiota analysis/supplementation method                                                                 | Performance metric(s)                                                                 | Performance results                                                                 | Host health results                                                                 |
|---------------------|----------|---------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Jäger et al. (135)  | Humans (29 recreationally-trained men) | Resistance training             | N/A Probiotic supplementation ($1 \times 10^{10}$ CFU *Bacillus coagulans* GBI-30)                        | 1 rep max (RM) one-legged leg press Vertical jump power                                 | Probiotic supplementation did not improve 1 RM or vertical jump power though a decrease in Wingate power was attenuated in the probiotic group | Probiotic supplementation increased perceived recovery and decreased perceived muscle soreness and measured muscle damage as indicated by CK |
| Lamprecht et al. (136) | Humans (23 trained men) | Cycling (cycle ergometer test) | N/A Probiotic supplementation ($1 \times 10^{10}$ CFU *Bifidobacterium bifidum* W23, *Bif. lactis* W61, *Enterococcus faecium* W54, *L. acidophilus* W22, *L. brevis* W63, *L. lactis* W58) | Incremental cycle ergometer exercise test                                             | Probiotic supplementation did not improve VO$_{2\text{max}}$ or VO$_{2\text{max}}$ relative to body weight | Probiotic supplementation decreased zonulin and tendentially decreased carbonyl proteins and TNF-α but had no significant effects on α1-antitrypsin, malondialdehyde, total oxidation status of lipids, or IL-6 |
| Martarelli et al. (137) | Humans (24 male cyclists) | Cycling | Plate and Randomly Amplified Polymorphic DNA (RAPD) Probiotic supplementation ($1 \times 10^{10}$ CFU/g 1:1 *Lactobacillus rhamnosus* IMC 501 and *Lactobacillus paracasei* IMC 502) vs. control | Intense exercise training                                                            | No performance results reported. Probiotic supplementation increased counts of Lactobacillus in stool (in different proportions for each subject) | Reactive oxygen metabolite (ROM) concentrations significantly increased after exercise in control group but not in probiotic group (though ROM levels not significantly different between the two groups) Biological antioxidant potential (BAP) increased after probiotic supplementation and were higher in probiotic group vs. control group |
| Salarkia et al. (138) | Humans (46 adolescent females) | Swimming | N/A Probiotic supplementation ($4 \times 10^{10}$ CFU/ml *Lactobacillus acidophilus* spp, *L. delbrueckii bulgaricus*, *Bif. bifidum*, *Streptococcus salivarius thermophilus*) vs. ordinary yogurt | 400m swim time Harvard step test                                                     | Probiotic supplementation increased VO$_{2\text{max}}$ but did not improve 400m swim time | Probiotic supplementation reduced frequency and duration of respiratory infections and some symptoms (dyspnea and ear pain) |
| Shing et al. (139)  | Humans (10 male runners) | Running (treadmill test)        | N/A Probiotic supplementation ($4.5 \times 10^{10}$ CFU/ml *Lactobacillus acidophilus*, *L. rhamnosus*, *L. casei*, *L. plantarum*, *L. fermentum*, *Bifidobacterium lactis*, *Bif. breve*, *Bif. Bifidum*, *Streptococcus thermophilus*) | Run time-to-fatigue                                                                  | Probiotic supplementation increased run time-to-fatigue                               | Probiotic supplementation reduced serum lipopolysaccharide (LPS), slightly reduced lactulose:rhhamnose (gastrointestinal permeability), and gastrointestinal discomfort |

(Continued)
| References          | Subjects                                      | Type of exercise                                      | Microbiota analysis/supplementation method                                                                 | Performance metric(s)                                      | Performance results                                                                 | Host health results                                                                 |
|---------------------|-----------------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Townsend et al. (140) | Humans (25 male baseball athletes)            | Off-season training                                   | N/A Probiotic supplementation (1 × 10⁹ CFU/day Bacillus subtilis DE111) vs. placebo                          | 1 rep max (RM) squat and deadlift, 10 yd sprint, standing long jump | No significant differences in performance between probiotic and placebo groups       | TNF-α concentrations significantly lower in probiotic group (not in any other biochemical markers) No significant differences in body composition, testosterone, cortisol, IL-10, zonulin, salivary immunoglobulin A (SigA), and SigM |
| Scheiman et al. (141) | Humans (15 athletes pre- and post-marathon, 87 ultramarathoners and olympic trial rowers pre- and post-exercise (validation cohort) vs. 10 sedentary controls) | Running Composition (16S)                             | Marathon run                                                                                             | No performance results reported. Veillonella increased post-exercise in athletes     |                                                                                      | Decreased inflammatory cytokines in Veillonella-treated mice                         |
| Soares et al. (142)  | Rats (Wistar, 11 wk, male)                    | Running (treadmill test)                              | Saccharomyces boulardii supplementation (Saccharomyces boulardii 1 × 10⁹ CFU/ml)                          | VO₂max, run time-to-fatigue                                | Saccharomyces boulardii increased VO₂max, run time-to-fatigue, max speed attained, and total work | Yeast supplementation had no effect on body mass gain or food intake                   |

BF, gnotobiotic colonized with Bacteroides fragilis; BMR, basal metabolic rate; CAT, catalase; CFU, colony forming unit; CK, creatine kinase; FFA, free fatty acid; GF, germ-free; GPx, glutathione peroxidase; ICR, Institute of Cancer Research; IL-6, interleukin-6; LPS, lipopolysaccharide; RM, rep max; SOD, superoxide dismutase; SPF, specific pathogen free; TAG, triacylglycerol; TNF-α, tumor necrosis factor alpha; VO₂max, maximal (O₂) oxygen uptake.
further research is needed to determine exactly what aspects or taxa contribute to this ergogenic effect. These studies also did not investigate responses to a dietary or training regimen, leaving room for further research on the potential of the gut microbiome to mediate or modify exercise performance response to diet.

