

● Review

Exercise and gut microbiota: clinical implications for the feasibility of Tai Chi

Hidetaka Hamasaki

Hamasaki Clinic, 2-21-4 Nishida, Kagoshima 890-0046, Japan

ABSTRACT

Recent studies have shown exercise is associated with changes in the gut microbiota in humans as well as in experimental animals. Tai Chi is an exercise that integrates a martial art, deep breathing and meditation, and has various beneficial effects for health. This review summarizes current knowledge and recent literature on the association between exercise and gut microbiota, and explores the feasibility of Tai Chi for improving gut microbiota composition and function. PubMed/MEDLINE was used to search the English literature for the keywords exercise and gut microbiota. Fourteen relevant studies were identified. In humans, exercise increases the gut microbial diversity. However, the evidence for this association is weak, as previous studies were small-scale, non-controlled studies of short duration or cross-sectional design. In animals, exercise alters the composition of gut microbiota, with some studies suggesting exercise increases the Bacteroidetes/Firmicutes ratio. However, these results are controversial, partly because host genetics and physical fitness also influence gut microbiota. Furthermore, the intensity of exercise may play a key role in how exercise affects gut microbiota. Tai Chi is a moderate-intensity exercise that improves immune function and inflammation of the gut. Tai Chi may also affect gut microbiota through vagal modulation and mediating the hypothalamic-pituitary-adrenal axis. However, no studies have investigated the association between Tai Chi and gut microbiota. Well designed studies exploring the effects of Tai Chi on gut microbiota are needed.

Keywords: exercise; Tai Chi; gut microbiota; intestinal bacteria; Bacteroidetes; Firmicutes; complementary medicine; alternative medicine

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1 Introduction

Exercise is a structured and repetitive physical activity that increases metabolic activity via contraction of skeletal muscles. Exercise therapy is beneficial for obesity,^[1] cardiovascular risk factors,^[2] prevention of colon cancer,^[3] depression^[4] and chronic fatigue syndrome (CFS).^[5] Regular exercise also has extensive benefits for human cardiovascular, immunological and neural systems.^[6] Recently, Clark et al.^[7] reported that exercise increased the diversity of gut microbiota in humans. The human

gut microbiota comprises approximately 100 trillion microbes.^[8] Firmicutes (60%–65%), Bacteroidetes (20%–25%) and Proteobacteria (5%–10%) comprise the majority of human gut microbiota, though there is considerable inter-individual variability in microbial composition.^[9] Microbiota can be clustered into enterotypes, characterized as a ratio of *Bacteroides*, *Prevotella* or *Ruminococcus*, and are affected by long-term diet.^[10] Exercise may affect gut microbiota, though evidence for this association is limited. Moderate intensity exercise can improve immune function,^[11] oxidative stress and inflammation.^[12] Exercise

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Correspondence: Hidetaka Hamasaki; E-mail: hhamasaki78@gmail.com

also modulates the autonomic nervous system (vagal nerve activity), which is sometimes referred to as the “brain-gut axis.”^[13] Dysregulation of vagal nerve activity influences the development of depression,^[14] inflammatory bowel disease^[15] and irritable bowel syndrome.^[16] Recently, an experimental study has shown that prebiotic treatment can have antidepressant and anxiolytic effects.^[17] Further, mucosal inflammation in inflammatory bowel disease was associated with the reduction in gut microbiota diversity.^[18] Growing evidence suggests that alterations in gut microbiota are associated with the condition of irritable bowel syndrome.^[19] In patients with type 2 diabetes, long-term (12 months) moderate- to high-intensity aerobic and resistance exercise decreased inflammatory cytokines, such as interleukin (IL)-1 β , IL-6, tumor necrosis factor- α (TNF- α), interferon- γ , and high-sensitivity C-reactive protein, and increased anti-inflammatory cytokines (e.g., IL-4 and IL-10).^[20] Exercise may modulate gut microbiota by regulating intestinal immune function and vagal tone; however, the underlying mechanism is not clear.

Tai Chi is an ancient Chinese martial art, characterized by slow, smooth and fluid movements. All sorts of people can practice Tai Chi as exercise which is defined as a planned, structured and repetitive physical activity with the objective to improve physical fitness and overall health.^[21] The health effects of Tai Chi have been investigated, and Tai Chi is considered safe and effective for the management of metabolic diseases.^[22] Previous studies reported that Tai Chi had a favorable effect on immune function and oxidative stress.^[23,24] However, no studies have investigated the association between Tai Chi and gut microbiota.

This review summarizes current knowledge and discusses recent literature on the association between exercise and gut microbiota. The focus is on clinical research in humans and experimental animals that explore the underlying mechanisms by which exercise beneficially affects gastrointestinal function. In addition, the feasibility of Tai Chi in improving gut microbiota composition and function is discussed.

2 Methods

The English language literature was searched for exercise and gut microbiota using PubMed/MEDLINE, using the search terms “exercise OR physical activity,” “gut microbiota” and “intestinal flora.” The search returned 136 published articles, including human and experimental animal studies. Inclusion criteria for study selection were: (1) the subjects in human studies were adults aged from 20 to 60 years; (2) the animal study was a controlled trial; (3) aerobic exercise was the intervention; and (4) the study duration was more than

6 d. The titles and abstracts of identified articles were reviewed to determine their relevance. In total, 14 studies met the inclusion criteria.

3 Association between exercise and gut microbiota in humans

Evidence for the association between exercise and gut microbiota in humans is sparse. A study by Ehrenpreis et al.^[25] was the first study to indicate a positive association between exercise and gut microbiota, though this was not a direct relationship. That study included 12 participants (6 men and 6 women), and examined whether short-duration moderate-intensity exercise increased hydrogen production after lactulose consumption. Exercise sessions lasted 5 min and used a treadmill set to 10 km/h with a 20% incline. Participants performed exercise sessions 180 min after ingesting 10 g of lactulose. All participants completed resting and exercise trials, and breath hydrogen levels were measured. The areas under the curve for breath hydrogen concentration for time periods of 0–420 min and 180–420 min were compared between resting and exercise sessions. The mean area under the curve for breath hydrogen concentration from 0–420 min increased by 37% in the exercise trial compared with the resting trial, whereas no difference was observed between resting and exercise trials for 0–180 min. The mean area under the curve for breath hydrogen concentration from 180–420 min increased by 61% in the exercise trial compared with the resting trial. Those authors suggested that exercise enhanced lactulose catabolism by colonic bacteria due to induced motion of the colonic contents. They reported that exercise, in part, had a beneficial effect on colonic mucosa. Alterations in colonic microbiota are associated with chronic constipation. Some probiotics may be beneficial for constipation,^[26] suggesting that colonic motility is important for maintaining normal intestinal flora. Short-duration (5 min) moderate-intensity exercise may therefore benefit gut microbiota. Conversely, long-distance endurance exercise may cause mucosal erosions and ischemic colitis by reducing intestinal blood flow.^[27,28] However, there may be a threshold in the duration and intensity of exercise whereby colonic function can be improved.

