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Systematic review: exercise-induced gastrointestinal syndrome—implications for health and intestinal disease

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Summary

Background: "Exercise-induced gastrointestinal syndrome" refers to disturbances of gastrointestinal integrity and function that are common features of strenuous exercise.

Aim: To systematically review the literature to establish the impact of acute exercise on markers of gastrointestinal integrity and function in healthy populations and those with chronic gastrointestinal conditions.

Methods: Search literature using five databases (PubMed, EBSCO, Web of Science, SPORTSdiscus, and Ovid Medline) to review publications that focused on the impact of acute exercise on markers of gastrointestinal injury, permeability, endotoxaemia, motility and malabsorption in healthy populations and populations with gastrointestinal diseases/disorders.

Results: As exercise intensity and duration increases, there is considerable evidence for increases in indices of intestinal injury, permeability and endotoxaemia, together with impairment of gastric emptying, slowing of small intestinal transit and malabsorption. The addition of heat stress and running mode appears to exacerbate these markers of gastrointestinal disturbance. Exercise stress of ≥2 hours at 60% VO_{2max} appears to be the threshold whereby significant gastrointestinal perturbations manifest, irrespective of fitness status. Gastrointestinal symptoms, referable to upper- and lower-gastrointestinal tract, are common and a limiting factor in prolonged strenuous exercise. While there is evidence for health benefits of moderate exercise in patients with inflammatory bowel disease or functional gastrointestinal disorders, the safety of more strenuous exercise has not been established.

Conclusions: Strenuous exercise has a major reversible impact on gastrointestinal integrity and function of healthy populations. The safety and health implications of prolonged strenuous exercise in patients with chronic gastrointestinal diseases/disorders, while hypothetically worrying, has not been elucidated and requires further investigation.

1 | INTRODUCTION

It is well established that exercise has beneficial effects for human health, especially in regards to musculoskeletal and cardiovascular health.[1] As such, exercise is readily promoted within public health policy, which has led to a plethora of public health initiatives, both

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internationally and nationally to cater for cultural differences.[2-4] Despite light exercise (eg, walking) being advocated for general well-being, the scientific literature clearly shows that moderate (3.0-5.9 metabolic equivalents (METs), which refers to the energy cost of physical activity in comparison to resting metabolic rate [ie, 1 MET]) to vigorous (≥6 METs) intensity exercise of substantial duration (eg, ≥1 hours) is required to provide a sufficient magnitude of physiological and metabolic strain to promote musculoskeletal and cardiovascular adaptations associated with improved health.[5,6] Although exercise is beneficial to the prevention and management of non-communicable diseases, substantial exposure to exercise stress may not be suitable or may exacerbate other medical conditions, especially of the gastrointestinal tract. Indeed, evidence has shown that even moderate intensity exercise of short duration has the ability to compromise the gastrointestinal tract and promote occurrence of gastrointestinal symptoms.[7,8]

Recently, there has been a substantial amount of research investigating the causal mechanisms for the perturbations to gastrointestinal integrity, function and symptoms induced by exercise.[8-12] The majority of research, however, has recruited healthy endurance-trained populations, with limited research being conducted on individuals presenting with gastrointestinal diseases/disorders, such as inflammatory bowel disease (IBD), functional gastrointestinal disorders (FGID) and gastro-oesophageal reflux disease. Moreover, the exponential growth of participation in endurance and ultra-endurance events over the last decade in the general population,[13] and the high reported incidence of gastrointestinal issues in such events,[14-16] has raised concerns regarding the impact of prolonged strenuous exercise on gastrointestinal health. Concerns have also been raised in regards to implications for acute and/or chronic medical complications including, and not limited to, septic shock, colitis, paralytic ileus, ischaemic bowel, and the development or progression of IBD and/or FGID in individuals with pre-disposition or presenting such conditions, respectively.

Previous reviews have focused on the impact of exercise stress on splanchnic blood flow and subsequent intestinal ischaemia and symptomatology,[8] cytokine responses,[17] gastrointestinal motility and absorption.[11,18] There is, however, a need to more comprehensively integrate the evidence for all elements of exercise-associated gastrointestinal disturbances. With this in mind, the aims of this review are, first, to explore the concept of "exercise-induced gastrointestinal syndrome". Second, to conduct a systematic review on the impact of acute exercise intensity and duration on markers of gastrointestinal integrity and function; and third, to review the current literature on gastrointestinal perturbation in populations with gastrointestinal diseases/disorders under exercise conditions.

2 | EXERCISE-INDUCED GASTROINTESTINAL SYNDROME

The term, "exercise-induced gastrointestinal syndrome", has recently been introduced to describe a complex array of normal physiological responses to exercise that perturbs and compromises gastrointestinal integrity and function.[14,19] As shown in Figure 1, responses are driven down two primary pathways: (1) a circulatory-gastrointestinal pathway involving redistribution of blood flow to working muscle and peripheral circulation, which aids skeletal muscle metabolism and thermoregulation, subsequently reducing total splanchnic perfusion;[12,20] and (2) a neuroendocrine-gastrointestinal pathway involving an increase in sympathetic activation, reducing overall gastrointestinal functional capacity.[11] The combination of splanchnic hypoperfusion and altered enteric nervous system activity leads to a cascade of events that may result in gastrointestinal symptoms, and/or acute or chronic health complications.

One key feature of splanchnic hypoperfusion is intestinal ischaemia.[8,20] Indeed, at the onset of steady-state exercise, portal blood flow has been reported to decrease by 20% within 10 minutes, and by 80% after 1 hour of running at 70% of maximal oxygen update (VO_{2max}).[21] While, 1 hour of cycling at 70% of maximal wattage output (W_{max}) resulted in a 1.7 kPa increase in gastric arterialised PCO_2, indicative of splanchnic ischaemia, with the most pronounced increase occurring within the first 10 minutes of exercise, and a return to baseline levels 1 hour after exercise.[20] Such profound ischaemia creates epithelial injury associated with apical erosion and likely dysfunction of all epithelial cell types (ie, enterocyte, goblet, Paneth and enteroendocrine cells).[9,12,22] A major consequence of such damage is increased intestinal permeability, by either, physical breaks in the epithelium, damaging the multi-protein complex (ie, claudins and occludin) of the tight-junction and/or promoting dysfunction to tight-junction regulatory proteins (ie, zona-occludens).[23] For example, it has previously been reported that 1 hour of running at 70% VO_{2max} perturbs tight-junction regulatory proteins and subsequently increases intestinal permeability.[24]

Acute local intestinal injury stimulates NF-κB gene expression within epithelial cells,[25,26] initiating a local inflammatory cascade by signalling release of pro-inflammatory cytokines such as interleukin (IL)-1β, tumour necrosis factor (TNF)-α and interferon (IFN)-γ. This cytokine profile also promotes tight-junction dysregulation and enhances intestinal permeability.[27] A consequence of such multi-pronged disruption to barrier integrity is heightened bacterial translocation with, for example, multiple reports of elevated circulatory bacterial endotoxins (eg, lipopolysaccharide) observed after endurance exercise.[15,28-30] The translocation of gram-negative and/or gram-positive bacteria with potential accompaniment of outer membrane vesicles containing peptidoglycan and lipopolysaccharide also stimulates NF-κB gene expression through the NOD receptors within the epithelium, which further contributes towards the magnitude of local and potentially systemic inflammatory responses.[25,26,31]

There are two protective mechanisms to deal with elevated bacterial translocation and pro-inflammatory cytokine responses. First, anti-endotoxin antibodies are critical for the destruction and clearance of bacterial endotoxins, and their reduced concentrations after exercise can be viewed as evidence of acute endotoxaemia.[28,32-35] The second protective mechanism targets the systemic pro-inflammatory cytokine response (ie, elevated IL-1β, TNFα and IL-6 within