The Effect of Probiotic Supplementation on Athlete Health and Performance

While there are a number of studies on probiotic supplementation in animals and human athletes, most focus on effects such as frequency of respiratory and gastrointestinal illness or biomarkers of inflammation and immune function (137, 144–146). Supplementation of probiotic bacteria to boost the abundance or activity of potentially beneficial taxa may also serve as a potential method of modifying performance response to training. Our review of the literature found eleven studies investigating the ergogenic effect of probiotic supplementation (133–142, 147) (Table 4). Common probiotic bacteria used were strains of Lactobacillus or Bifidobacterium (133, 134, 136–139, 147). Additional strains tested included those belonging to species Bacillus subtilis (140) or Bacillus coagulans (135), Veillonella atypica (141), or even yeast Saccharomyces boulardii (142).

The majority of studies investigated the effect of probiotic supplementation on aerobic exercise performance measures such as run time-to-fatigue, VO2max, max speed attained, 10-yard sprint, or 400-meter swim time (132–134, 136, 138, 139, 141, 142). However, some studies also investigated strength and anaerobic outcomes such as grip strength, vertical jump power, standing long jump, Wingate power, or 1 rep max (RM) lifts (133, 135, 140).

Effects on performance variables were highly mixed between studies, though a number of studies found beneficial effects on performance parameters such as time-to-fatigue (132–134, 139, 141, 142). However, some studies found no effects of probiotic supplementation on performance metrics (136, 140) while other studies found mixed effects, with probiotic supplementation improving some performance measures, but not others (134, 135, 138). For example, Huang et al. (134) found that probiotic supplementation with Lactobacillus plantarum TWK10 increased run time-to-fatigue but not VO2max. Thus, studies reporting effects of probiotic supplementation on only one performance outcome may not be providing a complete picture of the ergogenicity of probiotic bacteria. Additionally, all but one study (137) of probiotic supplementation of humans lacked confirmation of probiotic colonization and this study acknowledged that individuals showed different levels of colonization by the probiotic bacteria. It is important that future studies investigating probiotic supplementation also collect fecal samples from participants before and after the intervention to determine whether differences in probiotic colonization may contribute to inter-individual variability in the ergogenic effect of probiotic supplementation.

In addition to performance variables, many of these studies investigated effects on body composition and inflammation. Again, results were mixed, with some studies reporting significant effects of supplementation on outcomes such as fat mass and muscle mass (132, 133) or inflammatory markers (133, 137, 139, 141, 147), though results were often mixed with some biochemical markers showing no significant effect of probiotic treatment and some studies showing no significant effects at all on these outcomes (134, 142). However, as none of these variables were analyzed, further research is necessary to determine the mechanism of the effects as well as whether the same effects are seen in humans.

The Effect of Antibiotic Treatment on Exercise Performance

Conversely to the use of probiotics to determine the potential effect of the gut microbiome on athletic performance, the use of antibiotics in mouse models has recently been explored to determine the potential effects of a lack of gut microbes and their metabolites on exercise capacity and muscle function (148, 149). Table 5 displays the findings of these recent studies. In both studies, antibiotic treatment decreased the exercise capacity of the mice, tested using forced treadmill running. Additionally, this phenotype could be rescued by either natural reseeding (148) or acetate infusion (149). Nay et al. also found reduced gene expression of SCFA receptor G-protein coupled receptor 41 (GPR41) and sodium/glucose cotransporter 1 (SGLT1) as well as reduced muscle glycogen in antibiotic-treated mice, suggesting that the reduced exercise capacity in these mice may have been mediated by muscle glycogen availability (148). Okamoto et al. concluded that the reduced exercise capacity of antibiotic-treated mice was due to the lack of acetate available for use as a substrate during exercise as acetyl-CoA (149). With regards to changes in the gut microbial community, Okamoto et al. reported that relative abundance of Firmicutes was increased in antibiotic-treated mice while Bacteroidetes, α-diversity, and fecal bacterial DNA concentration was reduced (149). Nay et al. found that fecal bacterial DNA was reduced in antibiotic-treated mice but only reported differences in composition between control mice and mice treated with antibiotics but naturally reseeded, which showed no significant differences in α- and β-diversity, Bacteroides, and Firmicutes (148).