Shukla et al.^[29] examined microbiomes in blood and stool samples collected before and after (15 min, 48 h, and 72 h) a maximal exercise challenge in patients with myalgic encephalomyelitis (ME)/CFS. Participants included 10 patients with ME/CFS and 10 healthy controls. They performed a maximal exercise test on a cycle ergometer, keeping the pedal rate at 60–70 revolutions per min during the exercise test. Participants started exercise with a 3-minute warm-up at 25 W; the work rate was then increased by 5 W per 20 s. The exercise test was finished



when the pedal rate could not be maintained because of exhaustion or other reasons. The relative abundance of Bacteroidetes was higher, and that of Firmicutes and Actinobacteria was lower in stool samples for the patient group than in the control. The relative abundance of seven of nine major taxa in the gut increased 72 h after exercise in the patient group, whereas only two of nine major taxa (e.g., Bacteroidetes) increased after exercise in controls. The bacterial load in the patient group might have increased during post-exercise malaise. In addition, that study assessed the potential for translocation of Firmicutes into blood after exercise. In healthy controls, the relative abundance of Firmicutes/Bacilli in blood samples increased 48 h and 72 h after exercise, but decreased in stool samples. In the patient group, the relative abundance of Firmicutes/Bacilli in blood samples increased 48 h after exercise but decreased 72 h after exercise; however, this did not change in stool samples. The relative abundance of the *Clostridium* IV and XIV clusters (Firmicutes) in blood samples rapidly increased 15 min after maximal exercise in the patient group, but not in controls. These bacteria might have been translocated into the blood from the gut by exercise. This suggests that in humans, strenuous exercise may alter gut microbiota by increasing the relative abundance of major phyla, and cause bacterial translocation into the bloodstream. Patients with conditions such as ME/CFS are more susceptible to these changes than healthy people, possibly associated with post-exertion malaise and worsening of symptoms after exercise.

Gut microbiota appear to contribute to body composition, emotional behavior, stress and pain through the neuroendocrine system.^[30] Dysbiosis in the gut may induce such deconditioning. However, a causal relationship could not be determined. Exercise stress itself may cause malaise, or the changes in gut microbiota through exercise may result in worsening of symptoms in patients with ME/CFS. Shukla et al.^[29] reported smaller changes in gut microbiota in healthy controls than in the patient group. Moreover, although the symptom responses to maximal exercise (evaluated by the Fatigue Visual Analogue Scale, McGill Pain Questionnaire and Profile of Mood States) increased immediately and 48 h after exercise in the patient group, they appeared to decrease below baseline after exercise in healthy controls. In contrast to the patient group, the relative abundance of Firmicutes/Bacilli in controls' stool samples decreased after exercise, which may be beneficial for clinical symptoms. However, we should note that maximal exercise affects gut microbiota, and changes in gut microbiota differed between patients with ME/CFS and healthy individuals.

A cross-sectional study also showed that exercise had a favorable impact on gut microbiota diversity.^[7] Participants in that study included 40 male rugby players

(athletes) and 46 healthy controls. Healthy controls were divided into low body mass index (BMI) ($\leq 25 \text{ kg/m}^2$) controls ($n = 23$) and high BMI ($> 28 \text{ kg/m}^2$) controls ($n = 23$). Fecal and blood samples were collected and deoxyribonucleic acid (DNA) was extracted from fecal samples. The microbiota compositions were analyzed by sequencing the 16S ribosomal ribonucleic acid genes. Dietary intake was evaluated with a detailed food frequency questionnaire, body composition was measured by dual-energy X-ray absorptiometry scans, and creatinine kinase levels were used to evaluate exercise levels. Creatinine kinase levels increased in athletes compared with controls, but athletes had lower inflammation levels than controls. The α -diversity of athlete microbiota was also higher than that of controls. Athlete fecal samples showed 22 phyla, 68 families and 113 genera, whereas approximately 10 phyla, 30 families, and 60 genera were detected in controls. Athletes had greater proportions of 48 taxa than high BMI controls, but *Bacteroides* were less abundant in athletes. Athletes also had higher proportions of 40 taxa and lower proportions of *Bacteroides*, Lactobacillaceae and *Lactobacillus* than low BMI controls. Athletes and low BMI controls had higher proportions of the genus *Akkermansia* than high BMI controls. Microbial diversity was positively associated with protein intake, creatinine kinase levels and urea. As expected, athlete dietary intake was higher than that of controls. In particular, protein (including whey protein) made up 22% of the total energy intake for athletes, but accounted for approximately 15% of controls' energy intake. That study suggested that a combination of exercise and diet influences gut microbial diversity. Higher exercise levels and protein consumption may enhance the diversity of microbiota. Microbiotas have dynamic interactions with the host immune system and diversity may influence the development of diseases.^[31]

Gut microbiota composition has been associated with inflammatory bowel syndrome^[18] and metabolic disease,^[32] and may improve health in older adults.^[33] Specifically, *Akkermansia muciniphila* (which was abundant in athletes) is correlated with improved metabolic health due to enhanced gut barrier function.^[34] Individuals who engage in regular high-intensity exercise may have healthy microbiota, leading to the improvement of metabolic diseases.

Table 1 summarizes published articles that have investigated the association between exercise and gut microbiota in humans.

4 Effects of exercise on gut microbiota in mice or rats

A number of animal studies have investigated the

Table 1 Association between exercise and gut microbiota in humans

Authors, year	Study design	Subjects	Exercise	Results (changes in microbiota)
Ehrenpreis et al., 2002 ^[25]	Before-after study	Twelve volunteers who engaged in regular exercise Age: 27 years; Gender: 6 men and 6 women; BMI: no description	A single bout of treadmill running at a speed of 10 km/h with a 20% incline for 5 min	Lactulose catabolism enhanced by colonic bacteria
Shukla et al., 2015 ^[29]	Before-after study with controls	Ten patients with ME/CFS and 10 healthy controls Age: (48.6 ± 10.5) years vs (46.5 ± 13.0) years; Gender: 2 men and 8 women in both groups; BMI: (23.9 ± 4.3) kg/m ² vs (24.6 ± 3.3) kg/m ²	Maximal exercise test on a cycle ergometer	Seven out of nine major taxa increased in patients with ME/CFS Two out of nine major taxa such as Bacteroidetes increased in controls
Clarke et al., 2014 ^[7]	Cross-sectional study	Forty elite athletes and 46 controls Age: (29 ± 4) years vs (29 ± 6) years; Gender: all men; BMI: (29.1 ± 3.0) kg/m ² vs (22.7 ± 1.7) kg/m ² (low BMI group) and (31.2 ± 3.0) kg/m ² (high BMI group)	Rugby	Bacterial diversity was higher in athletes than in controls