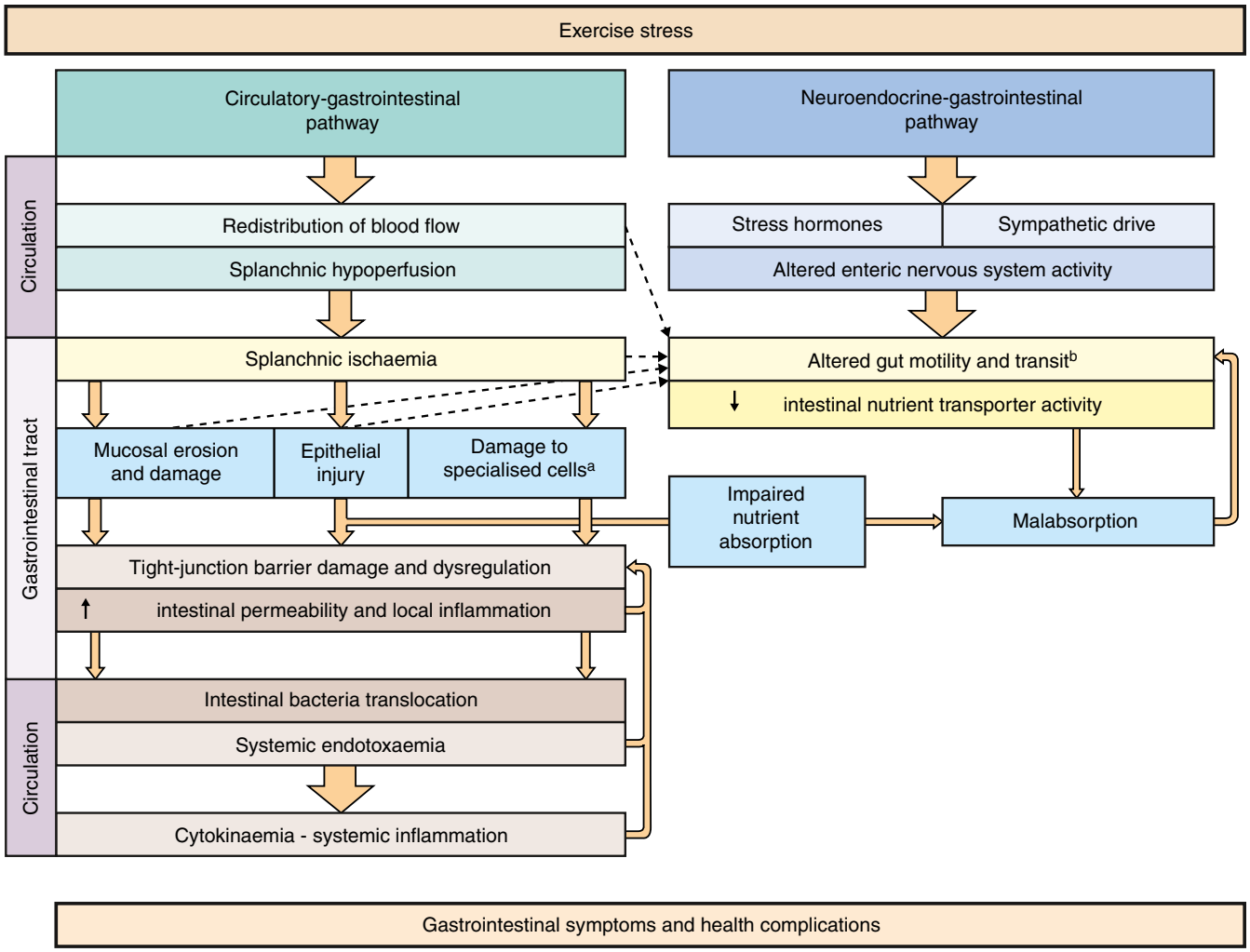

FIGURE 1 Schematic description of exercise-induced gastrointestinal syndrome: Physiological changes in circulatory and neuroendocrine pathways at the onset of exercise resulting in perturbed gastrointestinal integrity and function, and may lead to gastrointestinal symptoms, and/or acute or chronic health complications. [a]Specialised antimicrobial protein secreting (ie, Paneth cells) and mucus producing (goblet cells) cells- aid in preventing intestinal originating pathogenic microorganisms gaining entry into systemic circulation; [b]splanchnic hypoperfusion, and subsequent intestinal ischemia and injury (including mucosal erosion) results in direct (eg, enteric nervous system and/or enteroendocrine cell) or indirect (eg, nutrient malabsorption) alterations to gastrointestinal motility[9,42,120]

systemic circulation and phagocytic immune cell activation by IL-8), which activates a compensatory anti-inflammatory response with pronounced increases in IL-10 and IL-1ra.[17,26,29,30,36] Similar to localised inflammation at the intestinal epithelium, the systemic inflammation observed in response to increased intestinal permeability and translocation of bacterial endotoxins into circulation further contributes to the epithelial tight-junction dysregulation and heightened intestinal permeability.[23,27] Hence, local and systemic inflammatory responses feed into a vicious cycle for endotoxaemia.

Exercise is also associated with changes in gastrointestinal motility, with potential to slow gastric emptying and delay orocaecal transit, likely through exercise stimulated increases in sympathetic drive.[11,18] Indeed, gastrointestinal symptoms, such as bloating, belching, urge to regurgitate and regurgitation, are commonly reported by individuals partaking in strenuous exercise, and these appear to be exacerbated if foods and fluids are consumed whilst exercising.[7,14,19] There is also evidence that exercise impairs intestinal nutrient absorptive transport mechanisms leading to malabsorption.[10,37] Malabsorption of carbohydrates consumed during exercise is commonly seen after endurance running.[19,38] It is, however, unclear if the mechanisms underlying impaired nutrient absorption are due to intestinal ischaemic injury, down-regulated intestinal transporter activity, or a combination of both. Increased delivery of nutrients, due to exercise-associated malabsorption, to the distal ileum and colon has the potential to induce gastrointestinal symptoms through luminal distension from osmotically driven increases in small intestinal water content and gas production from bacterial fermentation.[39,40] In addition, nutrient presence in the ileum may promote gastrointestinal symptoms through suppressing gastric and duodeno-jejunal motility by the so-called "ileal brake" feedback mechanism, using either neural or enteroendocrine mediators.[41,42]

It is likely, therefore, that exercise-induced gastrointestinal syndrome is the result of complex multi-factorial interactions between the gastrointestinal tract with the circulatory, immune, and enteric nervous systems. It is thus clear that in assessing the impact of exercise on gastrointestinal status, a global approach, which encompass structural and functional markers, should be adopted.

3 | IMPACT OF EXERCISE STRESS ON MARKERS OF GASTROINTESTINAL INTEGRITY AND FUNCTION: A SYSTEMATIC REVIEW

A systematic literature search was undertaken by three researchers (RC, RS and CK), in accordance with methods used by Porter et al.,[43] to determine the impact of acute exercise (ie, intensity, duration, and mode) on markers of exercise-induced gastrointestinal syndrome, using five online scientific databases, which included PubMed, EBSCO, Web of Science (all databases), SPORTSdiscus and Ovid Medline (Table S1). Original field observational studies and/or laboratory controlled trials, presenting quantified data on markers of gastrointestinal integrity or function in a healthy (ie, absence of illness and disease) human population that required participants to perform an acute exercise bout were considered for the review. Studies were suitable for inclusion if they involved an acute or prolonged external intervention (eg, dietary, thermoregulatory or pharmacological intervention) and contained a control or placebo arm. To maintain a degree of consistency within measurement and analytical methods, only studies conducted in the previous 20 years were considered. Data were not considered appropriate for further synthesis into a meta-analysis due to the absence of homogeneous interventions and outcomes. An additional review (RC, RS, CK and PG) was also undertaken to determine gastrointestinal perturbation in populations with gastrointestinal diseases/disorders under acute exercise conditions. Due to the limited publications identified, a narrative description was used to depict outcomes.

4 | EXERCISE AND INTESTINAL INJURY

The main method for demonstrating intestinal epithelial injury has been by measuring changes in circulating concentrations of intestinal fatty-acid binding protein (I-FABP), a small (14-kD) cytosolic protein that is rapidly released into circulation upon injury and damage to mature enterocytes.[9] I-FABP correlates with exercise-associated splanchnic hypoperfusion and subsequent ischaemia,[12,20] and therefore, may be a useful surrogate indicator of reductions in villous microvascular blood flow. As shown in Table 1 (ie, eight studies were eligible for inclusion- Table S1), several laboratory studies have reported prolonged (≥1 hour) running and cycling, and resistance exercise of short duration (30 minutes) to induce significant increases in I-FABP. The greatest exercise-associated increase in plasma I-FABP concentrations have been reported in response to vigorous endurance exercise protocols involving running and cycling,[20,46,47] with the greatest concentration being observed when vigorous exercise was performed in hot ambient conditions (30°C).[47] A recent study, however, reported mean plasma I-FABP concentrations of >1000 pg/mL, on two separate occasions, after 3 hours of prolonged strenuous exercise (ie, 2 hours of running at 60% VO_{2max}, followed by a 1 hour self-paced running distance test) in thermoneutral conditions,[19] suggesting exercise duration may be a key contributing factor to the magnitude of exercise-associated intestinal epithelial injury. In contrast to the majority of studies, Sessions et al.[44] found a modest insignificant increase in plasma I-FABP concentration (88 pg/mL) in seven volunteers after 60 minutes running at 70% VO_{2max} in hot ambient conditions (30°C). These discrepant findings may be due to methodological differences such as sample timing (immediately post-exercise vs further into recovery [ie, 20 minutes post-exercise]) and participant characteristics (ie, fitness status). Indeed, Morrison et al.[47] found greater increases in post-exercise I-FABP concentration, in participants with greater weekly training loads, after 90 minutes of vigorous running and cycling exercise in the heat.