Okamoto et al. additionally tested the effect of a low microbiota-available carbohydrate diet (LMC) vs. a high microbiota-available carbohydrate (HMC) diet to determine with substrate availability for the gut microbiome altered exercise capacity. In these treatment groups, treadmill running time was decreased in the LMC mice, concomitant with a decrease in muscle mass, fecal SCFA, and plasma acetate and propionate as well as an increase in Firmicutes and decrease in Bacteroidetes and other SCFA producing bacterial taxa (149). This reduced exercise capacity phenotype was rescued when mice were given a fecal microbiota transplant (FMT) from HMC mice and a dose of inulin prior to exercise. The increased exercise capacity in LMC+FMT+inulin mice was not accompanied by changes in body mass or muscle mass but there was an increase in fecal SCFAs, again suggesting that SCFA concentration may act as a direct substrate or mediate substrate availability in such a way as to influence exercise capacity.
TABLE 5 | Summary of studies investigating the effect of antibiotics on exercise performance.

| References          | Subjects                        | Type of exercise | Type of study                  | Diet and treatment groups                                                                 | Microbiota method                                      | Performance effects                                                                 | Health effects                                                                 | Microbiota effects                  |
|---------------------|---------------------------------|------------------|--------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------|
| Nay et al. (148)    | Mice (C57BL/6J mice, 14 wk, male) | Forced treadmill running | Intervention                  | control (CTL) vs. antibiotics (ATB) vs. antibiotics followed by natural reseeding (NAT) | Composition and function (RT-qPCR, 16S, metagenomics) | ↔ maximal aerobic velocity (MAV), extensor digitorum longus (EDL) maximal strength in all groups ↓ time to exhaustion in ATB and NAT (restored in NAT after reseeding) ↓ EDL muscle fatigue index in ATB vs. CTL and NAT ↑ cecum weight in ATB vs. CTL ↓ cecum weight in NAT vs. ATB ↔ muscle mass (gastrocnemius, quadriceps, EDL soleus) in ATB vs. CTL (body weight normalized without cecum weight) ↔ myofiber phenotype, mitochondrial metabolism, inflammatory signaling, Lat1 expression, GPR40, GPR120, blood glucose ↑ Fiaf expression in ATB vs. CTL and NAT ↓ GPR41 and Sglt1 expression, muscle glycogen in ATB vs. CTL and NAT ↓ bacterial DNA in ATB and NAT (completely restored in NAT after reseeding) ↔ α- and β-diversity, Bacteroides, Firmicutes between CTL and NAT |
| Okamoto et al. (149) | Mice (C57BL/6J mice, 10 wk, male) | Forced treadmill running | Intervention                  | antibiotic treatment (Abx) or antibiotic-free (Abx-free) group Acetate vs. saline infusion in Abx Butyrate infusion in Abx Low microbiome-accessible carbohydrate (LMC) vs. high MC (HMC) diet FMT+inulin in LMC | Composition (16S)                                      | ↓ treadmill running time in Abx ↑ treadmill running time in Abx+acetate ↔ treadmill running time in Abx+butyrate and Abx+saline ↓ treadmill running time in LMC group ↑ treadmill running time in LMC+FM+inulin vs. LMC ↓ muscle, fecal SCFA, plasma acetate and propionate in LMC ↑ body mass gain, dietary intake ↑ white adipose in LMC ↔ body mass, muscle mass in Abx+acetate ↑ Firmicutes in Abx ↓ Bacteroidetes, diversity (Shannon), fecal bacterial DNA concentration in Abx |

Abx, antibiotic; Abx-free, non-antibiotic treated; ATB, antibiotic; CTL, control; EDL, extensor digitorum longus; F/B, Firmicutes/Bacteroidetes; FMT, fecal microbiota transplant; GPR, G-protein coupled receptor; HMC, high microbiome-accessible carbohydrate; LMC, low microbiota-accessible carbohydrate; MAV, maximal aerobic velocity; NAT, antibiotic-treated and naturally reseeded; RT-qPCR, real time quantitative polymerase chain reaction; SCFA, short-chain fatty acid.
Summary of Findings and Putative Mechanisms of the Effect of the Gut Microbiome on Athletic Performance

These studies suggest that there may be an effect of the gut microbiome on exercise performance via mechanisms such as SCFA availability, muscle glycogen content, antioxidant enzyme activity, gastrointestinal permeability, and lactate metabolism (Figure 4). Additional speculative mechanisms may involve alterations in substrate utilization (142) as well as glycogen metabolism and storage (150), changes in neural function (142), as well as immune modulation (142) or cross-talk between the gut microbiome and mitochondria in energy production and inflammation (45). The gut microbiota has been hypothesized to impact skeletal muscle physiology and function via metabolites such as SCFAs, folate, tryptophan, glycine betaine, vitamins B2 and B12, and urolithins that may act through various pathways such as stimulation of insulin-like growth factor-1 (IGF-1), prevention of oxidative stress or inflammation, and promotion of mitochondrial biogenesis (151). However, these data also indicate that improvements in these functions do not always translate to improvements in performance. Further research is needed to investigate the effects of different probiotic strains, the interaction with dietary composition (e.g., differences of effect in athletes who have different overall dietary patterns), the use of dietary supplements, and in different modes of exercise, such as strength training.

