

Food as Medicine: Food, Exercise and the Gut



- **Exacerbators and the endurance athlete**

Table. Extrinsic and intrinsic factors that may exacerbate disturbances to gut integrity and function, and promote greater incidence and severity of gastrointestinal symptoms.

| Exacerbatory Factor | Outcomes and Descriptive Examples |
|--|--|
| Exercise intensity ¹ | <ul style="list-style-type: none">• Exercise of moderate intensity appear to promote modest disturbance to markers of gut integrity, function, and gastrointestinal symptoms.• Exercise intensities of equivalent to $\geq 60\%$ VO_{2max} are reported to significantly disturbed markers of gut integrity, function, and promote gastrointestinal symptoms, with exercise intensities of $>70\%$ VO_{2max} and intermittent high intensity exercise reported to impair gastric emptying.• High exercise intensities (e.g., $\sim 80\%$ VO_{2max} equivalent) requires shorter exercise durations to promote gut disturbance. <p>Leiper JB. Fate of ingested fluids: factors affecting gastric emptying and intestinal absorption of beverages in humans. <i>Nutr Rev</i> 2015; 73(S2):57-72.</p> <p>ter Steege RW, Kolkman JJ. The pathophysiology and management of gastrointestinal symptoms during physical exercise, and the role of splanchnic blood flow. <i>Aliment Pharmacol Ther</i> 2012; 35:516-528.</p> <p>Horner KM, Schubert MM, Desbrow B, Byrne NM, King NA. Acute exercise and gastric emptying: a meta-analysis and implications for appetite control. <i>Sports Med</i> 2015; 45(5): 659-678.</p> |

Exercise duration ¹

- Field based exploratory work has clearly shown that the longer the exercise duration the greater disturbance to markers of gut integrity, function, and gastrointestinal symptoms.
- Greater exercise-induced increases in plasma I-FABP (i.e., marker of intestinal injury) after 3 hours of running (pre- to post-exercise peak value 4020pg/ml) in thermoneutral conditions (~20°C) compared with 2 hours of running (pre- to post-exercise peak value 583pg/ml) in the same conditions.
- Pronounced epithelial permeability, systemic endotoxaemia, systemic cytokinaemia, and symptoms in ultra-marathon competition with distances >100km.

Costa RJS, Snipe R, Camões-Costa V, Scheer BV, Murray A. The impact of gastrointestinal symptoms and dermatological injuries on nutritional intake and hydration status during ultramarathon events. *Sports Medicine-Open* 2016; 2(16):1-14.

Leiper JB. Fate of ingested fluids: factors affecting gastric emptying and intestinal absorption of beverages in humans. *Nutr Rev* 2015; 73(S2):57-72.

Costa, R.J.S., Miall, A., Khoo, A., Rauch, C., Snipe, R., Camões-Costa, V., Gibson, P., (2017). Gut-training: The impact of two weeks repetitive gut-challenge during exercise on gastrointestinal status, glucose availability, fuel kinetics, and running performance. *Appl.Physiol.Nutri.Metab.*, (In press).

Jeukendrup AE, Vet-Joop K, Sturk A, et al. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. *Clin Sci* 2000; 98: 47-55.

Gill SK, Hankey J, Wright A, et al. The Impact of a 24-hour Ultra-Marathon on Circulatory Endotoxin and Cytokine Profile. *Int J Sports Med* 2015; 36: 688-695.

Gill SK, Teixeira A, Rama L, et al. Circulatory endotoxin concentration and cytokine profile in response to exertional-heat stress during a multi-stage ultra-marathon competition. *Exerc Immunol Rev* 2015; 21:114-128.

Snipe R, Kitic C, Gibson P, Costa RJS. Heat stress during prolonged running results in exacerbated intestinal epithelial

injury and gastrointestinal symptoms. Exercise and Sports Science Australia 2016; abstract.

Exercise mode ¹

- Running exercise promotes greater gastrointestinal disturbance than other exercise modes (e.g., cycling, swimming, rowing, and gym fitness).
- The larger biomechanical vibration in the abdominal region in running compared with cycling, possibly contributing to the greater incidence and severity of gastrointestinal symptoms reported in running.
- Longer oro-caecal transit time and greater intestinal permeability has been observed in 90 minutes of steady state running compared with steady state cycling, resulting in greater gastrointestinal symptoms. - Mode of exercise does not appear to impact of gastric emptying in response to feeding during exercise.