BMI: body mass index; ME: myalgic encephalomyelitis; CFS: chronic fatigue syndrome.

association between exercise and gut microbiota. Matsumoto et al.^[35] hypothesized that exercise-induced gastrointestinal motility and environment changes suppress tumor development, and examined the effects of voluntary running exercise on cecal microbiota in a rat model. Exercised rats had larger cecal tissue compared with control rats. Cecal *n*-butyrate concentrations were higher in exercised rats than controls, though other short-chain fatty acid concentrations did not differ. The cecal microbiota composition differed between exercised and sedentary rats, with the butyrate-producing bacteria (SM7/11 and T2-87) appearing in the exercise group. Butyrate serves as an energy source for colonocytes, playing an important role in maintaining intestinal homeostasis (including cancer suppression, immune modulation and reduction of inflammation and oxidative stress).^[36] Exercise may improve immunity, inflammation and oxidative stress via butyrate production. Previous studies have shown that obese individuals have an imbalance in gut microbiota (e.g., Bacteroidetes and Firmicutes).^[37-39] Several experimental animal studies found that exercise increased the Bacteroidetes/Firmicutes ratio in gut microbiota.^[40-42] Exercise increased the percentage of the phylum Bacteroidetes and decreased the percentages of the phyla Firmicutes and Actinobacteria in mice on both high- and low-fat diets.^[41] A 12-week exercise intervention appeared to increase the Bacteroidetes/Firmicutes ratio in mice, and changed various families (Table 2). Post-exercise fecal microbiota showed a higher Shannon's diversity index compared

with pre-exercise fecal microbiota in obese and non-obese Wistar and hypertensive rats.^[43] The number of operational taxonomic units was higher in post-exercise than in pre-exercise. After four weeks of moderate-intensity exercise, the genus *Allobaculum* in hypertensive rats, and genera *Aggregatibacter* and *Sutterella* in obese rats became abundant. However, the genus *Streptococcus* in Wistar rats, and genera *Aggregatibacter* and *Sutterella* in hypertensive rats were less abundant after exercise. This indicated that exercise alters gut microbiota differently according to host characteristics.^[43] In rats fed a high-fat diet, the α -diversity of cecal microbiota did not differ among an exercise group, a sedentary group and a group weight-matched to the exercise group, suggesting that exercise did not affect species richness. However, principal coordinates analysis demonstrated that the β -diversity differed between the exercise and sedentary groups, denoting a significant difference in microbiota.

Another study found voluntary wheel-running exercise reduced the relative abundance of Bacteroidetes in obese rats; however, this was not statistically significant.^[44] Conversely, exercise significantly increased the relative abundance of the family Streptococcaceae, and decreased the family S24-7 and an undefined genus from the Rikenellaceae family in cecal samples. In addition, exercise improved insulin resistance, increased spontaneous physical activity, and increased indicators of mitochondrial function in brown adipose tissue, independent of weight loss.^[44] Exercise has various modes, including intensity, frequency and duration, and its effects may differ depending on whether

**Table 2** Effects of exercise on gut microbiota in experimental animals

Authors, year	Animals	Exercise	Results (changes in microbiota)
Matsumoto et al., 2008 ^[35]	Fourteen male 6-week-old Wistar rats	Voluntary wheel running for 5 weeks	Butyrate concentrations↑ Butyrate-producing bacteria (SM7/11 and T2-87) ↑
Evans et al., 2014 ^[41]	Forty-eight male 5-week-old C57BL/6 mice	Voluntary wheel running for 12 weeks	The phylum: Bacteroidetes/Firmicutes ratio↑, Bacteroidetes↑, Firmicutes↓, and Actinobacteria↓ The family: Lachnospiraceae↑, Ruminococcaceae↑, Lactobacillaceae↓, Turicibacteraceae↓, Erysipelotrichaceae↓, and S24-7↑
Petritz et al., 2014 ^[43]	Fifteen 18-week-old rats (5 obese Zucker rats (Obese rats), 5 Wistar-Kyoto rats with hypertension (hypertensive rats), and 5 Wistar rats (controls))	Structured running exercise: 30 min/d, 5 d/week for 4 weeks	The genus: <i>Allobaculum</i> ↑ in hypertensive rats <i>Aggregatibacter</i> ↑ and <i>Suturella</i> ↑ in obese rats <i>Streptococcus</i> ↓ in controls <i>Aggregatibacter</i> ↓ and <i>Suturella</i> ↓ in hypertensive rats
Welly et al., 2016 ^[44]	Thirty male 4-week-old obese rats	Voluntary wheel running for 14–16 weeks	The phylum: Bacteroidetes ↘ The family: Streptococcaceae↑, S24-7↓, and an undefined genus in Rikenellaceae↓
Allen et al., 2015 ^[45]	Twenty-nine male 6-week-old C57BL/6J mice	Voluntary wheel running vs forced treadmill running, for 6 weeks	Bacterial richness↓ in voluntary wheel running mice The phylum: Tenericutes↑, and Proteobacteria↑ in forced treadmill running mice No differences in Bacteroidetes and Firmicutes were observed between groups
Denou et al., 2016 ^[46]	Sixteen male 8-week-old mice	High-intensity interval training for 6 weeks	The phylum: Bacteroidetes/Firmicutes ratio↑
Liu et al., 2015 ^[47]	Thirty ovariectomized female 26-week-old rats	Voluntary wheel running for 11 weeks	The phylum: Bacteroidetes→, Bacteroidetes/Firmicutes ratio→, Firmicutes↓ in low-capacity running rats, and Firmicutes↑ in high-capacity running rats The family: Ruminococcaceae↑, Christensenellaceae↓, Proteobacteria↑, Cyanobacteria↑, Helicobacteraceae↑, Desulfovibrionaceae↑, and undefined family in the Cyanobacteria phylum↑ in low-capacity running rats Ruminococcaceae↑, Christensenellaceae↑, Proteobacteria↓, Cyanobacteria↓, Helicobacteraceae↓, Desulfovibrionaceae↓, undefined family in the Cyanobacteria phylum↓, and <i>Helicobacter</i> ↓ in high-capacity running rats
Campbell et al., 2016 ^[48]	Thirty-six male 6-week-old C57BL/6NTac mice	Voluntary wheel running for 12 weeks	The genus: <i>Allobaculum</i> ↑, and <i>Clostridium</i> ↑ <i>Faecalibacterium prausnitzii</i> emerged in the exercise mice
Queipo-Ortuño et al., 2013 ^[40]	Forty male 5-week-old Sprague-Dawley rats	Voluntary wheel running for 6 d	The phylum: Actinobacteria↑, Bacteroidetes↑, and Firmicutes↓ The genus: <i>Blautia coccoides-Eubacterium rectale</i> group↑, <i>Lactobacillus</i> ↑, <i>Clostridium</i> ↓, <i>Prevotella</i> ↓, <i>Bacteroides</i> ↓, and <i>Enterococcus</i> ↓
Kang et al., 2014 ^[49]	Forty male 8-week-old C57BL/6J mice	Structured running exercise: 1 h/d, 5 d/week for 16 weeks	The phylum: Bacteroidetes↓, Tenericutes↓, and Firmicutes↑
Lambert et al., 2015 ^[50]	Thirty-nine male 6-week-old db/db (C57BJ/KsJ-leprdb/leprdb) and db/+ mice	Low-intensity treadmill running, 5 d/week for 6 weeks	The genus: <i>Lactobacillus</i> spp. ↑, <i>Clostridium leptum</i> ↑, and <i>Bacteroides/Prevotella</i> ↓