Other less direct markers of intestinal epithelial injury might include faecal calprotectin, a marker of mucosal inflammation secondary to such injury, or faecal blood loss. However, unlike I-FABP, neither are specific to small intestine. Increased faecal calprotectin concentration following exercise was reported in one study of 20 healthy male participants,[20] but the change was small (median: 0.41 μg/g); one must be guarded in assigning physiological significance to such a change. Faecal blood loss remains a preferable endpoint and has been qualitatively reported in 14% of male triathletes in response to a 3 hours cycling-running protocol at 77% VO_{2max} in thermoneutral ambient conditions (22°C).[49] These findings support the commonly reported faecal blood loss after endurance events (ie, marathon and ultra-marathon competition).[16,50,51]

5 | EXERCISE AND INTESTINAL PERMEABILITY

As previously discussed, exercise-associated increases in gastrointestinal permeability are suggested to arise from intestinal epithelial injury and tight-junction dysfunction induced by splanchnic hypoperfusion, which may be exacerbated by local and systemic inflammatory responses. Dual-sugar tests have been used to determine exercise-associated changes in intestinal permeability; lactulose with rhamnose or mannitol is used for small intestine, sucralose and erythritol for large intestine, and sucrose for gastric permeability.[12,52,53] As outlined in Table 2 (seven studies were eligible for inclusion Table S1), gastrointestinal permeability appears to increase in proportion to the magnitude of exercise, with higher body temperature and running linked with greater permeability.[52,56,57] For example, marathon competition and running at ≥70% VO_{2max}, with or without heat stress, with body temperature ≥39°C, resulted in the highest reported rates of elevated small intestinal permeability.[52,54,56,57]

TABLE 1 Impact of exercise on epithelial injury

Reference [a]	Population	Exercise protocol	Body temperature[b]	Δ pre- to post-exercise I-FABP concentration (otherwise specified)[c]
Sessions et al.[44]	n=7 endurance trained male and female participants	60 minutes running at 70% VO_{2max} in 30°C T_{amb} (12% to 20% RH)	T_{re}: 39.5°C	88 pg/mL[d, ns]
van Wijck et al.[37]	n=12 recreationally trained male participants	30 minutes resistance exercise. T_{amb} not reported	Not measured	90 pg/mL[d*]
van Wijck et al.[45]	n=9 male cyclists and triathletes	60 minutes cycling at 70% W_{max}. T_{amb} not reported	Not measured	179 pg/mL[d*]
Lis et al.[46]	n=13 male and female competitive cyclists	45 minutes steady state cycling at 70% W_{max} + 15 minutes Time trial. T_{amb} not reported	Not measured	Steady state: 139 pg/mL [d, stat-x] Time trial: 210 pg/mL [d, stat-x]
Morrison et al.[47] Part A	n=8 recreationally trained male participants undertaking <3 exercise sessions per week	15 minutes cycling at 50% HRR + 60 minutes running (30 minutes at 80% HRR + 30 minutes TT) + 15 minutes cycling at 50% HRR in 30°C T_{amb} (50% RH)	T_{oes}: 38.6°C	283 pg/mL[d*]
Barberio et al.[48]	n=8 endurance trained male participants	Running at 78% VO_{2max} (4 mMol/L blood lactate) until T_c increases 2.0°C or volitional exhaustion (24 minutes) in T_{amb} 40°C (40% RH)	T_{re}: 39.0°C	297 pg/mL[d*]
van Wijck et al.[20]	n=20 healthy male participants	60 minutes cycling at 70% W_{max}. T_{amb} not reported	Not measured	306 pg/mL*
Morrison et al.[47] Part B	n=7 recreationally trained male participants undertaking >6 exercise sessions per week	15 minutes cycling at 50% HRR + 60 minutes running (30 minutes at 80% HRR + 30 minutes TT) + 15 minutes cycling at 50% HRR in 30°C T_{amb} (50% RH)	T_{oes}: 38.6°C	806 pg/mL[d*]

I-FABP, intestinal fatty-acid binding protein; T_{amb}, ambient temperature; RH, relative humidity; T_{re}, post-exercise (or peak) rectal temperature; W_{max}, watt maximum; HRR, heart rate reserve; T_{oes}, post-exercise (or peak) oesophageal temperature.

[a]In order of exercise-associated epithelial injury (ie, plasma or serum I-FABP concentration), otherwise specified.

[b]Post-exercise (or peak) body temperature of respective measurement technique.

[c]Data (mean or median) from text and tables, or extrapolated from figures to the nearest approximate value (pre-exercise resting to post-exercise peak value difference).

[d]Values of control or placebo group/trial of the respective intervention study.

*Significant pre- (rest) to post-exercise increase, [ns] no significant difference pre- (rest) to post-exercise. [stat-x] no statistical analysis provided or statistical analysis unclear.

In addition, factors such as restriction of fluid during exercise and/or dehydration may also contribute to the magnitude of change in intestinal permeability.[52,54-56] Pals et al.[52] highlighted the dose-response in small intestinal permeability with increasing exercise intensity following 1 hour running in thermoneutral ambient conditions at 40%, 60% and 80% VO_{2max}, in which final rectal temperature (38.0°C, 38.7°C and 39.6°C, respectively) and exercise-induced body mass loss (0.6%, 1.2% and 1.9%, respectively) also increased in proportion to exercise intensity.

The paucity of studies reporting changes in exercise-associated gastric and large intestinal permeability make it difficult to confidently conclude outcomes relating to the effect of exercise on permeability to these segments of the gastrointestinal tract. Gastric and large intestinal permeability was not affected by 1 hour cycling at 70% VO_{2max} in a small group of male participants,[20] but fluid restriction during running resulting in modest dehydration, and high intensity running (80% VO_{2max}) were associated with increased gastric permeability.[52,55]

Considering the variation in dual-sugar test outcomes observed between studies, methodological factors such as the length of urine collection, which varies from 1 hour to 24 hours, variations in dose of sugar/s administered, timing of ingestion (ie, before vs during vs. after exercise), and the format of data reporting (eg, ratio, %, or area-under-the-curve) make direct comparisons between studies difficult. One investigating group examined circulating levels of claudin and found it increased with strenuous running in two cohorts,[54] but the interpretation of this as representing changes in permeability requires validation.

TABLE 2 Impact of exercise on gastrointestinal permeability

Reference [a]	Population	Exercise protocol	Body temperature[b]	Exercise associated gastrointestinal permeability[c] (Δ pre- to post-exercise)
Yeh et al.[54] Part A	n=15 active male and female participants	60 minutes running at 70% VO_{2max} in T_{amb} 22°C (62% RH)	T_c: 38.4°C	Claudin-3: 0.9 ng/mL*
Yeh et al.[54] Part B	n=15 active male and female participants	60 minutes running at 70% VO_{2max} in T_{amb} 33°C (50% RH)	T_c: 39.1°C	Claudin-3: 1.6 ng/mL*
Van Wijck et al.[20]	n=6 healthy male participants	60 minutes cycling at 70% W_{max}. T_{amb} not reported	Not measured	Urinary lactulose-rhamnose ratio: 0.007 [ns] Urinary sucralose-erythritol ratio: -0.003 [n]
Pals et al.[52] Part A	n=6 active male and female participants	60 minutes running at 40% VO_{2peak} in T_{amb} 22°C (50% RH)	T_{re}: 38.0°C	Urinary lactulose-rhamnose ratio: 0.008 [ns] Urinary sucrose recovered: 0.07% [ns]
Van Wijck et al.[45]	n=9 male cyclist and triathletes	60 minutes cycling at 70% W_{max}. T_{amb} not reported	Not measured	Urinary lactulose-rhamnose ratio: 0.012 [d, ns] Urinary sucralose-erythritol ratio: 0.008 [ns]
Lambert et al.[55] Part A	n=20 male and female endurance runners	60 minutes running at 70% VO_{2max} in T_{amb} 24°C (33% RH	T_{re}: 38.5°C	Urinary lactulose-rhamnose ratio: 0.014 [ns] Urinary sucrose excretion: 0.02% [ns]
Pals et al.[52] Part B	n=6 active male and female participants	60 minutes running at 60% VO_{2peak} in T_{amb} 22°C (50% RH)	T_{re}: 38.7°C	Urinary lactulose-rhamnose ratio: 0.016 [ns] Urinary sucrose excretion: -0.04% [ns]
Lambert et al.[55] Part B	n=20 male and female endurance runners	60 minutes running at 70% VO_{2max} with fluid restriction in T_{amb} 24°C (33% RH)	T_{re}: 38.7°C	Urinary lactulose-rhamnose ratio: 0.028* Urinary sucrose excretion: 0.06%*
Zuhl et al.[56]	n=7 endurance trained male and female participants	60 minutes running at 70% VO_{2max} in T_{amb} 30°C (12-20% RH)	T_c: 39.5°C	Urinary lactulose-rhamnose ratio: 0.040[d]*
Buchman et al.[57]	n=15 male and female marathon runners	Road marathon competition. T_{amb} not reported	Not measured	Urinary lactulose-mannitol ratio: 0.040[d, ns]
Pals et al.[52] Part C	n=6 active male and female participants	60 minutes running at 80% VO_{2peak} in T_{amb} 22°C (50% RH)	T_{re}: 39.6°C	Urinary lactulose-rhamnose ratio: 0.059* Urinary sucrose excretion: 0.50%*

T_{amb}, ambient temperature; RH, relative humidity; T_c, post-exercise (or peak) core temperature; T_{re}, post-exercise (or peak) rectal temperature; W_{max}, watt maximum.

[a]In order of exercise-associated small intestinal permeability (ie, lactulose-rhamnose or lactulose-mannitol ratio), otherwise specified.

[b]Post-exercise (or peak) body temperature of respective measurement technique.