Rehrer NJ, Brouns F, Beckers EJ, ten Hoor F, Saris WH. Gastric emptying with repeated drinking during running and bicycling. *Int J Sports Med* 1990;11(3):238-243.

Rehrer NJ, Meijer GA. Biomechanical vibration of the abdominal region during running and bicycling. *J Sports Med Phys Fitness* 1991; 31:231-234.

Pfeiffer B, Stellingwerff T, Hodgson AB, et al. Nutritional intake and gastrointestinal problems during competitive endurance events. *Med Sci Sports Exerc* 2012; 44:344-351.

van Nieuwenhoven MA, Brouns F, Brummer RJ. Gastrointestinal profile of symptomatic athletes at rest and during physical exercise. *Eur J Appl Physiol* 2004; 91(4):429-434.

Fitness status ¹

- It has been previously reported that fatal health outcomes associated with exertional-heat stress induced gut perturbations (i.e., increased intestinal permeability and subsequent endotoxaemia leading to sepsis and systemic inflammatory response syndrome) is linked to the fitness level of individuals (i.e., individual not fit for task and exertional-heat stress was too great).
- Lower anti-endotoxin responses have been observed in sedentary and lower fitness individuals, compared with trained athletes.

Selkirk GA, McLellan TM, Wright HE, Rhind SG. Mild endotoxemia, NF- κ B translocation, and cytokine increase during exertional heat stress in trained and untrained individuals. *Am J Physiol Regul Integr Comp Physiol* 2008; 295:611-623.

O'Connor FG, Casa DJ, Bergeron MF, et al. American College of Sports Medicine round table on exertional heat stroke. Return to duty/return to play: Conference Proceedings. *Curr Sports Med Rep* 2010; 9:314-321.

Rav-Acha M, Hadad E, Epstein Y, Heled Y, Moran DS. Fatal exertional heat stroke: a case series. *Am J Med Sci* 2004; 328:84-87.

Environmental conditions ¹

- Running in cold to thermoneutral conditions (i.e., $\leq 20^{\circ}\text{C}$) appears to have minimal impact on gastrointestinal status, however at the onset of heat exposure there is an abrupt increase in the perturbations to gut integrity and subsequent systemic responses (endotoxaemia and cytokinaemia). For example, greater intestinal injury is observed after 2 hours of steady state running in 30°C and 35°C compared with 20°C (Figure 2).

Gill SK, Hankey J, Wright A, et al. The Impact of a 24-hour Ultra-Marathon on Circulatory Endotoxin and Cytokine Profile. *Int J Sports Med* 2015; 36: 688-695.

Gill SK, Teixeira A, Rama L, et al. Circulatory endotoxin concentration and cytokine profile in response to exertional-heat stress during a multi-stage ultra-marathon competition. *Exerc Immunol Rev* 2015; 21:114-128.

Snipe R, Kitic C, Gibson P, Costa RJS. Heat stress during prolonged running results in exacerbated intestinal epithelial injury and gastrointestinal symptoms. *Exercise and Sports Science Australia* 2016; abstract.

Horner KM, Schubert MM, Desbrow B, Byrne NM, King NA. Acute exercise and gastric emptying: a meta-analysis and implications for appetite control. *Sports Med* 2015; 45(5): 659-678.

Figure. Plasma I-FABP concentration (A) and gastrointestinal symptoms (B) in response to 2 hours of steady state running at 60% $\text{VO}_{2\text{max}}$ in 20°C , 30°C and 35°C ambient temperatures. Mean + SEM ($n=10$). ^{aa} $p < 0.01$ and ^a $p < 0.05$ vs. 20°C , ^b $p < 0.05$ vs. 30°C .