↘ : a tendency of decreasing in microbiota; →: no change in microbiota; ↑: means increase; ↓: means decrease.

exercise is spontaneous or compulsory. Interestingly, 6-week voluntary wheel running reduced bacterial richness (α -diversity, Chao1) in both fecal and cecal contents compared with forced treadmill running.^[45] Although the phyla Bacteroidetes and Firmicutes were not altered by either voluntary or forced exercise, the phyla Tenericutes and Proteobacteria were increased by forced treadmill running compared with voluntary wheel running. Exercise altered eight bacterial genera, particularly, *Dorea*, *Anaerotruncus* and *Turicibacter*, and was associated with immune function.^[45]

Denou et al.^[46] investigated the effect of high-intensity interval training on gut microbiota in diet-induced obese mice. High-intensity interval training improved insulin tolerance without altering body and fat mass. This type of exercise increased the α -diversity of colon microbiota and the Bacteroidetes/Firmicutes ratio in the cecum. Fecal sample analysis revealed that only the genus *Lactococcus* decreased 1 h after exercise. However, this change disappeared 1 week after exercise, suggesting that the changes in microbiota were not caused by the chronic effect of exercise. High-intensity interval training also increased the fecal microbiota related to the citrate cycle, glycan biosynthesis and carbon fixation.^[46] A study using ovariectomized female rats (providing a model of human menopause) indicated that exercise differentially affected gut microbial communities between individuals with high- and low-aerobic capacities.^[47] Voluntary exercise over 11 weeks decreased the relative abundance of Firmicutes in low-capacity running rats, whereas this was increased in high capacity running rats. Exercise increased the relative abundance of Proteobacteria and Cyanobacteria in low-capacity running rats, but decreased it in high-capacity running rats. However, the relative abundance of Bacteroidetes and the Bacteroidetes/Firmicutes ratio did not differ between the groups. Exercise also differently altered cecal bacterial families and genera in the low- and high-capacity running groups (Table 2). Recently, the effects of exercise on duodenal and ileal intestinal tissues and gut microbiota have been investigated in mice.^[48] Free running wheel exercise for 12 weeks reduced cyclooxygenase-2 expression in obese mice. Exercise also reduced intestinal inflammation and protected duodenal morphology. *Allobaculum* spp. and *Clostridium* spp. were abundant, but *Faecalibacterium prausnitzii* was only detected in exercised mice.

In an activity-based anorexia rat model, Queipo-Ortuño et al.^[40] evaluated gut microbiota composition and its association with physical activity and appetite-regulating hormones such as leptin and ghrelin. In activity-based anorexia rats, the phyla Actinobacteria, Bacteroidetes and Firmicutes decreased, whereas the phylum Proteobacteria increased. Actinobacteria and Bacteroidetes increased

and Firmicutes decreased in the exercise group. Exercise appeared to increase the *Blautia coccooides-Eubacterium* rectale group as well as *Lactobacillus*, and decrease *Clostridium*, *Prevotella*, *Bacteroides* and *Enterococcus*. In addition, serum leptin levels were positively correlated with the quantity of *Bifidobacterium* and *Lactobacillus*. Serum ghrelin levels were inversely correlated with the quantity of *Bifidobacterium*, *Lactobacillus*, and the *B. coccooides-Eubacterium* rectale group, and positively correlated with the quantity of *Bacteroides* and *Prevotella*. This indicated that exercise increased Bacteroidetes and decreased Firmicutes; however, inconsistent results have been reported.

Kang et al.^[49] reported that exercise alone decreased the relative abundance of Bacteroidetes and Tenericutes and increased Firmicutes; however, exercise was unable to counteract the effects of a high-fat diet on gut microbiota. Moreover, a high-fat diet caused anxiety in mice; exercise did not reduce this diet-induced anxiety, though it improved cognition. Lambert et al.^[50] also showed that the cecal abundance of total bacteria and Enterobacteriaceae was lower with exercise in db/db mice. *Bifidobacterium* spp. increased in exercised mice without diabetes; however, it was lower with exercise in diabetic dyslipidemia (db/db) mice. Exercise was associated with increased Firmicutes (*Lactobacillus* spp. and *Clostridium leptum*) and decreased *Bacteroides/Prevotella*. Interestingly, voluntary exercise also attenuated polychlorinated biphenyl-induced changes in gut microbiota, such as decreasing Proteobacteria in mice.^[51] Exercise may protect against chemical toxicity by changing the gut microbiota.

5 Clinical implications

Obesity is associated with a decreased Bacteroidetes/Firmicutes ratio in both humans and mice.^[37-39,52] Weight loss through exercise or diet therapy may alter gut microbiota, though the mechanism by which exercise promotes gastrointestinal health has not been clarified.^[53] Several experimental animal studies suggested that exercise increased the Bacteroidetes/Firmicutes ratio. However, the results are controversial. The current literature does not conclude specifically which bacteria are increased or decreased by exercise. In human studies, it is unclear whether exercise confers benefits for health via altering gut microbiota, as there is a lack of well designed and prospective controlled trials. Diet modifies the composition and function of gut microbiota,^[54] making it difficult to investigate the effect of exercise alone in human studies. The present detailed review of animal studies also highlighted two issues. In addition to dietary intake, the host's



genetic background and physical fitness influence gut microbiota composition. The complex interactions among host genetics, diet, exercise, individual habits and other environmental factors create variations in gut microbiota, which plays a role in the development of obesity and diabetes.^[55] In animals, the host genetic background may shape the gut microbiota.^[56] However, an exploratory study investigating gut microbiota in a healthy dichorionic triplet set showed that host genetics played a role in individual gut microbiota composition at the first month, and environmental factors became major determinants at the 12th months.^[57] The influence of host genetics on gut microbiota may be more easily attenuated by environmental factors in humans than in animals. Moreover, as Liu et al.^[47] showed in their comparative study with high- and low-aerobic capacity rats, the host's physical fitness may modulate the effects of exercise on gut microbiota. These human and animal study results should be interpreted carefully, given that various confounding factors cannot be eliminated. However, it is likely that exercise alters the diversity of gut microbiota. Exercise, as long as it is not so intense that it impairs intestinal function or causes gastrointestinal ischemia^[58–60] (moderate- to high-intensity and forced exercise), increased microbial diversity, whereas voluntary exercise did not.^[45,46]

Considering that the microbial diversity of highly trained athletes increased relative to controls,^[7] cultivating gut microbiota richness with exercise requires exertion above a certain level of intensity (probably moderate to vigorous). High-intensity exercise increased the Bacteroidetes/Firmicutes ratio, whereas low-intensity exercise increased the phylum Firmicutes.^[50] This indicated that the intensity of exercise may be crucial in altering gut microbiota. However, the required intensity, frequency and duration of exercise to improve gut microbiota are unknown. Current evidence is inconclusive.