CONCLUSIONS AND FUTURE DIRECTIONS

The gut microbiome represents an open field of study in the realm of personalized sports nutrition. High interindividual variability in response to training and physical activity is regularly reported (152) and the gut microbiome may contribute to this variability by impacting individual metabolism of food components and/or adaptation to the homeostatic stress, or training load, of the exercise stimulus (153). More research is needed to determine whether the gut microbiome could be an important predictor of athletic performance in response to dietary and exercise interventions. Researchers should refer to guides such as Ross et al. (36), Hecksteden et al. (152), Mann et al. (153), Swinton et al. (154), and Hopkins et al. (155) for statistical frameworks to interpret inter-individual variability in response and identify factors that contribute to this variability.

Specific questions that could be addressed are the role of specific bacterial taxa or groups of taxa involved in gains in athletic performance in response to certain dietary factors (e.g., protein sources such as whey, casein, soy, etc.; macronutrient distribution; or supplements such as caffeine, beta-alanine, antioxidants) or exercise stimuli. This could be investigated by using a combined dietary-exercise intervention, measuring both baseline and final microbiome and performance variables, and using predictive machine learning algorithms such as random forests (156) to determine whether baseline abundance or changes in certain bacterial taxa can predict an individual’s physical performance response. Another question is whether different taxa are involved in different responses (e.g., VO2max, time-to-fatigue, rep max loads, etc.) and the mechanisms of these effects (e.g., SCFA production, antioxidant enzyme activity, muscle protein synthesis, glycogen formation, energy harvest and fuel utilization, inflammation, etc.). While the first question could be addressed by a study measuring multiple exercise performance outcomes within the same population, determining the mechanisms of these effects would require in vitro or animal models and measurement of potential mediating metabolites, such as SCFAs, and physiological variables, such as muscle mass or muscle glycogen content. Furthermore, larger and longer studies are needed to address whether effects or responses differ between demographics (e.g., gender, age, ethnicity, etc.) and whether modulation of the gut microbiome via probiotics and/or prebiotics or modulation of the dietary or exercise stimulus (e.g., amount or type of supplement; mode, duration, intensity of exercise) may serve to increase positive response to the stimulus, decreasing the number of “non-responders.” For example, a study using the same participants and measuring microbiome and performance responses to stepwise increases in the duration and/or intensity of exercise may serve to elucidate what type of exercise may be optimal for certain individuals and their microbiomes. Additionally, studies that have measured changes in performance in response to probiotic supplementation have
not looked at individual's gut microbiota composition directly. This is a limitation of these studies as different strains of probiotic bacteria show differing rates of survival through the gastrointestinal tract (157) and the composition of an individual's gut microbiota may also influence the persistence and function of probiotic bacteria in the gut (158–160). Therefore, not all probiotic strains may survive in sufficient quantities to make it down to the gut microbiome and, even if the probiotic bacteria reach the gut microbiome, it may not last as long or have the same effect in each individual.

Additional challenges and limitations in the area of research are numerous and must be taken into consideration when making claims about the exercise-microbiome connection. While the effects of diet and exercise have been shown to be orthogonal to one another (61), diet can still be a confounding factor within and between studies. Thus, conclusive effects of exercise on the gut microbiome must standardize the diet of participants, which has not yet been done. In addition to diet, variables such as genetics (32, 161), epigenetics (162), sleep behavior (163, 164), gender (165, 166), age (66, 167), and a host of other factors contribute to variability in the gut microbiome as well as performance response. This variability makes it extremely difficult to draw concrete conclusions about the effects of the gut microbiome and should always be considered when designing or interpreting studies on the interaction of the gut microbiome and host.

A related body of research has developed investigating the “gut-muscle axis” as it relates to age-related changes in muscle mass (i.e., sarcopenia) and physical frailty (151, 168–174) as well as its potential role in the “muscle-gut-brain” axis and neurodegenerative diseases in aging (175, 176). This field of research has the potential to inform the research in the field of the gut microbiome and exercise performance. Though this research focuses on preservation of muscle mass rather than physical or athletic performance, it may contribute to sarcopenia and decreases in muscle function, which has not yet been done. In addition to diet, variables such as genetics (32, 161), epigenetics (162), sleep behavior (163, 164), gender (165, 166), age (66, 167), and a host of other factors contribute to variability in the gut microbiome as well as performance response. This variability makes it extremely difficult to draw concrete conclusions about the effects of the gut microbiome and should always be considered when designing or interpreting studies on the interaction of the gut microbiome and host.

REFERENCES
1. Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. Nature. (2012) 489:242–9. doi: 10.1038/nature11552
2. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Science. (2012) 336:1262–7. doi: 10.1126/science.1223813
3. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JL. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. (2006) 444:1027–31. doi: 10.1038/nature05414
4. Musso G, Gambino R, Cassader M. Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. Annu Rev Med. (2011) 62:361–80. doi: 10.1146/annurev-med-012510-175505
5. de Groot PF, Belzer C, Aydin O, Levin E, Levels JH, Alavink S, et al. Distinct fecal and oral microbiota composition in human type 1 diabetes, an observational study. PLoS ONE. (2017) 12:e0188475. doi: 10.1371/journal.pone.0188475
6. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. (2012) 490:55–60. doi: 10.1038/nature11450
7. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JL. Human nutrition, the gut microbiome and the immune system. Nature. (2011) 474:327–36. doi: 10.1038/nature10213
8. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science. (2012) 336:1268–73. doi: 10.1126/science.1223490
9. Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. Gut Microbes. (2012) 3:177–90. doi: 10.4161/gm.21703
10. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. (2012) 490:55–60. doi: 10.1038/nature11450
11. Lamichhane S, Sen P, Dickens AM, Oresic M, Bertram HC. Gut metabolome meets microbiome: a methodological perspective to understand the relationship between host and microbe. Methods. (2018) 149:3–12. doi: 10.1016/j.ymeth.2018.04.029
12. Tolfhur G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes. (2012) 61:364–71. doi: 10.2373/diab.11-1019