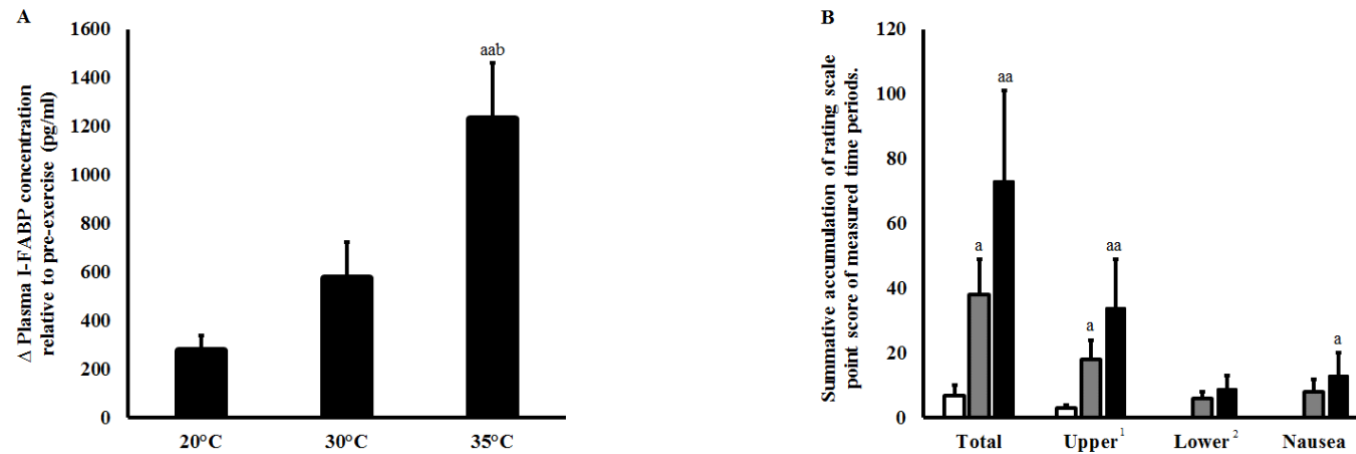


Figure 2B: White bars= 20°C, grey bars= 30°C, and black bars= 35°C. ¹ Upper-gastrointestinal symptoms (gastro-oesophageal and gastro-duodenal originated): projectile vomiting, regurgitation, urge to regurgitate, gastric bloating, belching, stomach pain, and heartburn/gastric acidosis), and ² lower-gastrointestinal symptoms (intestinal originated): flatulence including lower-abdominal bloating, urge to defecate, abdominal pain, abnormal defecation including loose watery stools, diarrhoea and blood in stools.

Snipe R, Kitic C, Gibson P, Costa RJS. Heat stress during prolonged running results in exacerbated intestinal epithelial injury and gastrointestinal symptoms. Exercise and Sports Science Australia 2016.

Feeding tolerance ¹

- Concerns have recently been raised by sports nutrition practitioners and endurance athletes (especially triathlon, running, ultra-endurance and adventure athletes) that carbohydrate intake during exercise, when the gut is in a compromised state, is not tolerable, leading to debilitating gastrointestinal symptoms. This intolerance is also dependant on consumption volume (i.e., the higher the intake the more likelihood for gastrointestinal symptoms).
- Consuming 90g/h of multi-transportable carbohydrates (2:1 glucose to fructose ratio) during 2 hours of running at 60% VO_{2max} in thermoneutral conditions contributes considerably to gastrointestinal symptoms compared with consuming water alone or 45g/h of a glucose solution during 2 hours of running at 60% VO_{2max} in 35°C ambient conditions (Figure 3a). Such high dosage resulted in symptoms appear 30 minutes into running, peaking post-exercise, with 100% of participants reported at least one gastrointestinal symptom during the gut-challenge trial, with 67% reporting at least one severe gastrointestinal symptom and 28% regurgitation into the oral cavity during the gut-challenge protocol.
- Consuming 90g/h of multi-transportable carbohydrates (2:1 glucose to fructose ratio) during 2 hours of running at 60% VO_{2max} in thermoneutral conditions resulted in carbohydrate malabsorption in 68% of endurance athletes (Figure 3b), which was associated with reported gut discomfort and upper-gastrointestinal symptoms.
- Total energy density and subsequent osmolality of the consumed bolus (i.e., foods and (or) fluids) during running influences the rate of gastric emptying, whereby the higher the energy density and osmolality the slower the emptying rate.