6 Feasibility of Tai Chi

6.1 Tai Chi as a holistic integrative medicine

Tai Chi has beneficial effects on cardiovascular risks, immune function, pain syndromes and psychological states as well as physical fitness.^[61] A recent systematic review and meta-analysis has shown that Tai Chi improves blood pressure, serum lipid profile, physical function and depressed mood in patients with cardiovascular disease.^[62] In addition, Tai Chi has a beneficial effect on mobility and balance in patients with stroke^[63] and Parkinson's disease.^[64] Tai Chi may also relieve disease- and treatment-related symptoms in cancer patients.^[65] A holistic integrative view, instead of specialization and subdivision, is necessary for the

future development of medicine,^[66] and Tai Chi has the potential to become such a holistic therapy. The 3-month peer-assisted Tai Chi program strengthens social network and improves psychosocial health in older Chinese individuals who are socially isolated.^[67] A systematic review of randomized controlled trials has shown that Tai Chi appears to be effective for improving health-related quality of life in patients with musculoskeletal disorders, respiratory diseases and cardiovascular disease.^[68] Growing evidence suggests that bidirectional interactions between the gut microbiota and neuropsychiatric disorders exist.^[69] Although the underlying mechanism is not clear, psychosociological effects of Tai Chi can be associated with the change in gut microbiota.

6.2 Tai Chi and gut microbiota

Tai Chi is certainly an effective mode of exercise for health benefits. Over a decade ago, a systematic review showed that Tai Chi has physiological benefits, such as improving balance control, flexibility and cardiovascular fitness in older individuals with chronic diseases.^[70] A recent systematic review and meta-analysis has given new insight into the physiological benefits of Tai Chi. Tai Chi improves physical performance including 6-minute walking distance and knee extensor strength in patients with cancer, osteoarthritis, heart failure and chronic obstructive pulmonary disease.^[71] Tai Chi also improves cardiorespiratory fitness in healthy individuals as well as patients with chronic diseases.^[72] Estaki et al.^[73] showed that cardiorespiratory fitness is associated with increased microbial diversity and butyrate production; thus, Tai Chi may modulate gut microbiota via improving cardiorespiratory fitness. During a Tai Chi session, oxygen consumption is at 55% of peak consumption and the heart rate is 58% of the reserve;^[74] therefore, Tai Chi is classified as a moderate-intensity exercise. Exercise stimulates gut microbiota diversity, and may develop the gut immune system by enhancing the sensitivity of Toll-like receptors that recognize bacterial DNA.^[75] As a pure moderate-intensity exercise, Tai Chi may improve gut immune function by a similar mechanism. There are a number of published studies that investigate the effects of Tai Chi on immunity, although these studies do not discuss the gut immune system. Mind-body therapies including Tai Chi, Qigong and Yoga, which integrate exercise, deep breathing and meditation, increase the immune response to vaccination.^[76] A systematic review showed that Tai Chi improves cell-mediated immunity (i.e., the number of T-lymphocytes).^[23] Furusawa et al.^[77] showed that microbial-derived butyrate regulated the differentiation of regulatory T cells in mice. Regular Tai Chi exercise for 12 weeks increases the ratio of T helper to suppressor cells and CD4CD25 regulatory T cells,^[78] and improves helper T cell function in patients with type 2 diabetes.^[79] A 16-week Tai

Chi exercise also decreases a complement regulatory protein (CD55) in T cell immunity among post-surgical lung cancer survivors.^[80] Moreover, Tai Chi increases the number of circulating myeloid dendritic cells, linking innate and adoptive immunity.^[81] These, together with the study by Matsumoto et al.^[35], suggest that Tai Chi may improve gut immune function by increasing butyrate-producing bacteria. Moreover, Tai Chi also decreases oxidative stress in middle-aged individuals^[82] and obese patients with type 2 diabetes.^[22] Exercise has a demonstrated anti-inflammatory effect mediated by various myokines, such as IL-6, TNF- α and IL-10,^[83] however, Tai Chi may involve other potential effects on inflammation related to gut microbiota. The brain-gut axis, including the central nervous system, the autonomic nervous system, the stress system (hypothalamic-pituitary-adrenal (HPA) axis) and the intestinal immune system, has a key role in modulating psychophysiological vulnerability of patients with inflammatory bowel disease.^[84] Recently, crosstalk between the HPA axis and gut microbiota has been suggested. In animal studies, a social stressor decreased the relative abundance of the genus *Bacteroidetes*, and increased the relative abundance of the genus *Clostridium* in the cecum.^[85] Gut microbiota is linked to the development of the HPA axis; therefore, the interaction between stress and HPA response may alter gut microbiota composition.^[75] Tai Chi also significantly reduces salivary cortisol levels in healthy individuals^[86] and cancer survivors.^[87] Tai Chi may therefore benefit gut microbiota by decreasing stress.^[61] In addition, several studies support the role of Tai Chi in enhancing vagal modulation, decreasing sympathetic modulation and achieving a balance with parasympathetic dominance, resulting in increased heart rate variability.^[88] Autonomic nervous system modulation has important effects on the quality of the intestinal mucus layer, where most enteric bacteria reside, along with epithelial mechanisms associated with the gut immune system.^[29] The vagus nerve integrates the inflammatory reflex, which controls the immune response and inflammation; it also regulates heart rate, gastrointestinal motility and other visceral functions.^[89] Inflammatory diseases, including inflammatory bowel disease, are associated with autonomic dysfunction.^[89] Ott et al.^[18] reported that *Bacteroides*, *Eubacterium* and *Lactobacillus* species were reduced in patients with inflammatory bowel disease. This alteration of gut microbiota by mucosal inflammation reflected an imbalance of the complex microbial ecosystem and impairment of the mucosal barrier^[18] and decreased vagal nerve function. Tai Chi can alter gut microbiota through parasympathetic (vagus) nerve stimulation and mediating the HPA system (Figure 1).