[c]Data (mean or median) from text and tables, or extrapolated from figures to the nearest approximate value (pre-exercise resting to post-exercise peak value difference).

[d]Values of control or placebo group/trial of the respective intervention study.

*Significant pre- (rest) to post-exercise increase, [ns]no significant difference pre- (rest) to post-exercise.

6 | EXERCISE AND ENDOTOXAEMIA

Endotoxaemia is characterised by the presence of circulating bacterial lipopolysaccharides, which attach to lipopolysaccharide-binding protein to form immune complexes that initiate a cell-mediated immune cascade.[58,59] The reference cut-off value indicative of exercise-associated endotoxaemia as reported in the literature is ≥5 pg/mL increase in plasma or serum lipopolysaccharide from baseline, with adjunct reduction in anti-endotoxin antibody concentration (eg, IgG and IgM).[15,28,34,60,61] Multiple studies have measured these endpoints in response to exercise (ie, seventeen studies were eligible for inclusion- Table S1), predominantly using a limulus amebocyte lysate chromogenic assay for determination of gram-negative bacterial endotoxin concentration, and the results are shown in Table 3.

The greatest exercise-associated endotoxaemia have been reported in response to extreme endurance exercise, such as ultra-marathon events.[29,30] Moreover, one study that measured plasma sCD14, a phosphatidylinositol-linked membrane glycoprotein on polymorphonuclear leucocytes that serves as a receptor for endotoxin and hence increases in response to septic conditions, significantly increased from pre- to post-exercise in ultra-endurance runners after a 161 km ultra-marathon competition.[69] These outcomes are supported by earlier studies, reporting total plasma endotoxin concentrations of 213 pg/mL, 254 pg/mL and 64-330 pg/mL in response to an Ironman distance triathlon, 89.4 km ultra-marathon and 100 mile cycle events respectively.[34,60,70] One paradoxical finding was the absence of endotoxaemia after a 160 km ultra-marathon,[62] even in the presence of a systemic immune response, indicated by elevated cytokines,[62] and sCD14[69] reported at the same ultra-marathon event (ie, Western States 100 Mile Endurance Run).

From the data available in the literature, moderate exercise durations (eg, <2 hours) produce negligible rises in circulating endotoxin concentration. Although, more prolonged exercise bouts (eg, ≥2 hours) at steady state (eg, 60%-70% VO_{2max}), and/or the inclusion of heat stress (eg, ≥33°C resulting in ≥39.0°C body temperature)

TABLE 3 Impact of exercise on systemic endotoxaemia

Reference[a]	Population	Exercise protocol	Body temperature[b]	Δ pre- to post-exercise endotoxin concentration[c] (otherwise specified)
Yeh et al.[54] Part A	n=15 recreationally active male and female participants	60 minutes running at 70% VO_{2max} in 22°C T_{amb} (62% RH)	T_c: 38.4°C[e]	−1.1 pg/mL[ns]
Nieman et al.[62]	n=25 male and female ultra-endurance runners	160 km ultramarathon competition in T_{amb} ranging from 10°C to 25°C (56% RH)	Not measured	−0.1 pg/mL[d, ns]
Zuhl et al.[63]	n=7 endurance trained male and female participants	60 minutes running at 70% VO_{2max} in 30°C T_{amb} (12% to 20% RH)	T_{re}: 39.5°C	0.2 pg/mL[d, ns]
Sessions et al.[44]	n=7 endurance trained male and female participants	60 minutes running at 70% VO_{2max} in 30°C T_{amb} (12% to 20% RH)	T_{re}: 39.5°C	0.6 pg/mL[d, ns]
Ng et al.[64]	n=30 male endurance runners	21 km road running competition in 27°C T_{amb} (84% RH)	T_c: 40.7°C [e]	0.6 pg/mL*
Shing et al.[65]	n=8 male endurance runners	Running to fatigue at 80% ventilatory threshold (33 minutes) in 35°C T_{amb} (40% RH)	T_c: 39.4°C [e]	4.0 pg/mL[d,*]
Jeukendrup et al.[15]	n=29 male and female triathletes	Mountain Ironman triathlon competition in 32°C peak T_{amb}	Not measured	4.0 pg/mL*
Yeh et al.[54] Part B	n=15 recreationally active male and female participants	60 minutes running at 70% VO_{2max} in 33°C T_{amb} (50% RH)	T_c: 39.1°C [e]	5.0 pg/mL*
Ashton et al.[66]	n=10 male physical education students	Incremental exercise test to volitional exhaustion on a cycle ergometer. T_{amb} not reported	Not measured	10 pg/mL*
Gill et al.[67]	n=8 endurance trained male participants	2 h running at 60% VO_{2max} in 34°C T_{amb} (32% RH)	T_{re}: 39.0°C	10 pg/mL[d, ns]
Lim et al.[35]	n=18 male endurance runners	Running at 70% VO_{2max} until T_c reached 39.5°C or volitional exhaustion (time not given) in T_{amb} 35°C (40% RH)	T_c: 39.5°C	10 pg/mL[d,*]
Camus et al.[61]	n=12 male triathletes	Olympic course triathlon competition. T_{amb} not given	Not measured	12 pg/mL*
Guy et al.[68]	*n*= 8 trained male participants	3 × 10 minutes cycling at 50%, 60%, and 70% consecutively of peak wattage of VO_{2max}, then a 5 km time trial in T_{amb} 35°C (70% RH)	T_{re}: 38.7°C	13 pg/mL[d, ns]
Camus et al.[28]	n=9 male endurance runners	Marathon competition. T_{amb} not given	Not measured	16 pg/mL[stat-x]
Barberio et al.[48]	n=8 endurance trained male participants	Running at 78% VO_{2max} (4 mMol/L blood lactate) until T_c increases 2.0°C or volitional exhaustion (24 minutes) in T_{amb} 40°C (40% RH)	T_{re}: 39.0°C	28 pg/mL[d,*]
Gill et al.[29]	n=19 male and female ultra-endurance runners	Multi-stage ultramarathon (stage 1: 37 km) in T_{amb} ranging from 30°C to 32°C (RH 31% to 32%)	T_{tymp}: 37.5°C (↑ 1.0°C)	40 pg/mL*
Gill et al.[30]	n=17 male and female ultra-endurance runners	24 hours continuous ultramarathon competition (distance range 122 km to 208 km) in T_{amb} ranging from 0°C to 20°C (RH 54% to 82%)	T_{tymp}: 37.5°C (↑ 1.5°C)	122 pg/mL*
Stuempfle et al.[69]	n=20 male and female ultra-endurance runners	161 km ultramarathon competition in T_{amb} ranging from 0°C to 32°C (RH not given)	T_c: 38.2°C	sCD14: 0.6 μg/mL*

T_{amb}: ambient temperature, RH: relative humidity, T_c: post-exercise (or peak) core temperature, T_{re}: post-exercise (or peak) rectal temperature, T_{tymp}: post-exercise tympanic temperature.

[a]In order of exercise-associated endotoxaemia, otherwise specified.

[b]Post-exercise (or peak) body temperature of respective measurement technique.

[c]Data (mean or median) from text and tables, or extrapolated from figures to the nearest approximate value (pre-exercise resting to post-exercise peak value difference). Where values are reported as EU/mL, for consistency these have been converted to pg/mL using standardised conversion rates.

[d]Values of control, placebo, or neutral group/trial of the respective intervention study.

[e]Core temperature determined by wireless ingestible temperature sensor.

*Significant pre- (rest) to post-exercise increase, [ns] no significant difference pre- (rest) to post-exercise, [stat-x] no statistical analysis provided or statistical analysis unclear.

within shorter high intensity exercise bouts to exhaustion, appear to result in circulating endotoxin concentrations above the reference criterion. In studies reporting substantial elevations in post-exercise endotoxin concentration, a pronounced cytokinaemia is also observed, featuring both systemic pro-inflammatory and compensatory anti-inflammatory responses, remaining elevated from 24 hours to 1 week after cessation of exercise.[15,29,30,69] This is accordance with the cytokine response seen in septicaemia (ie, increase in IL-1β, TNF-α, IL-6, IL-8, IL-10 and IL-1ra). Moreover, mild to severe gastrointestinal symptoms (ie, nausea, regurgitation and faecal blood loss) have also been reported in studies observing endotoxaemia and cytokinaemia post-exercise. However, associations between gastrointestinal symptoms and endotoxaemia have not always been consistent.[15,16,29,30,60,70]

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 (eg, *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 2).[71] For example, an intestinal microbiome diversity with high abundance of short chain fatty-acid (eg, butyrate) producing microorganisms (eg, *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,[72-74] may be protective against exercise-associated gastrointestinal barrier perturbations and systemic responses. Although, a microbiome profile abundant in bacterial species with endotoxins (eg, *Escherichia coli* lipopolysaccharide) and associated pathogenic structures (ie, outer membrane vesicles containing peptidoglycan)[25,26,31] may promote exacerbated endotoxaemia, local epithelial and systemic responses.[75,76]

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 (ie, oral iron replacement therapy) may have major effects on the intestinal microbiome total abundance and diversity, some of which are regarded as dysbiotic.[77-79] 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[80] and sustaining an active lifestyle[81] creates changes in the intestinal microbiome diversity in human populations (ie, higher *Firmicutes* to *Bacteroides* ratio compared to healthy controls, and higher abundance of *Bifidobacterium*, *Lactobacillus*, and *Clostridium leptum*;[80] and higher abundance of *Faecalibacterium prausnitzii*, *Roseburia hominis* and *Akkermansia muciniphila*).[81] 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.