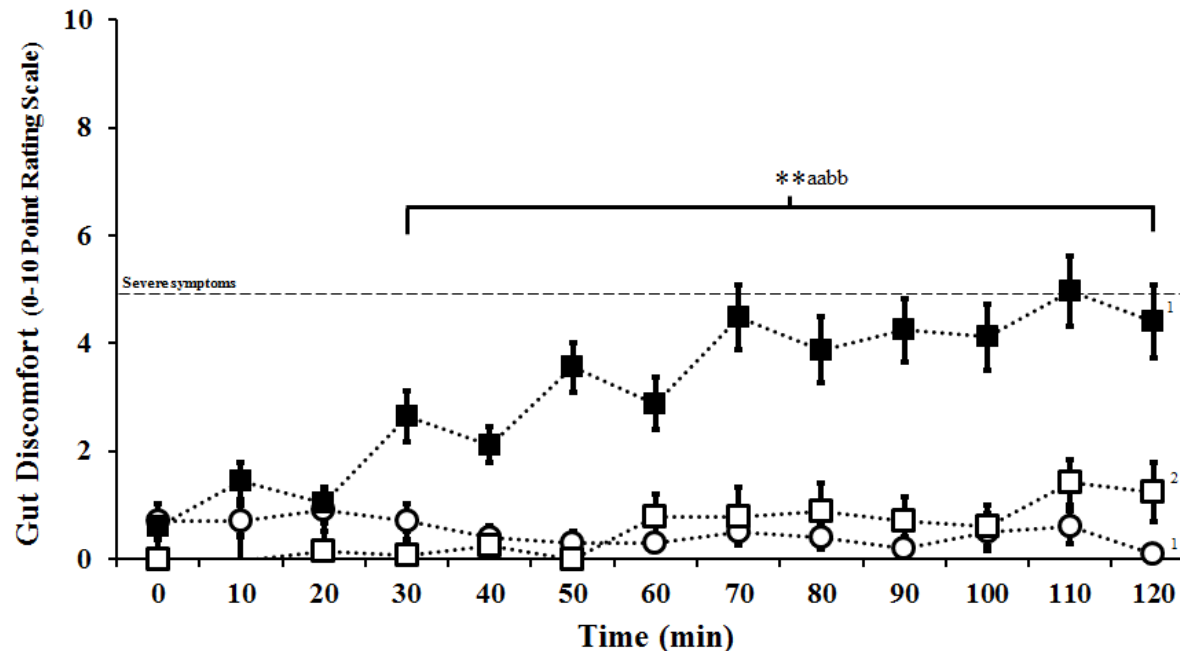
Costa, R.J.S., Miall, A., Khoo, A., Rauch, C., Snipe, R., Camões-Costa, V., Gibson, P., (2017). Gut-training: The impact of two weeks repetitive gut-challenge during exercise on gastrointestinal status, glucose availability, fuel kinetics, and running performance. *Appl.Physiol.Nutri.Metab.*, (In press).

Pfeiffer B, Stellingwerff T, Hodgson AB, et al. Nutritional intake and gastrointestinal problems during competitive endurance events. *Med Sci Sports Exerc* 2012; 44:344-351.

Costa RJS, Swancott A, Gill S, et al. Compromised energy and nutritional intake of ultra-endurance runners during a multi-stage ultra-marathon conducted in a hot ambient environment. *Int J Sports Sci* 2013; 3(2):51-61.

Costa RJS, Gill SK, Hankey J, Wright A, Marczak S. Perturbed energy balance and hydration status in ultra-endurance runners during a 24 h ultra-marathon. *Br J Nutri* 2014; 112:428-437.

Figure 3. Gut discomfort reported during 2 hours of steady state running at 60% VO_{2max} while consuming water (white circles), 45g/h glucose (white squares), and 90g/h in a 2:1 glucose to fructose ratio. Mean \pm SEM ($n=36$): ** $p < 0.01$ vs. 0 minutes, ^{aa} $p < 0.01$ vs. water, ^{bb} $p < 0.01$ vs. 45g/h.