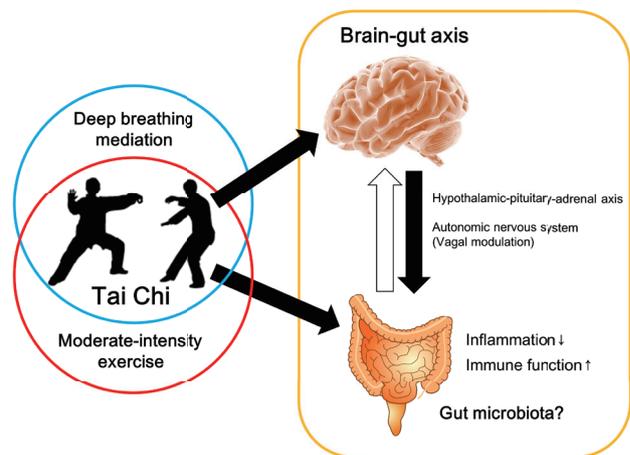


Figure 1 The crosstalk between Tai Chi and brain-gut axis. Moderate-intensity exercise may improve gut function. Tai Chi may also improve gut immune function and inflammation through mediating the hypothalamic-pituitary-adrenal axis and vagal modulation. The association between Tai Chi and gut microbiota remains unknown.

7 Limitation of this review

Current evidence regarding the link between exercise and gut microbiota in humans is sparse, and the feasibility of Tai Chi to induce changes in human gut microbiota may be speculative.

8 Summary

Current evidence suggests that exercise may increase the diversity of gut microbiota and alter the composition of microbiota at phylum, family and genus levels. However, the specific bacteria constantly altered by exercise have not been identified, partly because diet, genetic backgrounds and other environmental factors also affect composition of gut microbiota. The optimal intensity, frequency and duration of exercise for beneficial effects on gut microbiota are also unknown. “Exercise and gut microbiota” is an intriguing field; however, evidence in humans is limited. Further studies, preferably controlled, prospective studies are needed. Tai Chi has potential to improve gut immune function and inflammation by altering gut microbiota in humans. Tai Chi is a moderate-intensity exercise that integrates a soft style martial art, deep breathing and mediation. Tai Chi decreases stress by mediating the HPA axis and increasing vagal modulation, which may improve gut microbiota composition and function. However, the association between Tai Chi and gut microbiota has not yet been investigated. This is a challenge for the future.



9 Competing interests

The author declares no conflicts of interest.

REFERENCES

- 1 Thorogood A, Mottillo S, Shimony A, Filion KB, Joseph L, Genest J, Pilote L, Poirier P, Schiffrin EL, Eisenberg MJ. Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. *Am J Med.* 2011; 124(8): 747–755.
- 2 Chudyk A, Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. *Diabetes Care.* 2011; 34(5): 1228–1237.
- 3 Robsahm TE, Aagnes B, Hjartåker A, Langseth H, Bray FI, Larsen IK. Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies. *Eur J Cancer Prev.* 2013; 22(6): 492–505.
- 4 Kvam S, Kleppe CL, Nordhus IH, Hovland A. Exercise as a treatment for depression: a meta-analysis. *J Affect Disord.* 2016; 202: 67–86.
- 5 Larun L, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev.* 2016; (6): CD003200.
- 6 Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. *Cell.* 2014; 159(4): 738–749.
- 7 Clarke SF, Murphy EF, O’Sullivan O, Lucey AJ, Humphreys M, Hogan A, Hayes P, O’Reilly M, Jeffery IB, Wood-Martin R, Kerins DM, Quigley E, Ross RP, O’Toole PW, Molloy MG, Falvey E, Shanahan F, Cotter PD. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut.* 2014; 63(12): 1913–1920.
- 8 Rosenbaum M, Knight R, Leibel RL. The gut microbiota in human energy homeostasis and obesity. *Trends Endocrinol Metab.* 2015; 26(9): 493–501.
- 9 Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature.* 2012; 486(7402): 207–214.
- 10 Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011; 334(6052): 105–108.
- 11 Cook MD, Allen JM, Pence BD, Wallig MA, Gaskins HR, White BA, Woods JA. Exercise and gut immune function: evidence of alterations in colon immune cell homeostasis and microbiome characteristics with exercise training. *Immunol Cell Biol.* 2016; 94(2): 158–163.
- 12 Sallam N, Laher I. Exercise modulates oxidative stress and inflammation in aging and cardiovascular diseases. *Oxid Med Cell Longev.* 2016; 2016: 7239639.
- 13 O’Mahony SM, Clarke G, Dinan TG, Cryan JF. Early-life adversity and brain development: is the microbiome a missing piece of the puzzle? *Neuroscience.* 2017; 342: 37–54.
- 14 Grimonprez A, Raedt R, Baeken C, Boon P, Vonck K. The antidepressant mechanism of action of vagus nerve stimulation: evidence from preclinical studies. *Neurosci Biobehav Rev.* 2015; 56: 26–34.
- 15 Pellissier S, Dantzer C, Mondillon L, Trocme C, Gauchez AS, Ducros V, Mathieu N, Toussaint B, Fournier A, Canini F, Bonaz B. Relationship between vagal tone, cortisol, TNF- α , epinephrine and negative affects in Crohn’s disease and irritable bowel syndrome. *PloS One.* 2014; 9(9): e105328.
- 16 Liu Q, Wang EM, Yan XJ, Chen SL. Autonomic functioning in irritable bowel syndrome measured by heart rate variability: a meta-analysis. *J Dig Dis.* 2013; 14(12): 638–646.
- 17 Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, Stanton C, Dinan TG, Cryan JF. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biol Psychiatry.* 2017; Epub ahead of print.
- 18 Ott SJ, Musfeldt M, Wenderoth DF, Hampe J, Brant O, Fölsch UR, Timmis KN, Schreiber S. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut.* 2004; 53(5): 685–693.
- 19 Ringel Y. The gut microbiome in irritable bowel syndrome and other functional bowel disorders. *Gastroenterol Clin North Am.* 2017; 46(1): 91–101.
- 20 Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, Fallucca S, Alessi E, Letizia C, Jimenez A, Fallucca F, Pugliese G. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis.* 2010; 20(8): 608–617.
- 21 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep.* 1985; 100(2): 126–131.
- 22 Hamasaki H. Martial arts and metabolic diseases. *Sports.* 2016; 4: 28.
- 23 Chen SC, Ueng KC, Lee SH, Sun KT, Lee MC. Effect of T’ai chi exercise on biochemical profiles and oxidative stress indicators in obese patients with type 2 diabetes. *J Altern Complement Med.* 2010; 16(11): 1153–1159.
- 24 Shi N, Han X, Yu W, Wang L, Lu A. Adoption in China of clinical practice guidelines for hypertension using traditional Chinese medical approaches: a literature review based on clinical studies. *J Altern Complement Med.* 2013; 19(1): 1–8.
- 25 Ehrenpreis ED, Swamy RS, Zaitman D, Noth I. Short duration exercise increases breath hydrogen excretion after lactulose ingestion: description of a new phenomenon. *Am J Gastroenterol.* 2002; 97(11): 2798–2802.
- 26 Quigley EM. The enteric microbiota in the pathogenesis and management of constipation. *Best Pract Res Clin Gastroenterol.* 2011; 25(1): 119–126.