7 | EXERCISE AND GASTROINTESTINAL MOTILITY

Understanding the effect of prolonged strenuous exercise on gastrointestinal motility is important since the consumption of foods/fluids during exercise aids in the maintenance of blood glucose

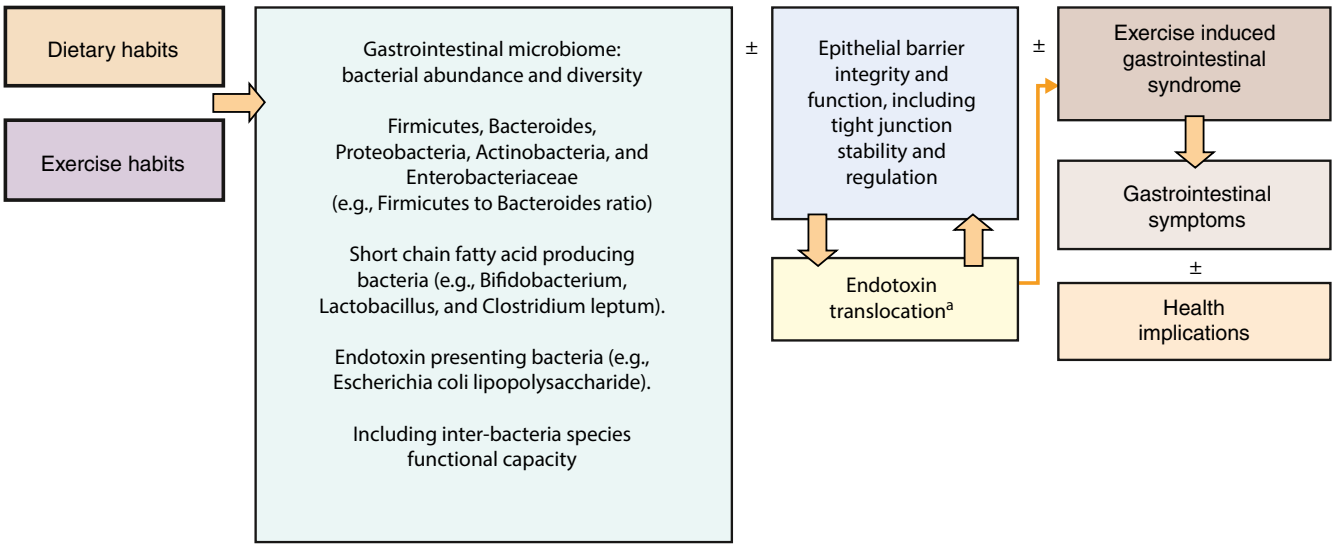

FIGURE 2 The intestinal microbiome and exercise-induced gastrointestinal syndrome: a speculative model. [a]Increases in bacterial endotoxin translocation and subsequent local and systemic inflammatory responses further exacerbates disturbances to epithelial integrity and tight-junction stability and regulation[25-27]

concentration and euhydration, aimed at attenuating fatigue and enhancing exercise performance.[82,83] However, consumption during a period when gastrointestinal motility is compromised may create a symptomatic burden, owing to pronounced intra-gastric pressure associated with reduced gastric empting rates, reduced orocaecal transit time (OCTT), and/or potentially malabsorption increasing intestinal luminal distention due to, for example, osmotic effects of short-chain carbohydrates and/or their fermentation.[11,18,19,39,40] The majority of studies identified included a measure of gastric emptying, and four studies also included a measure of OCTT (Table S1). The result of those studies are shown in Table 4.

Exercise intensity appears to be a key regulator of gastric emptying rate, with higher intensity exercise (≥70% peak power output) causing the greatest disturbance to gastric motility. For example, gastric empting of a pre-exercise carbohydrate electrolyte solution, determined by direct aspiration, was reduced in response to intermittent sprint cycling (alternating between 100% VO_{2max} and 75% VO_{2max}), when compared to steady state exercise (66% VO_{2max}) and rest.[87] Intermittent high intensity running has also been shown to slow gastric emptying compared with walking.[88] However, steady state moderate exercise (60% to 70% peak power output or 66% VO_{2max} equivalent) does not appear to influence gastric emptying and intestinal transit compared to rest in well-trained individuals.[87,90,91] The impact of high intensity exercise on gastric motility appears to be short-lived, as the intensity of prior exercise (rest, 33% peak power output, or 10×1 minutes intervals at peak power output) has negligible effect on post-exercise gastric emptying rate of a glucose solution.[84] A systematic review of exercise and gastric emptying by Horner et al.[18] supports these observations, reporting a dose-response of slower emptying with exercise of higher intensities and longer duration.

The impact of acute exercise on OCTT is unclear (Table 4). When measured using a lactulose challenge breath test and subsequent appearance of H_2 over time, OCTT decreases by 40% and 19% following vigorous cycling for 90 minutes at 70% and ~80% VO_{2max}, respectively;[90,91] while a greater decrease was reported with running at the same intensity (~74%).[80] In contrast, when fluoroscopy was used, faster intestinal transit times were found post-exercise in trained orienteers undertaking a week of heavy training,[89] and a 30 minutes bout of acute exercise in trained males had minimal influence on the transit time of food up to the ileocaecal valve.[85] Consistency in the measures of OCTT employed in future studies should help to better elucidate the effect of diverse-exercise (ie, intensity, duration and mode) on OCTT.

Gastric myoelectrical activity may be used to infer gastric motility, and two identified studies employed the technique of electrogastrography following exercise. Supine cycling for 20 minutes at 60 W increased signal amplitude compared to that at rest,[92] and low intensity cycling (~25 minutes) in non-regular exercising individuals has been shown to increase motility.[93] Whether such effects were mediated by changes in vagal pathways is not known; but, in rats, exercise-induced gastric antral motility is abolished with vagotomy.[94] Considering exercise promotes a potent sympathetic drive, it is thought that sympathetic activation may delay gastric emptying in response to stress,[95] since reducing sympathetic activity in an animal model of spinal cord injury was associated with an increase in gastric emptying and intestinal transit.[96]

Exercise bouts of low to moderate intensity, of short duration (ie, <60 minutes), appear to promote gastrointestinal motility, while more prolonged (ie, up to 90 minutes) and vigorous exercise may cause inhibition. Given the complex interaction of hormonal and neurological control of gastric motility (reviewed by Browning and Travagli),[97] further studies are required to elucidate the role of acute and prolonged exercise on gastric and intestinal motility. For example, endurance and ultra-endurance athletes often report rapid and aggressive onset of severe regurgitation, abdominal pain, and inability to tolerate feeding when exercise duration reaches ≥3 hours. It is reasonable to hypothesise that gastroparesis and paralytic ileus might underlie these symptoms. To date, no study has investigated gastric emptying and/or OCTT in extreme endurance events; therefore, the question of whether the duration of exercise promotes paralytic ileus needs to be addressed. Furthermore, the impact of heat stress during exercise on gastrointestinal motility is still largely unknown and warrants investigation.

8 | EXERCISE AND MALABSORPTION

The competent functioning of nutrient transporters on intestinal enterocytes during exercise is important for achieving nutrient intake requirements during prolonged exercise and avoiding the occurrence of gastrointestinal symptoms arising from nutrient malabsorption, as well as aiding post-exercise nutrient absorption that can optimise recovery processes.[14,19,37] Intestinal nutrient transporter activity during exercise can be determined by urinary excretion of non-metabolisable glucose analogues, such as D-xylose that is passively absorbed (ie, GLUT5 activity), and 3-O-methyl-D-glucose (3MG) that is actively absorbed (ie, SGLT1 activity).[10] Reduced active and passive carbohydrate absorption has been observed in response to running at 70% VO_{2max} compared to rest, or after running at 30% and 50% VO_{2max} in thermoneutral ambient conditions.[10] Body temperature and dehydration were higher with increasing exercise intensity, but whether these factors affected the absorption of the glucose analogues consumed at the start of exercise is unknown. A reduction in post-exercise protein absorption, as measured by in vivo combination of 20 g L-[1-13C]phenylalanine-labelled protein ingestion with continuous intravenous L-[ring-2H5] phenylalanine infusion,[98] was observed after a single bout of resistance-type exercise.[37] Plasma I-FABP concentration increased 35% after the resistance exercise, suggesting impairment in protein absorption during the post-exercise recovery period was possibly due to injury associated loss of intestinal absorptive function. It is speculated that exercise-associated splanchnic hypoperfusion may contribute to the reduced intestinal epithelial absorptive activity seen in response to exercise, but further research is required to elucidate the exact mechanisms.