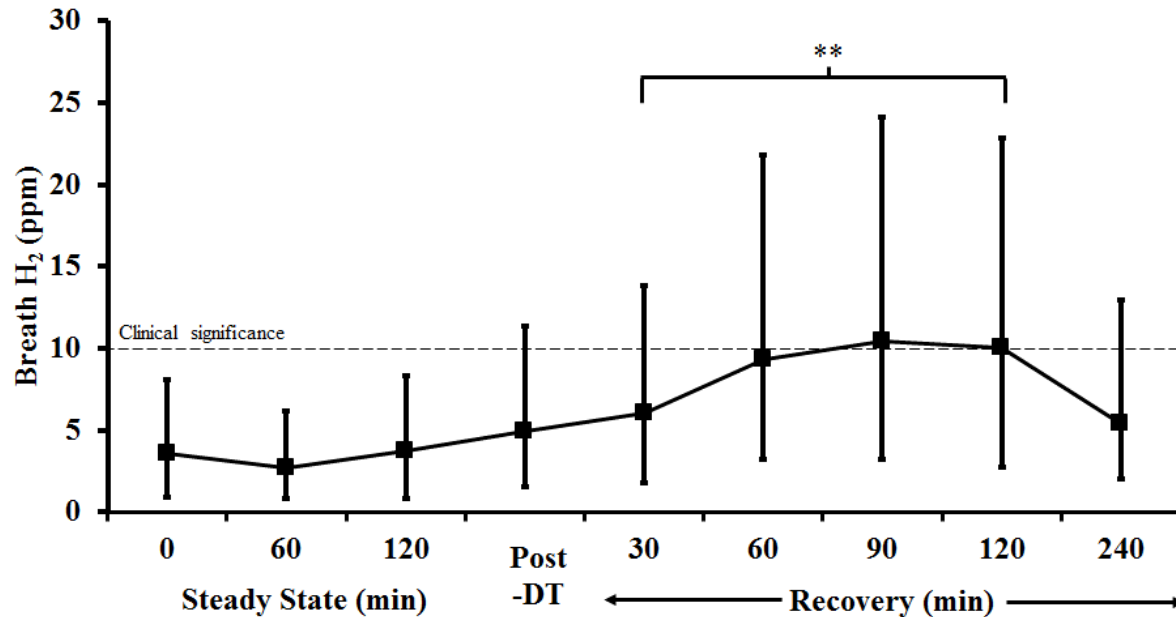
¹ running performed in 20°C ambient conditions and ² running performed in 35°C ambient conditions.

Snipe R, Kitic C, Gibson P, Costa RJS. Heat stress during prolonged running results in exacerbated intestinal epithelial

injury and gastrointestinal symptoms. Exercise and Sports Science Australia 2016.

Costa, R.J.S., Miall, A., Khoo, A., Rauch, C., Snipe, R., Camões-Costa, V., Gibson, P., (2017). Gut-training: The impact of two weeks repetitive gut-challenge during exercise on gastrointestinal status, glucose availability, fuel kinetics, and running performance. *Appl.Physiol.Nutri.Metab.*, (In press).

Figure . Individual breath H₂ in response to 2 hours of steady state running at 60% VO_{2max} while consuming 30g/20min (90g/h) in a 2:1 glucose to fructose ratio and 1 hour running distance test (DT). Mean and 95% confidence interval (upper and lower bound) (n= 25): ** p< 0.01 vs. 0 minutes.



Costa, R.J.S., Miall, A., Khoo, A., Rauch, C., Snipe, R., Camões-Costa, V., Gibson, P., (2017). Gut-training: The impact of two weeks repetitive gut-challenge during exercise on gastrointestinal status, glucose availability, fuel kinetics, and running performance. *Appl.Physiol.Nutri.Metab.*, (In press).