- 27 Moses FM. Exercise-associated intestinal ischemia. *Curr Sports Med Rep.* 2005; 4(2): 91–95.
- 28 Choi SC, Choi SJ, Kim JA, Kim TH, Nah YH, Yazaki E, Evans DF. The role of gastrointestinal endoscopy in long-distance runners with gastrointestinal symptoms. *Eur J Gastroenterol Hepatol.* 2001; 13(9): 1089–1094.
- 29 Shukla SK, Cook D, Meyer J, Vernon SD, Le T, Clevidence D, Robertson CE, Schrodi SJ, Yale S, Frank DN. Changes in gut and plasma microbiome following exercise challenge in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *PLoS One.* 2015; 10(12): e0145453.
- 30 Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. *J Clin Invest.* 2015; 125(3): 926–938.
- 31 Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell.* 2012; 148(6): 1258–1270.
- 32 Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P, Li J, Burgdorf K, Grarup N, Jørgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clément K, Doré J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker JD, Raes J, Hansen T; MetaHIT consortium, Bork P, Wang J, Ehrlich SD, Pedersen O. Richness of human gut microbiome correlates with metabolic markers. *Nature.* 2013; 500(7464): 541–546.
- 33 Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris HM, Coakley M, Lakshminarayanan B, O'Sullivan O, Fitzgerald GF, Deane J, O'Connor M, Harnedy N, O'Connor K, O'Mahony D, van Sinderen D, Wallace M, Brennan L, Stanton C, Marchesi JR, Fitzgerald AP, Shanahan F, Hill C, Ross RP, O'Toole PW. Gut microbiota composition correlates with diet and health in the elderly. *Nature.* 2012; 488(7410): 178–184.
- 34 Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A.* 2013; 110(22): 9066–9071.
- 35 Matsumoto M, Inoue R, Tsukahara T, Ushida K, Chiji H, Matsubara N, Hara H. Voluntary running exercise alters microbiota composition and increases *n*-butyrate concentration in the rat cecum. *Biosci Biotechnol Biochem.* 2008; 72(2): 572–576.
- 36 Leonel AJ, Alvarez-Leite JI. Butyrate: implications for intestinal function. *Curr Opin Clin Nutr Metab Care.* 2012; 15(5): 474–479.
- 37 Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature.* 2006; 444(7122): 1022–1023.
- 38 Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature.* 2006; 444(7122): 1027–1031.
- 39 Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A.* 2005; 102(31): 11070–11075.
- 40 Queipo-Ortuño MI, Seoane LM, Murri M, Pardo M, Gomez-Zumaquero JM, Cardona F, Casanueva F, Tinahones FJ. 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(5): e65465.
- 41 Evans CC, LePard KJ, Kwak JW, Stancukas MC, Laskowski S, Dougherty J, Moulton L, Glawe A, Wang Y, Leone V, Antonopoulos DA, Smith D, Chang EB, Ciancio MJ. Exercise prevents weight gain and alters the gut microbiota in a mouse model of high fat diet-induced obesity. *PLoS One.* 2014; 9(3): e92193.
- 42 Mika A, Van Treuren W, González A, Herrera JJ, Knight R, Fleshner M. Exercise is more effective at altering gut microbial composition and producing stable changes in lean mass in juvenile versus adult male F344 rats. *PLoS One.* 2015; 10(5): e0125889.
- 43 Petriz BA, Castro AP, Almeida JA, Gomes CP, Fernandes GR, Kruger RH, Pereira RW, Franco OL. Exercise induction of gut microbiota modifications in obese, non-obese and hypertensive rats. *BMC Genomics.* 2014; 15: 511.
- 44 Welly RJ, Liu TW, Zidon TM, Rowles JL 3rd, Park YM, Smith TN, Swanson KS, Padilla J, Vieira-Potter VJ. Comparison of diet versus exercise on metabolic function and gut microbiota in obese rats. *Med Sci Sports Exerc.* 2016; 48(9): 1688–1698.
- 45 Allen JM, Berg Miller ME, Pence BD, Whitlock K, Nehra V, Gaskins HR, White BA, Fryer JD, Woods JA. Voluntary and forced exercise differentially alters the gut microbiome in C57BL/6J mice. *J Appl Physiol (1985).* 2015; 118(8): 1059–1066.
- 46 Denou E, Marcinko K, Surette MG, Steinberg GR, Schertzer JD. High-intensity exercise training increases the diversity and metabolic capacity of the mouse distal gut microbiota during diet-induced obesity. *Am J Physiol Endocrinol Metab.* 2016; 310(11): E982–E993.
- 47 Liu TW, Park YM, Holscher HD, Padilla J, Scroggins RJ, Welly R, Britton SL, Koch LG, Vieira-Potter VJ, Swanson KS. Physical activity differentially affects the cecal microbiota of ovariectomized female rats selectively bred for high and low aerobic capacity. *PLoS One.* 2015; 10(8): e0136150.
- 48 Campbell SC, Wisniewski PJ, Noji M, McGuinness LR, Häggblom MM, Lightfoot SA, Joseph LB, Kerkhof LJ. The effect of diet and exercise on intestinal integrity and microbial diversity in mice. *PLoS One.* 2016; 11(3): e0150502.
- 49 Kang SS, Jeraldo PR, Kurti A, Miller ME, Cook MD, Whitlock K, Goldenfeld N, Woods JA, White BA, Chia N, Fryer JD. Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. *Mol Neurodegener.* 2014; 9: 36.
- 50 Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise training modifies gut microbiota in normal and diabetic mice. *Appl Physiol Nutr Metab.* 2015; 40(7): 749–752.
- 51 Choi JJ, Eum SY, Rampersaud E, Daunert S, Abreu MT, Toborek M. Exercise attenuates PCB-induced changes in the mouse gut microbiome. *Environ Health Perspect.* 2013;