TABLE 4 The impact of exercise on gastrointestinal motility

Reference [a]	Population	Exercise protocol	Provision of meal and (or) fluid	Method (M) and outcome measure (O)	% change compared to rest (or walking) [b]
Gastric emptying					
Evans et al.[84]	n=8 active male and female participants	1. 30 minutes cycling 33% of PPO. 2. 10×1 minutes at PPO followed by 2 minutes rest	595 mL CES post-exercise	M: gastric aspiration, O: T½	0% change for 33% [ns], 0% change for 10×1 minutes [ns]
Kuznetsov et al.[85]	n=11 active male participants and male athletes	30 minutes cycling 75% VO_{2max}	200 g porridge post-exercise	M: radio-isotope scanning, O: T½	↑ 24% athletes [stat-x], ↓ 20% active [stat-x]
Leiper et al.[86]	n=7 male soccer players	2×15 minutes periods of a competitive 5-a-side indoor soccer match (~59% VO_{2max})	500 mL CES pre-exercise.	M: gastric aspiration, O: volume emptied	↓ 133% compared to walking [ns]
Leiper et al.[87]	n=8 active male participants	1. 60 minutes cycling 66% VO_{2max}, 2. 3×30 s sprints at 100% VO_{2max} with 60s recovery at 60% VO_{2max}, 3. 3×30 s sprints at 100% VO_{2max} with 60 s recovery at 70% VO_{2max}	600 mL CES pre-exercise	M: gastric aspiration, O: T½	↓ 5% with 66% VO_{2max} [ns], ↓ 50% with sprints and recovery at 60% VO_{2max} [*#], ↓ 210% with sprints and recovery at 70% VO_{2max} [*#]
Leiper et al.[88]	n=8 trained male participants	2×15 minutes of intermittent sprinting	~588 mL carbohydrate-free electrolyte solution or CES consumed pre- and during exercise	M: gastric aspiration, O: volume emptied	↓ 47% in carbohydrate-free [#], ↓ 29% in CES compared to walking [#]
Strid et al.[89]	n=15 male and female trained orienteers	100 minutes running at ~80% VO_{2max} following a week heavy training	400 kcal solid meal pre-exercise	M: radiopaque markers with fluoroscopy, O: Gastric emptying time	↓ 33% [ns]
van Nieuwenhoven et al.[90]	n=10 trained male participants	90 minutes cycling at ~80% VO_{2max}	CES (5 mL/kg) at 40 minutes during exercise containing ^{13}C-acetate	M: ^{13}C-acetate breath test, O: ^{13}C-acetate	↑ 2% [ns]
van Nieuwenhoven et al.[91]	n=10 trained male and female participants	1. 90 minutes cycling 70% PPO, 2. 90 minutes running 70% $speed_{max}$	CES (5 mL/kg) at 40 minutes during exercise containing ^{13}C-acetate	M: ^{13}C-acetate breath test, O: ^{13}C-acetate	↑ 18% cycling [ns], ↓ 14% running [ns]
Orocaecal transit					
Kuznetsov et al.[85]	n=11 active male participants and male athletes	30 minutes of cycling at 75% VO_{2max}	200 g solid meal post-exercise	M: radio-isotope scanning, O: time of transit to ileocaecal valve	↑ 3.8% in athlete group [stat-x], ↑ 16.3% in active group [stat-x]
Strid et al.[89]	n=15 male and female trained orienteers	100 minutes running at ~80% VO_{2max} following a week heavy training	400 kcal solid meal pre-exercise	M: radiopaque markers with fluoroscopy, O: Small intestine and colon transit time	↑ 46% intestinal transit *, ↑ 14% colon transit [ns], ↑ 300% descending colon transit *
van Nieuwenhoven et al.[90]	n=10 trained male and female participants	90 minutes cycling at ~80% VO_{2max}	Liquid meal (4 mL/kg) with CES containing lactulose (2 mL/kg) pre-exercise and CES during exercise (2 mL/kg at 20 minutes and 5 mL/kg at 40 minutes)	M: lactulose challenge breath test, O: H_2	↓ 19% [ns]
van Nieuwenhoven et al.[91]	n=10 trained male and female participants	1. 90 minutes cycling 70% PPO, 2. 90 minutes running 70% $speed_{max}$	Liquid meal (4 mL/kg) with CES containing lactulose (2 mL/kg) pre-exercise and CES during exercise (2 mL/kg at 20 minutes and 5 mL/kg at 40 minutes)	M: lactulose challenge breath test, O: H_2.	↓ 40% in cycling *, ↓ 74% in running *
Myoelectrical activity					
Kato et al.[92]	n=8 healthy male participants.	20 minutes supine cycling at 60 W	No meal	M: EGG, O: peak amplitude	↑ 120% *

(Continues)

TABLE 4 (Continued)

Reference [a]	Population	Exercise protocol	Provision of meal and (or) fluid	Method (M) and outcome measure (O)	% change compared to rest (or walking) [b]
Lu et al.[93]	n=9 healthy but sedentary male and female participants	Incremental exercise until reaching 50% HHR for 10 minutes (~25 minutes)	450 kcal solid meal post-exercise	M: EGG, O: 2-4 cpm slow waves	↑ 25% *

PPO: peak power output, CES: carbohydrate electrolyte solution, T½: time taken for half of the original test meal or fluid volume to empty from the stomach, BM: body mass, $speed_{max}$: maximal speed, H_2: hydrogen, W: watts, HHR: heart rate reserve, EGG: electrogastrogram.
[a]In alphabetical order.
[b]Data (mean or median) from text and tables, or extrapolated from figures to the nearest approximate value.
*Significant pre- (rest) to post-exercise change. #Significantly different compared to low intensity condition, [ns] no significant difference pre- (rest) to post-exercise, [stat-x] no statistical analysis provided.

Carbohydrate malabsorption can be measured by breath hydrogen (H_2) excretion after the consumption of glucose and/or fructose that is normally absorbed. During 3 hours of alternating running and cycling at 75% VO_{2max},[38] breath H_2 was higher during running than cycling, and consumption of both fluid (1.3 g/kgBM/h) and semi-solid (1.2 g/kgBM/h) glucose-rich carbohydrates resulted in higher breath H_2 excretion (increase in 2 and 3 ppm, respectively) compared with a non-carbohydrate placebo. However, such increases are minimal and of uncertain significance. Comparison of breath hydrogen before and during exercise must take into account that breath H_2 may be reduced during the increased ventilation rate associated with exercise.[99] Post-exercise values taken when respiratory rate returns to resting levels may be a more accurate measure of nutrient malabsorption. For example, of the 25 healthy endurance trained runners challenged with 90 g/h of carbohydrate (2:1 glucose to fructose, 10% w/v) during a 3 hours running protocol, 68% showed evidence of carbohydrate malabsorption (breath H_2 ≥10 ppm above baseline)[100] during the recovery period.[19] Moreover, breath H_2 responses in this study correlated with incidence and severity of gastrointestinal symptoms, suggesting factors contributing to exercise-associated malabsorption (eg, epithelial injury, nutrient transport impairment and/or poor nutrient tolerance) may pre-dispose an individual to gastrointestinal issues during exercise.

9 | EXERCISE-ASSOCIATED GASTROINTESTINAL SYMPTOMS

The incidence of gastrointestinal symptoms during exercise (ie, predominantly endurance exercise) has previously been reviewed by ter Steege and Kolkman[8]. More recently, however, several field-based observational studies that have comprehensively assessed gastrointestinal symptoms during extreme endurance events identified a high incidence and severity of symptoms from both presumed upper- (eg, regurgitation, upper abdominal bloating, belching, epigastric pain and heartburn) and lower- (eg, flatulence, urge to defecate, lower abdominal bloating, abdominal pain, abnormal defecation including loose water stools, diarrhoea and faecal blood loss) gastrointestinal origin, and nausea far above what has previously been reported. Such symptoms have been major factors associated with withdrawal from competition due to their severity and to more worrying clinical features of acute colitis that included faecal blood loss (Table 5).[7,14-16,101,102] The types and prevalence of different gastrointestinal symptoms reported during a multi-stage and 24 hours continuous ultra-marathon can be viewed in Figure 3, and are consistent with those reported in response to other endurance events (ie, marathon distance, long course triathlon and 161 km ultra-marathon).[7,14-16] These findings and those of other endurance events clearly highlight that symptoms referable to the upper-gastrointestinal tract, including nausea, are the predominant symptoms reported during exercise, in comparison to those referable to the lower-gastrointestinal tract.

Several risk factors for developing symptoms during exercise have been identified. First, the duration of exercise is not unexpectedly a factor. For example, 96%, 85% and 73% of an ultra-endurance athlete cohort competing in a 161 km, multi-stage, and 24 hours continuous ultra-marathon, respectively, reported severe gastrointestinal symptoms during competition.[14,16] In contrast, only 11% and 7% of endurance runners who had completed a half-marathon and marathon, respectively, reported gastrointestinal symptom.[7] Second, the type of exercise influences risk, with running repeatedly shown to promote greater incidence and severity of gastrointestinal symptoms compared to other exercise modes (eg, cycling).[8,91,102] Third, ambient temperature is important with higher incidence and severity of gastrointestinal symptoms in hot ambient conditions (ie, ≥30°C) compared to those reported in cold to thermoneutral ambient conditions.[14] Fourth, women are more prone to exercise-associated gastrointestinal symptoms than men.[7,19] Fifth, individuals with history of recurrent exercise-associated gastrointestinal symptoms appear to suffer greater incidence and severity of symptoms during exercise,[7,19] suggesting some degree of pre-disposition. Finally, feeding during exercise at a time when the gastrointestinal tract is compromised may be a risk factor. Indeed, 100% and 52% of participants during a gut-challenge protocol suffered from mild and severe symptoms, respectively, when challenged with 90 g/h CHO (2:1 glucose-fructose, 10% w/v) during running at 60% VO_{2max} in thermoneutral ambient conditions, in which euhydration was maintained throughout.[19]

10 | IMPLICATIONS FOR CHRONIC GASTROINTESTINAL DISEASES

Hypothetically, the components of exercise-induced gastrointestinal syndrome may have adverse health implications for patients with chronic gastrointestinal diseases already associated with

TABLE 5 Field based exploratory research assessing the impact of endurance sports on the incidence and severity of gastrointestinal symptoms.