ACKNOWLEDGMENTS
Thank you to James P. Hughes and Nancy L. Keim who assisted in proofing this manuscript. Figures were generated using Piktochart.

AUTHOR CONTRIBUTIONS
RH performed the literature review, conceived, and composed the manuscript.

FUNDING
Partial funding for this manuscript was provided by the UC Davis Open Access Fund.

Frontiers in Nutrition | www.frontiersin.org 22 January 2020 | Volume 6 | Article 191
Hughes Gut Microbiome Personalized Sports Nutrition

53. Monda V, Villano I, Messina A, Valenzano A, Esposito T, Moscatelli F, et al. Exercise modifies the gut microbiota with positive health effects. Oxid Med Cell Longev. (2017) 2017:3831972. doi: 10.1155/2017/3831972

54. 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. (2015) 13:35–48. doi: 10.1115/13.35

55. Hawley JA. Microbiota and muscle highway—two way traffic. Nat Rev Endocrinol. (2019). doi: 10.1038/s41574-019-0291-6 [Epub ahead of print]

56. Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome–gut–brain axis. Gut Microbes. (2019) 10:555–68. doi: 10.1080/2150413X.2019.1562268

57. Matsumoto M, Inoue R, Tsukahara T, Ushida K, Chiji H, Matsubara N, et al. Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum. Biosci Biotechnol Biochem. (2008) 72:572–6. doi: 10.1271/bbb.70474

58. Queipo-Ortuno MI, Seoane LM, Murri M, Pardo M, Gomez-Zumaquero JM, Cardona F, et al. Gut microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels. PLoS ONE. (2013) 8:e56456. doi: 10.1371/journal.pone.0056456

59. Allen JM, Berg Miller ME, Pence BD, Whitlock K, Nehra V, Gaskins JM, et al. Comparison of diet versus exercise on metabolic function and its association with weight gain in obese, non-obese and hypertensive rats. PLoS ONE. (2015) 10:e0125889. doi: 10.1371/journal.pone.0125889

60. Choi JJ, Eum SY, Rampersaud E, Daunert S, Abreu MT, Toborek M. Exercise training modifies gut microbiota in normal and diabetic mice. PLoS ONE. (2013) 8:e65465. doi: 10.1371/journal.pone.0065465

61. Kang SS, Jeraldo PR, Kurti A, Miller ME, Cook MD, Whitlock K, et al. Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. Mol Neurodegener. (2014) 9:36. doi: 10.1186/1750-1326-9-36

62. Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise influence on the gut microbiome and gut-brain axis. Front Longev Health Perspect. (2016) 312:G559–71. doi: 10.1152/ajpgi.00066.2017

63. Mika A, Van Treuren W, Gonzalez A, Herrera JJ, Knight R, Fleshner Campbell SC, Wisniewski PF, Noji M, McGuinness LR, Häggblom MM, Laskowski S, Dougherty Petriz BA, Castro AP, Almeida JA, Gomes CP, Fernandes GR, Kruger JM, et al. Genetic variability in forced and voluntary endurance exercise training in seven inbred mouse strains. J Appl Physiol. (2017) 122:1627–38. doi: 10.1152/japplphysiol.00132.2016

64. Evans CC, LePard KJ, Kwak JW, Stancukas MC, Laskowski S, Dougherty J, et al. Exercise prevents weight gain and alters the gut microbiota in mice. Environ Health Perspect. (2013) 131:725–30. doi: 10.1289/ehp.1306534

65. Allen JM, Berg Miller ME, Pence BD, Whitlock K, Nehra V, Gaskins JM, et al. Exercise prevents weight gain and alters the gut microbiota in a mouse model of high fat diet-induced obesity. PLoS ONE. (2014) 9:e92193. doi: 10.1371/journal.pone.0092193

66. Liu Z, Liu HY, Zhou H, Zhan Q, Lai W, Zeng Q, et al. Moderate-intensity exercise affects gut microbiome composition and influences cardiac function in myocardial infarction mice. Front Microbiol. (2017) 8:1687. doi: 10.3389/fmicb.2017.01687

67. Munukka E, Ahtianen IP, Puigbo P, Jalkanen S, Pahkala K, Keskitalo A, et al. Six-week endurance exercise alters gut metagenome that is not reflected in systemic metabolism in over-weight women. Front Microbiol. (2018) 9:2323. doi: 10.3389/fmicb.2018.02323