- 121(6): 725–730.
- 52 Tehrani AB, Nezami BG, Gewirtz A, Srinivasan S. Obesity and its associated disease: a role for microbiota? *Neurogastroenterol Motil.* 2012; 24(4): 305–311.
- 53 Cronin O, Molloy MG, Shanahan F. Exercise, fitness, and the gut. *Curr Opin Gastroenterol.* 2016; 32(2): 67–73.
- 54 Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. *Nature.* 2016; 535(7610): 56–64.
- 55 Ussar S, Fujisaka S, Kahn CR. Interactions between host genetics and gut microbiome in diabetes and metabolic syndrome. *Mol Metab.* 2016; 5(9): 795–803.
- 56 Dąbrowska K, Witkiewicz W. Correlations of host genetics and gut microbiome composition. *Front Microbiol.* 2016; 7: 1357.
- 57 Murphy K, O’Shea CA, Ryan CA, Dempsey EM, O’Toole PW, Stanton C, Ross RP. The gut microbiota composition in dichorionic triplet sets suggests a role for host genetic factors. *PLoS One.* 2015; 10(4): e0122561.
- 58 Rehner NJ, Smets A, Reynaert H, Goes E, De Meirleir K. Effect of exercise on portal vein blood flow in man. *Med Sci Sports Exerc.* 2001; 33(9): 1533–1537.
- 59 van Wijck K, Lenaerts K, Grootjans J, Wijnands KA, Poeze M, van Loon LJ, Dejong CH, Buurman WA. Physiology and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention. *Am J Physiol Gastrointest Liver Physiol.* 2012; 303(2): G155–G168.
- 60 ter Steege RW, Geelkerken RH, Huisman AB, Kolkman JJ. Abdominal symptoms during physical exercise and the role of gastrointestinal ischaemia: a study in 12 symptomatic athletes. *Br J Sports Med.* 2012; 46(13): 931–935.
- 61 Field T. Tai Chi research review. *Complement Ther Clin Pract.* 2011; 17(3): 141–146.
- 62 Wang XQ, Pi YL, Chen PJ, Liu Y, Wang R, Li X, Chen BL, Zhu Y, Yang YJ, Niu ZB. Traditional Chinese exercise for cardiovascular diseases: systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2016; 5(3): e002562.
- 63 Chen BL, Guo JB, Liu MS, Li X, Zou J, Chen X, Zhang LL, Yue YS, Wang XQ. Effect of traditional Chinese exercise on gait and balance for stroke: a systematic review and meta-analysis. *PLoS One.* 2015; 10(8): e0135932.
- 64 Ni X, Liu S, Lu F, Shi X, Guo X. Efficacy and safety of Tai Chi for Parkinson’s disease: a systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2014; 9(6): e99377.
- 65 Zeng Y, Luo T, Xie H, Huang M, Cheng AS. Health benefits of qigong or tai chi for cancer patients: a systematic review and meta-analyses. *Complement Ther Med.* 2014; 22(1): 173–186.
- 66 Fan D. Holistic integrative medicine: toward a new era of medical advancement. *Front Med.* 2017; Epub ahead of print.
- 67 Chan AW, Yu DS, Choi KC, Chan HY, Wong EM. Effects of a peer-assisted tai-chi-qigong programme on social isolation and psychological wellbeing in Chinese hidden elders: a pilot randomised controlled trial. *Lancet.* 2016; 388(Suppl 1): S23.
- 68 Li G, Yuan H, Zhang W. Effects of Tai Chi on health related quality of life in patients with chronic conditions: a systematic review of randomized controlled trials. *Complement Ther Med.* 2014; 22(4): 743–755.
- 69 Rieder R, Wisniewski PJ, Alderman BL, Campbell SC. Microbes and mental health: a review. *Brain Behav Immun.* 2017; Epub ahead of print.
- 70 Wang C, Collet JP, Lau J. The effect of Tai Chi on health outcomes in patients with chronic conditions: a systematic review. *Arch Intern Med.* 2004; 164(5): 493–501.
- 71 Chen YW, Hunt MA, Campbell KL, Peill K, Reid WD. The effect of Tai Chi on four chronic conditions—cancer, osteoarthritis, heart failure and chronic obstructive pulmonary disease: a systematic review and meta-analyses. *Br J Sports Med.* 2016; 50(7): 397–407.
- 72 Zheng G, Li S, Huang M, Liu F, Tao J, Chen L. The effect of Tai Chi training on cardiorespiratory fitness in healthy adults: a systematic review and meta-analysis. *PLoS One.* 2015; 10(2): e0117360.
- 73 Estaki M, Pither J, Baumeister P, Little JP, Gill SK, Ghosh S, Ahmadi-Vand Z, Marsden KR, Gibson DL. Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. *Microbiome.* 2016; 4(1): 42.
- 74 Lan C, Chen SY, Lai JS. The exercise intensity of Tai Chi Chuan. *Med Sport Sci.* 2008; 52: 12–19.
- 75 Bermon S, Petriz B, Kajėnienė A, Prestes J, Castell L, Franco OL. The microbiota: an exercise immunology perspective. *Exerc Immunol Rev.* 2015; 21: 70–79.
- 76 Morgan N, Irwin MR, Chung M, Wang C. The effects of mind-body therapies on the immune system: meta-analysis. *PLoS One.* 2014; 9(7): e100903.
- 77 Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature.* 2013; 504(7480): 446–450.
- 78 Yeh SH, Chuang H, Lin LW, Hsiao CY, Eng HL. Regular tai chi chuan exercise enhances functional mobility and CD4CD25 regulatory T cells. *Br J Sports Med.* 2006; 40(3): 239–243.
- 79 Yeh SH, Chuang H, Lin LW, Hsiao CY, Wang PW, Liu RT, Yang KD. Regular Tai Chi Chuan exercise improves T cell helper function of patients with type 2 diabetes mellitus with an increase in T-bet transcription factor and IL-12 production. *Br J Sports Med.* 2009; 43(11): 845–850.
- 80 Zhang YJ, Wang R, Chen PJ, Yu DH. Effects of Tai Chi Chuan training on cellular immunity in post-surgical non-small cell lung cancer survivors: a randomized pilot trial. *J Sport Health Sci.* 2013; 2(1): 104–108.
- 81 Chiang J, Chen YY, Akiko T, Huang YC, Hsu ML, Jang TR, Chen YJ. Tai Chi Chuan increases circulating myeloid dendritic cells. *Immunol Invest.* 2010; 39(8): 863–873.
- 82 Goon JA, Aini AH, Musalmah M, Anum MY, Nazaimoon WM, Ngah WZ. Effect of Tai Chi exercise on DNA damage,

- antioxidant enzymes, and oxidative stress in middle-age adults. *J Phys Act Health*. 2009; 6(1): 43–54.
- 83 Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol (1985)*. 2005; 98(4): 1154–1162.
- 84 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology*. 2013; 144(1): 36–49.
- 85 Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav Immun*. 2011; 25(3): 397–407.
- 86 Jin P. Changes in heart rate, noradrenaline, cortisol and mood during Tai Chi. *J Psychosom Res*. 1989; 33(2): 197–206.
- 87 Campo RA, Light KC, O'Connor K, Nakamura Y, Lipschitz D, LaStayo PC, Pappas LM, Boucher KM, Irwin MR, Hill HR, Martins TB, Agarwal N, Kinney AY. Blood pressure, salivary cortisol, and inflammatory cytokine outcomes in senior female cancer survivors enrolled in a tai chi chih randomized controlled trial. *J Cancer Surviv*. 2015; 9(1): 115–125.
- 88 Cole AR, Wijarnpreecha K, Chattipakorn SC, Chattipakorn N. Effects of Tai Chi exercise on heart rate variability. *Complement Ther Clin Pract*. 2016; 23: 59–63.
- 89 Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex—linking immunity and metabolism. *Nat Rev Endocrinol*. 2012; 8(12): 743–754.



Submission Guide

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