Competition characteristics[a]	Population	Incidence of gastrointestinal symptoms[b]	Gastrointestinal symptoms reported
Marathon[102] (42.2 km) T_{amb} range: 7°C to 14°C	n=28 male and female marathon runners	4%[c]	Greater reports of upper-gastrointestinal symptoms compared with lower-gastrointestinal symptoms[d]
Cycling[102] (100 km or 155 km) T_{amb} range: 15°C to 24°C	n=28 male cyclists	4%[c]	Greater reports of upper-gastrointestinal symptoms compared with lower-gastrointestinal symptoms[d]
Professional cycling[102] (182-228 km) T_{amb} range: 10°C to 23°C (171-205 km) T_{amb} range: 19°C to 31°C	n=7 male cyclists. n=8 male cyclists	7%[c]	Greater reports of lower-gastrointestinal symptoms compared with upper-gastrointestinal symptoms[d]
Recreational running[7] 10 km 21 km 42 km T_{amb} not provided	 n=261 n=766 n=227 Male and female recreational runners	 10% [e] 11% [e] 7% [e]	Nausea[g], regurgitation, belching[g], side stitch[f], abdominal cramps[f,g], urge to defecate, flatulence, and diarrhoea
Half Ironman triathlon[102] T_{amb} range: 15°C to 34°C	*n*= 43 male and female triathletes	14% [c]	Greater reports of upper-gastrointestinal symptoms compared with lower-gastrointestinal symptoms [d]
Ironman triathlon[102] Germany T_{amb} range: 15°C to 33°C Hawaii T_{amb} range: 26°C to 36°C	n=54 male and female triathletes n=53 male and female triathletes	31% [c] 32% [c]	Greater reports of upper-gastrointestinal symptoms compared with lower-gastrointestinal symptoms [d] Greater reports of upper-gastrointestinal symptoms compared with lower-gastrointestinal symptoms [d]
161 km ultra-marathon[103] T_{amb} range: 15°C to 28°C	n=15 male and female ultra-endurance runners	60%	Nausea[f,g], regurgitation, abdominal cramps, and diarrhoea
24 hours continuous ultra-marathon[14] (122-208 km distance range) T_{amb} range: 0°C to 20°C	n=22 male and female ultra-endurance runners	73% [c]	Nausea[f], urge to regurgitate[f], regurgitation, belching, bloating, stomach pain, gastric acidosis, abdominal pain, constipation, and diarrhoea
Multi-stage ultra-marathon (5-stages, 230 km)[14] T_{amb} range: 32°C to 40°C	n=54 male and female ultra-endurance runners	85% [c]	Nausea[f], urge to regurgitate[f], regurgitation, belching, bloating, stomach pain, gastric acidosis, abdominal pain, constipation, and diarrhoea
Mountain Ironman triathlon[15] T_{amb} range: 9°C to 32°C	n=29 male and female triathletes	93%	Nausea[g], urge to regurgitate[g], regurgitation, stomach problems[f,g], belching[f], heartburn, bloating, stomach cramps, intestinal cramps[g], side aches, diarrhoea, flatulence[f], and urge to defecate
161 km ultra-marathon[16] T_{amb} range: 5°C to 39°C	n=272 male and female ultra-endurance runners	96% [c]	Nausea[f], regurgitation, belching[f], stomach bloating, reflex/ heartburn, stomach cramps/pain[f], side ache/stitch, intestinal cramps/pain[f], flatulence[f], urge to defecate, loose stools/diarrhoea, intestinal bleeding/bloody faeces.

[a]In order of gastrointestinal symptom incidence.
[b]Percentage incidence of gastrointestinal symptoms within the participant cohort.
[c]Severe or serious gastrointestinal symptoms.
[d]Detailed incidence and severity of specific symptoms was not reported.
[e]Symptom incidence of runners who completed the running distance.
[f]Most predominate symptoms reported.
[g]Most severe symptoms reported.

compromised gastrointestinal integrity and function. This would apply particularly to the patients with IBD or FGID such as, IBS and functional dyspepsia. The adverse effects of strenuous exercise of greatest concern are: (1) the repetitive injury to the intestinal epithelium with insufficient recovery time in-between insults; (2) effects on gut motility associated with intestinal hypoperfusion, ischaemia and altered enteric nervous activity during exercise and (3) local and systemic inflammatory responses associated with intestinal injury, enhanced epithelial permeability, endotoxaemia and the oxidative stress associated with reperfusion.[9,27,36] Concern also generates from studies in murine models of chemically induced colitis, in which voluntary exercise reduces inflammation, but vigorous exercise programs have led to increased inflammation and mortality.[104]

Exercise has generally been advocated for populations suffering from IBD and FGID for relapse prevention, management and improving quality of life.[105,106] There are associations between low

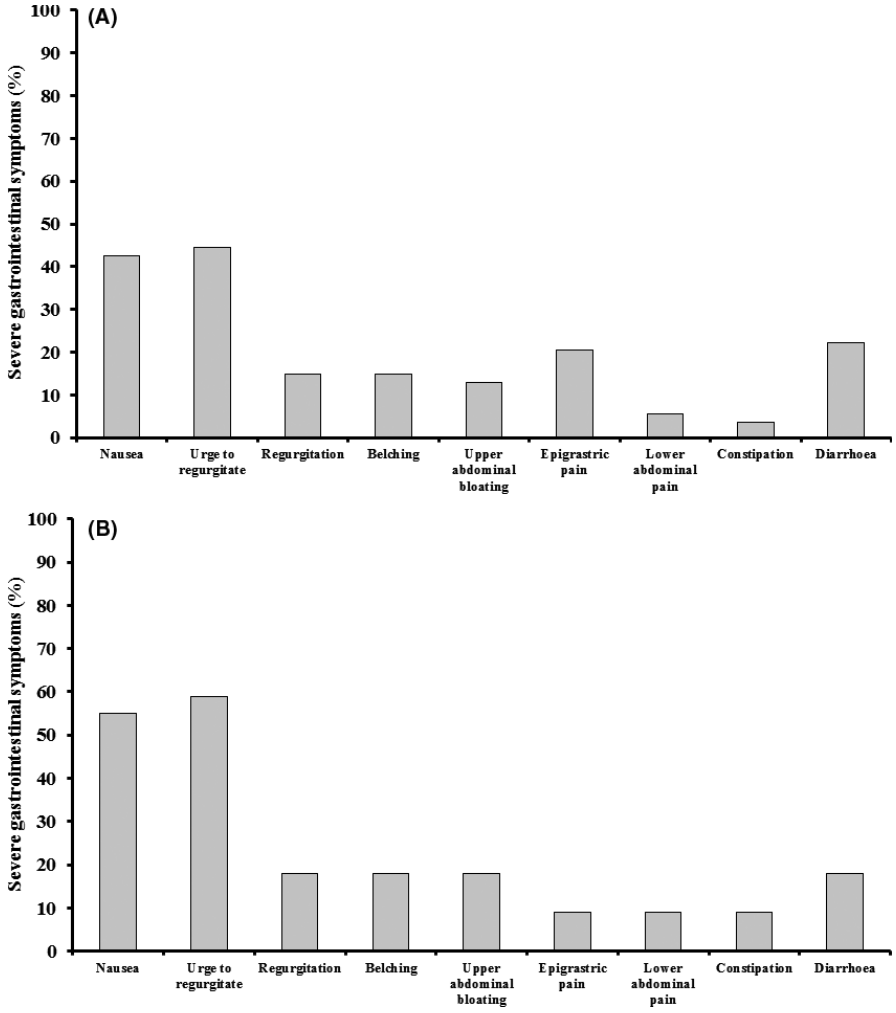

FIGURE 3 Types of gastrointestinal symptoms reported by ultra-marathon runners during a multi-stage ultramarathon (n=54) (A) and a 24-hours continuous ultramarathon (n=22) (B) (MSUM and 24 hours). Adapted from Costa et al[14]

levels of habitual exercise (eg, walking or equivalent) and the prevention and management of IBD and FGID, and lower risk of relapse in IBD with higher exercise adherence.[104,106] Moderate levels of exercise that have included thrice weekly running or walking programs over 10-12 weeks were well tolerated without changes in disease activity and associated with improvement of various indices of well-being.[107-109] Likewise, an individually tailored increase in physical activity has been shown to improve gastrointestinal symptom severity in a cohort with IBS, compared to a control group with IBS who received no intervention.[110] The benefits appear to be maintained over several years.[111] The mechanisms for the improvements are likely to be multifactorial. Improvements in gas clearance and subsequent bloating and discomfort symptoms have been observed during mild cycling exercise of 75 minutes duration in patients with IBS.[112] It is important to note that the overall exercise stress (ie, modest intensity and duration) in such interventions would not be anticipated to prompt exercise-induced gastrointestinal syndrome to any significant degree in healthy individuals.