Nonsteroidal anti-inflammatory drugs ¹

- Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin and ibuprofen) are known as gastrointestinal irritants, impacting stomach gastric secretions, bicarbonate release in the duodenum, and erosion of the mucosal lining along the gastrointestinal tract. NSAIDs use has been linked to gastrointestinal injury and dysfunction, including nausea, regurgitation, dyspepsia, gastrointestinal ulceration, gastrointestinal bleeding, and abnormal defecation (e.g., diarrhoea).
- Increases in intestinal injury, and increased gastric and intestinal permeability can be markedly increased after exercise with the use of NSAIDs before exercise. For example, gastroduodenal permeability was substantially increased, compared with placebo, after 1.3g of aspirin administration the night before and immediately before 60 minutes of running at 68% VO_{2max} . While, I-FABP was substantially elevated after endurance cycling, in which 400mg of ibuprofen was administered before exercise (peak I-FABP value 875 pg/ml), compared with no ibuprofen administration (474 pg/ml).

Lambert GP, Boylan M, Laventure JP, Bull A, Lanspa S. Effect of aspirin and ibuprofen on GI permeability during exercise. *Int J Sports Med* 2007; 28(9):722-726.

Ryan AJ, Chang RT, Gisolfi CV. Gastrointestinal permeability following aspirin intake and prolonged running. *Med Sci Sports Exerc* 1996; 28(6):698-705.

Warden SJ. Prophylactic use of NSAIDs by athletes: a risk/benefit assessment. *Phys Sportsmed* 2010; 38(1):132-138.

van Wijck K, Lenaerts K, Van Bijnen AA, *et al.* Aggravation of exercise-induced intestinal injury by Ibuprofen in athletes. *Med Sci Sports Exerc* 2012; 44(12): 2257-2262.

Predisposition ²

- Longer oro-caecal transit time and increased intestinal permeability has been observed in symptomatic athletes after 90 minutes of steady state running compared with asymptomatic athletes, suggesting there may be some predisposition to exercise-induced gastrointestinal syndrome.
- There exists two groups of runners, those who experience gastrointestinal symptoms occasionally and those who experience gastrointestinal symptoms repeatedly, suggesting a potential gene variant/s for predisposition, which warrants further investigation.
- It is speculated that individuals with predisposition to gastrointestinal diseases or disorders associated with intestinal damage, inflammation, autoimmune responses and (or) sensitivity (e.g., coeliac disease, inflammatory bowel disease, irritable bowel syndrome, diverticular disease, gastro-oesophageal reflux disease) may be more prone to exercise-induced gastrointestinal perturbations and associated symptoms.

van Nieuwenhoven MA, Brouns F, Brummer RJ. Gastrointestinal profile of symptomatic athletes at rest and during physical exercise. *Eur J Appl Physiol* 2004; 91(4):429-434.

Caradonna L, Amati L, Magrone T, Pellegrino NM, Jirillo E, Caccavo D. Enteric bacteria, lipopolysaccharides and related cytokines in inflammatory bowel disease: biological and clinical significance. *J Endotoxin Res* 2000; 6(3):205-214.

Morris G, Berk M, Galecki P, Maes M. The Emerging Role of Autoimmunity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/cfs). *Mol Neurobiol* 2014; 49:741-756.

Gut microbiota ²

- There is currently evidence to suggest that exercise and diet has the ability to alter the gut microbiota composition, to either enhance gut protective bacterial communities or promote dysbiosis.
- Athletes (rugby players) training on a regular basis show higher gut bacterial diversity and higher *Firmicutes* to *Bacteroides* ratio compared to healthy controls. Moreover, regular exercise is associated with higher levels of *Bifidobacterium*, *Lactobacillus*, and *Clostridium leptum*, which are key short chain fatty acid (e.g., butyrate) producing bacteria, linked to augmented epithelial barrier function.
- To date no research has investigate whether the gut microbiota composition influences the degree of

exercise-induced perturbations to gut integrity and function, and gastrointestinal symptoms in response to an acute bout of exercise. Considering dysbiosis has the ability to alter the structure and function of the epithelial lining (e.g., mucosal barrier erosion, intestinal injury and permeability, and injury to specialised anti-microbial protein secreting cells), it is speculated that the proportion of *Firmicutes*, *Bacteroides*, *proteobacteria*, and *actinobacteria*, and numbers of short chain fatty acid producing bacterial communities may influence gut status in response to exercise.

Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients* 2012, 4:1095-1119.

Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut* 2014; 63(12):1913-1920.

Mach N, Fuster-Botella. Endurance exercise and gut microbiota: A review. *J Sport Health Sci* 2016. In press.

Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and Butyrate-Producing Colon Bacteria: Importance and Strategies for Their Stimulation in the Human Gut. *Front Microbiol* 2016; 28(7):979.

¹ extrinsic factor, ² intrinsic factor.

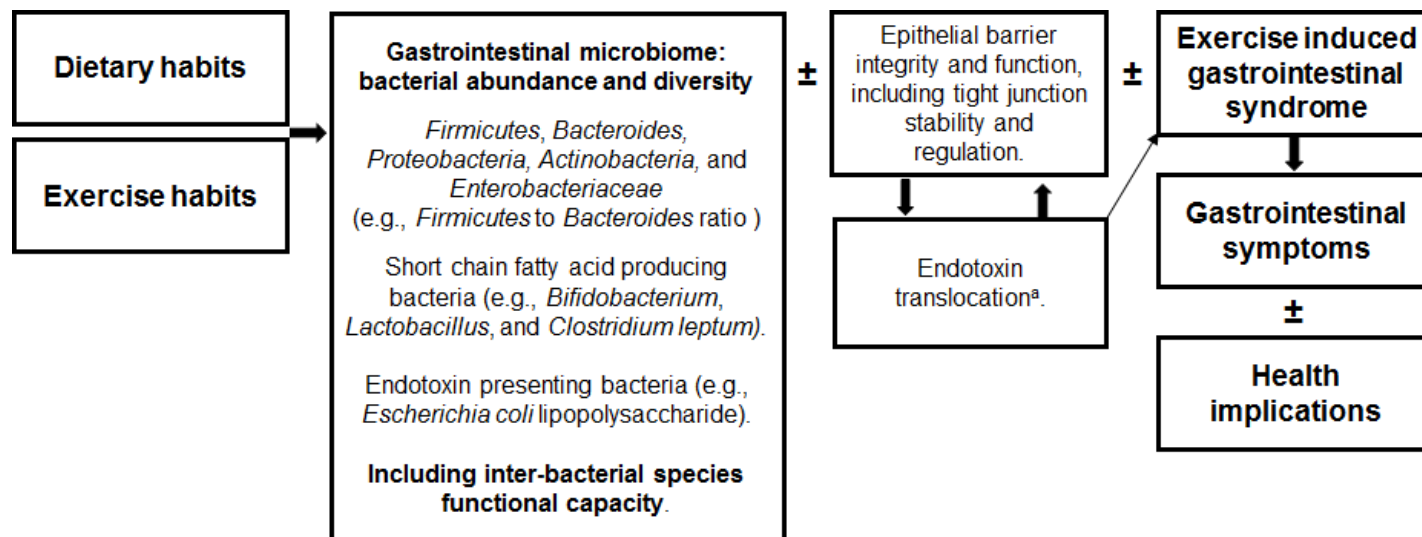
Extra information

Gut microbiota:

Considering the translocation of endotoxic microorganisms into circulation is dependent on the presence of indigenous bacterial species within the gastrointestinal tract, it is plausible that the total bacterial abundance and bacterial diversity (e.g., *Firmicutes*, *Bacteroides*, *Proteobacteria*, *Actinobacteria*, and ***Enterobacteriaceae***) of the intestinal microbiome may influence the magnitude of endotoxaemia in response to exercise, and subsequent systemic immune responses (Figure). For example, an intestinal microbiome diversity with high abundance of short chain fatty acid (e.g., butyrate) producing microorganisms (e.g., *Bifidobacterium*, *Lactobacillus*, and *Clostridium leptum*), known to enhance epithelial barrier and tight-junction integrity, stability and function, and in addition to enhancing restitution of epithelial lesions, may be protective against exercise-associated gastrointestinal barrier perturbations and systemic responses. Whereas, a microbiome profile abundant in bacterial species with endotoxins (e.g., *Escherichia coli* lipopolysaccharide) and associated pathogenic structures (i.e., outer membrane vesicles containing peptidoglycan) may promote exacerbated endotoxaemia, local epithelial and systemic responses.