68. Taniguchi H, Tanisawa K, Sun X, Kubo T, Hoshino Y, Hosokawa M, et al. Effects of short-term endurance exercise on gut microbiota in elderly men. J Physiol Rep. (2018) 4:e13935. doi: 10.1186/p4y2.13935

69. O’Donovan CM, Madigan SM, Garcia-Perez I, Rankin A, O’Sullivan E, Cotter PD. Distinct microbiome composition and metabolism exists across subgroups of elite Irish athletes. J Sci Med Sport. (2019) 23:63–8. doi: 10.1111/jss.2019.08.290

70. Bressa C, Baillén-Andrino M, Pérez-Santiago J, González-Soltero R, Pérez M, Montalvo-Lomichar MG, et al. Differences in gut microbiota profile between women with active lifestyle and sedentary women. PLoS ONE. (2017) 12:e0171352. doi: 10.1371/journal.pone.0171352

71. O’Donovan CM, Madigan SM, Garcia-Perez I, Rankin A, O’Sullivan E, Cotter PD. Distinct microbiome composition and metabolism exists across subgroups of elite Irish athletes. J Sci Med Sport. (2019) 23:63–8. doi: 10.1111/jss.2019.08.290

72. Yu Y, Mao G, Wang J, Zhu L, Lai X, Tong Q, et al. Gut dysbiosis is associated with the reduced exercise capacity of elderly patients with hypertension. Hypertens Res. (2018) 41:1636. doi: 10.1007/s10992-018-0110-9

73. Tian Y, Shan H, Lv X, Tong Q, et al. Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiological stress. Am J Physiol-Gastr Liver Physiol. (2017) 312:G559–71. doi: 10.1152/ajpgi.00066.2017

74. Lerman I, Harrison BC, Freeman K, Hewett TE, Allen DL, Robbins JD, et al. Gut microbiome composition associated with exercise training and resveratrol supplementation on gut microbiota composition in high-fat diet fed mice. Physiol Rep. (2018) 6:e13881. doi: 10.14814/phy2.13881

75. McCabe LR, Irwin R, Tekulur J, Kruger M, Parkes J, Hemingway M, et al. Acute exercise training and resveratrol supplementation on gut microbiota composition in male C57BL/6 mice. J Appl Physiol. (2015) 118:1059–69. doi: 10.1152/japplphysiol.00177.2014

76. Sohail MU, Yassine HM, Sohail A, Al Thani AA. Impact of physical exercise on the gut microbiota in men. PLoS ONE. (2018) 9:2323. doi: 10.3389/fmicb.2018.02323
Hughes Gut Microbiome Personalized Sports Nutrition

Aird D, Ross MG, Chen WS, Daniellsom M, Fennell T, Russ C, et al. Analyzing and minimizing PCR amplification bias in illumina sequencing libraries. *Genome Biol.* (2011) 12:R18. doi: 10.1186/gb-2011-12-2-r18

Burd NA, Beals JW, Martinez IG, Skinner SK. Achieving optimal training and competition. *J Sports Sci.* (2011) 29(Suppl. 1):S17–27. doi: 10.1080/02640414.2011.585473

Burke LM, Hawley JA, Wong SH, Jeukendrup AE. Carbohydrates for training and competition. *J Sports Sci.* (2019) 37:1673–87. doi: 10.1080/02640414.2018.1477256

Chassard C, Lacroix C. Carbohydrates and the human gut microbiota. *Curr Opin Clin Nutr Metab Care.* (2013) 16:453–60. doi: 10.1097/MCO.0b013e3283619e63

Hamaker BR, Tuncil YE. A perspective on the complexity of dietary fiber structures and their potential effect on the gut microbiota. *J Mol Biol.* (2014) 426:3838–50. doi: 10.1016/j.jmb.2014.07.028

Sharma P, Bhandari C, Kumar S, Sharma B, Bhadwal P, Agnihotri N. Dietary fibers: a way to a healthy microbiome. *Diät Microbiome Health.* (2018) 2018:299–345. doi: 10.1007/BF03391815-4530-l-2-811440-7-00011-9

Paoli A, Bianco A, Grimaldi KA. The ketogenic diet and sport: a possible marriage? *Exerc Sport Sci Rev.* (2015) 43:153–62. doi: 10.1249/EXS.0000000000000050

Fritzen AM, Lundsgaard AM, Kiens B. Dietary fuels in athletic performance. *Annu Rev Nutr.* (2019) 39:45–73. doi: 10.1146/annurev-nutr-082018-124357

Noble EG, Moraska A, Mazzeo RS, Roth DA, Olsson MC, Moore RL, et al. Personalizing protein nourishment. *Sports Med.* (2018) 57:213–32. doi: 10.1007/s40279-017-0805-9

Estaki M, Pither J, Raue Y, Xu J, Yang J, Harley IM, et al. Gut microbiota composition is related to cardiorespiratory fitness and gut microbiota on intestinal and hepatic levels of phase 2 xenobiotic-metabolizing enzymes in the rat. *Drug Metab Dispos.* (2009) 37:1179–86. doi: 10.1124/dmd.108.025916

Djuric Z, Bassis CM, Plegue MA, Ren J, Chan R, Sidahmed E, et al. Energy availability, macronutrient intake, and nutritional supplementation for improving exercise performance in endurance athletes. *Curr Sport Med Rep.* (2018) 17:215–23. doi: 10.1249/JSR.00000000000000494