From a practical perspective, there is accumulating evidence that diets excessively high in protein, fat, and/or sugars, or low in fibre and fermentable carbohydrates, or even micronutrient administration (i.e., oral iron replacement therapy) may have major effects on the intestinal microbiome total abundance and diversity, some of which are regarded as dysbiotic. Such diets are common among individuals partaking in sports and exercise programs, and thus certain adherence to 'extreme diets' may contribute to the endotoxaemia observed after prolonged strenuous exercise. In addition, there is also evidence that repetitive exercise training and sustaining an active lifestyle creates changes in the intestinal microbiome diversity in human populations (i.e., higher *Firmicutes* to *Bacteroides* ratio compared to healthy controls, and higher abundance of *Bifidobacterium*, *Lactobacillus*, and *Clostridium leptum*; and higher abundance of *Faecalibacterium prausnitzii*, *Roseburia hominis* and *Akkermansia muciniphila*). However, it is unclear the clinical relevance of these changes, and how they contribute to the overall gastrointestinal response to exercise. To date, no research has determined if the total bacterial abundance, diversity, and functional interaction of the intestinal microbiome influences the various components of exercise-induced gastrointestinal syndrome, which warrants substantiation. It is also unknown whether acute exercise stress and the physiological alteration of the gastrointestinal tract in response to acute exercise promotes abrupt changes to the intestinal microbiome total bacterial abundance and diversity.

Figure. The intestinal microbiome and exercise-induced gastrointestinal syndrome: a speculative model. ^a Increases in bacterial endotoxin translocation and subsequent local and systemic inflammatory responses further exacerbates disturbances to epithelial integrity and tight-junction stability and regulation.



Costa RJS. Exercise-induced gastrointestinal syndrome: does the intestinal microbiome have a role to play? Australian Academy of Science-Microbiome Symposium, 2016.

Mariadason JM, Barkla DH, Gibson PR. Effect of short-chain fatty acids on paracellular permeability in Caco-2 intestinal epithelium model. *Am J Physiol* 1997; **272**: G705-G712.

Mariadason JM, Catto-Smith A, Gibson PR. Modulation of distal colonic epithelial barrier function by dietary fibre in normal rats. *Gut* 1999; **44**: 394-399.

Wilson AJ, Gibson PR. Short-chain fatty acids promote the migration of colonic epithelial cells in vitro. *Gastroenterol* 1997; **113**: 487-496.

Arumugam M, Raes J, Pelletier E, *et al.* Enterotypes of the human gut microbiome. *Nature* 2011; **473**(7346): 174-180.

Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiol Rev* 2010; **90**(3): 859-904.

David LA, Maurice CF, Carmody RN, *et al.* Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014; **505**: 559-563.

Halmos EP, Christophersen CT, Bird AR, *et al.* Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut* 2015; **64**: 93-100.

Lee T, Clavel T, Smirnov K, *et al.* Oral versus intravenous iron replacement therapy distinctly alters the gut microbiota and metabolome in patients with IBD. *Gut* 2017; **66**(5): 863-871.

Clarke SF, Murphy EF, O'Sullivan O, *et al.* Exercise and associated dietary extremes impact on gut microbial diversity. *Gut* 2014; **63**(12):1913-1920.

Bressa C, Bailén-Andrion M, Pérez-Santiago, *et al.* Differences in gut microbiota profile between women with active lifestyle and sedentary women. *PLoS One* 2017; **12**(2): e0171352.

NSAID:

It is well established that NSAIDs are gastrointestinal irritants, impacting stomach gastric secretions, bicarbonate release in the duodenum, and erosion of the mucosal lining along the gastrointestinal tract. NSAID use has been linked to gastrointestinal injury and dysfunction, including nausea, regurgitation, dyspepsia, gastrointestinal ulceration, gastrointestinal bleeding, and abnormal defecation (e.g., diarrhoea). The administration of NSAIDs prior to exercise can markedly increase intestinal injury and permeability in response to exercise, so avoidance of NSAIDs prior to exercise would be recommended to minimise exercise-associated gastrointestinal damage.