Keurentjes J. A step towards personalized sports nutrition: carbohydrate intake during exercise. *Sports Med.* (2014) 44(Suppl. 1): S25–33. doi: 10.1007/s40279-014-0148-z

Margaretis NV, Paschalis V, Theodorou AA, Kyparos A, Nikolaidis MG. Antioxidants in personalized nutrition and exercise. *Adv Nutr.* (2018) 9:813–23. doi: 10.1093/advances/nmy052

Meinl W, Sczesny S, Brigelius-Flohe R, Blaut M, Glatt H. Impact of whole food consumption. *Curr Sport Med Rep.* (2018) 17:215–23. doi: 10.1249/JSR.00000000000000494

Selma MV, Espin JC, Tomas-Barberan FA. Interaction between phenolics and gut microbiota: role in human health. *J Agric Food Chem.* (2009) 57:6485–501. doi: 10.1021/jf902107d

Meinl W, Sczesny S, Brigelius-Flohe R, Blaut M, Glatt H. Impact of gut microbiota on intestinal and hepatic levels of phase 2 xenobiotic-metabolizing enzymes in the rat. *Drug Metab Dispos.* (2009) 37:1179–86. doi: 10.1124/dmd.108.025916

Djuric Z, Bassis CM, Plegue MA, Ren J, Chan R, Sidahmed E, et al. Colonic mucosal bacteria are associated with inter-individual variability in serum carotenoid concentrations. *J Acad Nutr Diet.* (2018) 118:606–16. e3. doi: 10.1016/j.jand.2017.09.013

Duck RP, Sartor E, Marquez-Magana L, Grosicki GJ, Bolter ND, Lee CM, et al. Gut microbiota composition is related to cardiorespiratory fitness in healthy young adults. *Int J Sport Nutr Exerc Metab.* (2018) 29:249–53. doi: 10.1123/ijsnem.2018-0024

Estaki M, Pither J, Raue Y, Xu J, Yang J, Harley IM, et al. Gut microbiota composition is related to cardiorespiratory fitness in healthy young adults. *Int J Sport Nutr Exerc Metab.* (2018) 29:249–53. doi: 10.1123/ijsnem.2018-0024
diversity and distinct metagenomic functions. Microbiome. (2016) 4:42. doi: 10.1186/s40168-016-0189-7

130. Yang Y, Shi Y, Wiklund P, Tan X, Wu N, Zhang X, et al. The association between cardiorespiratory fitness and gut microbiota composition in premenopausal women. Nutrients. (2017) 9:792. doi: 10.3390/nu9080792

131. Huang WC, Chen YH, Huang HL, Chu CC, Huang CC. Investigation of the effects of microbiota on exercise physiological adaption, performance, and energy utilization using a gnotobiotic animal model. Front Microbiol. (2019) 10:1906. doi: 10.3389/fmicb.2019.01906

132. Huang WC, Chu YS, Hsu YJ, Tsai TY, Wang MR, et al. Lactobacillus plantarum TWK10 supplementation improves exercise performance and increases muscle mass in mice. Nutrients. (2016) 8:205. doi: 10.3390/nu8040205

133. Huang WC, Hsu YJ, Li H, Kan NW, Chen YM, Lin JS, et al. Effect of Lactobacillus plantarum TWK10 on improving endurance performance in humans. Chin Physiol J. (2018) 61:163–70. doi: 10.4077/CJP.2018.BAH587

134. Jäger R, Shields KA, Lowery RP, De Souza EO, Partl JM, Hollmer C, et al. Probiotic Bacillus coagulans GBI-30, 6086 reduces exercise-induced muscle damage and increases recovery. Peer J. (2016) 4:e2276. doi: 10.7717/peerj.2276

135. Lamprecht M, Bogner S, Schippinger G, Steinbauer K, Fankhauser F, Salarkia N, Ghadamli L, Zaeri F, Rad LS. Effects of probiotic yogurt on cardiovascular, barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial. J Int Soc Sport Nutr. (2012) 9:45. doi: 10.1186/1550-2783-9-45

136. Martarelli D, Verdenelli MC, Scuri S, Cocchiioni M, Silvi S, Cecchinì C, Pyne DB, West NP, Cox AJ, Cripps AW. Probiotics supplementation for athletic performance: a systematic review. Ann Nutr Metab. (2017) 71:158–71. doi: 10.1159/000481452

137. Martarelli D, Verdenelli MC, Scuri S, Cocchiioni M, Silvi S, Cecchinì C, Pyne DB, West NP, Cox AJ, Cripps AW. Probiotics supplementation for athletic performance: a systematic review. Ann Nutr Metab. (2017) 71:158–71. doi: 10.1159/000481452

138. Nichols AW. Probiotics and athletic performance: the effects of sleep loss on exercise performance, and physiological and cognitive responses to exercise. Sports Med. (2015) 45:161–86. doi: 10.3389/fncel.2015.00944

139. Nichols AW. Probiotics and athletic performance: the effects of sleep loss on exercise performance, and physiological and cognitive responses to exercise. Sports Med. (2015) 45:161–86. doi: 10.3389/fncel.2015.00944

140. Ossinska L, Cotter PD, O’Sullivan O, Guinnane C. The potential impact of probiotics on the gut microbiome of athletes. Nutrients. (2019) 11:2270. doi: 10.3390/nu11082270

141. Owczarzak D, Kuczynska M, Zawadzki D, Bieniasz A, Problanska M, et al. Microbiome potentiates endurance exercise through intestinal acetate production. Am J Physiol Endocrinol Metab. (2016) 316:E956–66. doi: 10.1152/ajpendo.00510.2018

142. Owczarzak D, Kuczynska M, Zawadzki D, Bieniasz A, Problanska M, et al. Microbiome potentiates endurance exercise through intestinal acetate production. Am J Physiol Endocrinol Metab. (2016) 316:E956–66. doi: 10.1152/ajpendo.00510.2018

143. Tarnopolsky L, MacDougall J, Atkinson S, Tarnopolsky M, Sutton J. Gender differences in substrate for endurance exercise. J Appl Physiol. (1990) 68:302–8. doi: 10.1152/jappl.1990.68.1.302

144. Tarnopolsky L, MacDougall J, Atkinson S, Tarnopolsky M, Sutton J. Gender differences in substrate for endurance exercise. J Appl Physiol. (1990) 68:302–8. doi: 10.1152/jappl.1990.68.1.302

145. Tarnopolsky L, MacDougall J, Atkinson S, Tarnopolsky M, Sutton J. Gender differences in substrate for endurance exercise. J Appl Physiol. (1990) 68:302–8. doi: 10.1152/jappl.1990.68.1.302

146. Tarnopolsky L, MacDougall J, Atkinson S, Tarnopolsky M, Sutton J. Gender differences in substrate for endurance exercise. J Appl Physiol. (1990) 68:302–8. doi: 10.1152/jappl.1990.68.1.302
167. O’Toole PW, Claesson MJ. Gut microbiota: changes throughout the lifespan from infancy to elderly. *Int Dairy J.* (2010) 20:281–91. doi: 10.1016/j.idairyj.2009.11.010

168. Ni Lochlainn M, Bowyer R, Steves C. Dietary protein and muscle in aging people: the potential role of the gut microbiome. *Nutrients.* (2018) 10:929. doi: 10.3390/nu10070929

169. Shin HE, Kwak SE, Lee JH, Zhang D, Bae JH, Song W. Exercise, the gut microbiome, and frailty. *Ann Geriatr Med Res.* (2019) 23:105–14. doi: 10.4235/agmr.19.0014

170. Grosicki GJ, Fielding RA, Lustgarten MS. Gut microbiota contribute to age-related changes in skeletal muscle size, composition, and function: biological basis for a gut-muscle axis. *Calcified Tissue Int.* (2018) 102:433–42. doi: 10.1007/s00223-017-0345-5

171. Claesson MJ, Jeffery IB, Conde S, Power SE, O’connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. *Nature.* (2012) 488:178. doi: 10.1038/nature11319

172. Ticinesi A, Tana C, Nouvenne A. The intestinal microbiome and its relevance for functionality in older persons. *Curr Opin Clin Nutr Metab Care.* (2019) 22:4–12. doi: 10.1097/MCO.0000000000000521

173. Siddharth J, Chakrabarti A, Pannerec A, Karaz S, Morin-Rivron D, Masoodi M, et al. Aging and sarcopenia associate with specific interactions between gut microbes, serum biomarkers and host physiology in rats. *Aging.* (2017) 9:1698. doi: 10.18632/aging.101262

174. 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. Available online at: http://eir-isei.de/2019/eir-2019-084-article.pdf

175. Gubert C, Kong G, Renoir T, Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: implications for neurodegenerative diseases. *Neurobiol Dis.* (2019) 134:104621. doi: 10.1016/j.nbd.2019.104621

176. Schlegel P, Novotny M, Klimova B, Valis M. "Muscle-gut-brain axis": can physical activity help patients with Alzheimer’s disease due to microbiome modulation? *J Alzheimers Dis.* (2019) 71:861–78. doi: 10.3233/JAD-190460

177. Buiques C, Fernández-Garrido J, Pruimboom L, Hoogland A, Navarro-Martínez R, Martínez-Martínez M, et al. Effect of a prebiotic formulation on frailty syndrome: a randomized, double-blind clinical trial. *Int J Mol Sci.* (2016) 17:932. doi: 10.3390/ijms17060932

178. Walsh ME, Bhattacharya A, Sataranatarajan K, Qaisar R, Sloane L, Rahman MM, et al. The histone deacetylase inhibitor butyrate improves metabolism and reduces muscle atrophy during aging. *Aging Cell.* (2015) 14:957–70. doi: 10.1111/acel.12387

179. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Moullan N, Nicolet-dit-Félix AA, et al. Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. *Nat Med.* (2016) 22:879. doi: 10.1038/nm.4132

180. Andreux PA, Blanco-Bose W, Ryu D, Burdet F, Ibberson M, Arbischer P, et al. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nat Metab.* (2019) 1:595–603. doi: 10.1038/s42255-019-0073-4

**Conflict of Interest:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Copyright © 2020 Hughes. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*