Only two studies have examined the effects of higher intensity exercise in patients with Crohn's disease. First, 1 hour running at 60% VO_{2max} in six patients with ileal Crohn's disease in remission did not cause further disturbances to gastrointestinal permeability, OCTT or symptoms compared with matched controls; but evidence of neutrophil activation, increased oxidative stress, and zinc loss in the urine were noted.[113] Second, 30 minutes cycling at 50% peak power output, followed by four 15 s sprints at 100% peak power output, induced mild perturbations to inflammatory profile in 15 young patients with Crohn's disease;[114] although these were generally similar to those observed in 15 matched healthy controls. The results of these studies confirm that systemic inflammatory activation will occur in patients with Crohn's disease in association with exercise of moderate intensity, but detrimental effects on the disease itself over the short term were not apparent. Moreover, it is currently unknown if individuals with IBD present greater exercise-associated endotoxaemia compared with healthy counterparts. Where intestinal barrier is already compromised, it is plausible that prolonged strenuous exercise may lead to greater endotoxaemia in

comparison to those individuals with an intact intestinal barrier. Indeed, increases in epithelial injury associated local inflammatory cytokines (eg, TNF-α, IL-1β and INF-γ) have been linked to greater tight-junction perturbation and enhanced permeability of pathogenic bacterial endotoxins, leading to an endotoxin-induced cytokinaemia.[27,115,116] The safety of prolonged strenuous exercise in patients with active disease is not known. With symptoms such as joint pains and fatigue being common in patients with active IBD, there are significant barriers to participation in such activities.[117] Considering no research has yet identified the impact of vigorous exercise on gastrointestinal integrity, function and symptoms in individuals suffering from gastrointestinal diseases/disorders, it should be considered a risk to undergo prolonged strenuous exercise until its safety is demonstrated, especially in IBD patients.

The final issue is whether strenuous exercise can induce or precipitate IBD or FGID in previously healthy individuals. There are anecdotal reports of IBD diagnosis in ultra-endurance athletes following repetitive participation in extreme endurance exercise,[118,119] but no formal examination of this association has been reported. The difficulty with proving such an association is that the pathophysiological changes associated with exercised-induced gastrointestinal syndrome may potentially precipitate a flare of inflammation in individuals with IBD who believed themselves to be healthy, but had relatively asymptomatic IBD prior to the exercise stimulus. Since FGID is a syndrome characterised by chronic symptoms, it would be challenging causally associating strenuous exercise bouts with the development of the condition. However, as outlined above, gastrointestinal symptoms developing during exercise invariably resolve. Large cohort observational studies are needed to provide clues of a potentially causal association between participation in prolonged strenuous exercise and the onset of IBD and FGID.

Overall, there is limited research that explores greater magnitudes of exercise stress (intensity and duration) on markers of gastrointestinal status (injury, inflammation, permeability, endotoxaemia, motility and malabsorption) in populations suffering with diseases/disorders of the gastrointestinal tract. Therefore, it is currently unknown if individuals with gastrointestinal diseases/disorders present greater incidence and severity of exercise-induced gastrointestinal syndrome compared with healthy counterparts in response to acute exercise. Given the current evidence to date, it is unlikely that individually prescribed low to moderate intensity (≤60% VO_{2max}) exercise of short duration (≤1 hour) in the absence of additional stressors such as hot ambient conditions, elevated body temperature, and/or dehydration will exacerbate factors that contribute to the development of exercise-induced gastrointestinal syndrome. However, the physiological changes elicited by more intensified exercise stress theoretically may have major impact on the underlying gastrointestinal diseases/disorders, and it makes clinical sense to advise patients against such at-risk situations, particularly for those with IBD. In these populations, prior to participating in vigorous sporting events or exercise programs, it would be advised to undertake a individually tailored gastrointestinal assessment (ie, comprehensive integrity, function and symptoms markers) in response to exercise stress (ie, within tolerable and safe limits), to determine the magnitude of exercise-associated gastrointestinal perturbations, and to ascertain which primary causal and/or exacerbating factor/s may be contributing to the greatest extent. Such information may guide potential preventive and management strategies, and/or appropriate exercise prescription on a case-by-case basis; bearing in mind that the impact of vigorous exercise on gastrointestinal health of populations with gastrointestinal diseases/disorders requires further research.

11 | PREVENTION STRATEGIES

There are several strategies that have been evaluated for their efficacy to prevent or reduce the severity of exercise-associated gastrointestinal perturbations. These include the following:

11.1 | Maintenance of euhydration

There is evidence that dehydration may exacerbate exercise-associated gastrointestinal disturbances. Acute body mass loss of 2.7%, via sauna exposure, prior to cycling exercise (70% VO_{2max}) has been shown to impair gastric emptying and increase gastrointestinal symptoms, including nausea, compared with starting exercise in a euhydrated state.[120] Hydration status, however, had no effect on orocaecal transit time, intestinal permeability or glucose intestinal absorption in response to the exercise. Dehydration (2.7% acute body mass loss) 12 hours prior to exercise (via low intensity treadmill walking in the heat), however, did not influence gastric emptying during steady state exercise (65% VO_{2max}).[121] In these two investigations, fluid was provided during exercise but it is reasonable to suggest that fluid restriction would further exacerbate any dehydration related exercise-associated gastrointestinal disturbances as withholding fluid during running exercise (acute body mass loss of ~1.5%) increases gastroduodenal and intestinal permeability above resting levels.[55] Maintaining euhydration during ultra-marathon competition may be an important factor in attenuating exercise-induced endotoxaemia and cytokinaemia.[29,30] Indeed, participants who had an exercise-induced body mass loss of >2% and a plasma osmolality >300 mOsmol/kg showed higher average circulating endotoxin concentrations compared with those who maintained euhydration with *ad libitum* water intake during 2 hours running at 60% VO_{2max} in hot ambient condition (34°C).[67] Attention must also be given to avoid over-hydration during exercise, considering exercise-associated hyponatraemia has been linked to gastrointestinal symptoms, particularly nausea and regurgitation.[122,123] It therefore appears that starting exercise euhydrated and maintaining euhydration throughout attenuates various components of exercise-induced gastrointestinal syndrome.

11.2 | Consumption of carbohydrate during exercise

Frequent and consistent consumption of carbohydrate during exercise is a protective strategy against exercise-induced gastrointestinal

perturbations. Carbohydrate presence in chyme, increased intestinal carbohydrate transport activity and carbohydrate post-absorption stimulate nitric oxide induced vasodilation, the most potent stimulator for increasing post-prandial microvascular blood flow in intestinal villi.[124] Carbohydrate intake during exercise maintains splanchnic perfusion (attenuates exercise-induced hypoperfusion)[125] and ameliorates intestinal permeability in response to exercise stress and NSAID administration.[126] Indeed, we have observed an abolition of intestinal injury, reduced intestinal permeability, and improved endotoxin and cytokine profile with the consumption of 15 g of carbohydrate pre-exercise and every 20 minutes during running at 60% VO_{2max} in 35°C, compared with water alone.[127] Such quantities of carbohydrate (45 g/h) appear to be well tolerated[127]. However, higher rates (up to 90 g/h) of multiple-transportable carbohydrate intake during running appear to be less tolerable,[19] despite their recommended intake.[128] Interestingly, 15 g of whey protein hydrolysate administered pre-exercise and every 20 minutes during running also results in similar gastrointestinal integrity outcomes, however symptoms were much higher, suggesting difficulties in tolerating protein during exercise.[127] It would therefore be beneficial to identify individual carbohydrate intake tolerance levels (ie, quantity and quality) during exercise that requires an exogenous fuel supply (ie, ≥2 hours), and consume carbohydrates evenly and more frequently throughout exercise.

11.3 | Dietary adaptation of the gastrointestinal tract pre-exercise

To date, only one study has comprehensively investigated a strategic gut-training protocol to prevent or attenuate exercise-associated gastrointestinal disturbances and symptoms. 2 weeks of carbohydrate ingestion during daily running exercise (90 g/h of carbohydrate in either a gel disk 2:1 glucose to fructose ratio, or a carbohydrate-rich food) significantly reduced overall gut discomfort, total and upper-gastrointestinal symptoms by more than 40%, with reductions in lower-gastrointestinal symptoms and nausea also reported, in response to a 3 hours gut-challenge protocol, with no changes in placebo observed.[19] In addition, the gut-training resulted in an abolition of malabsorption and increased blood glucose availability, thus providing some evidence for upregulation of intestinal carbohydrate transporters.

There has recently been an exponential growth in the number of non-coeliac athletes adhering to a gluten-free diet. Over 41% of a non-coeliac athletic population surveyed reported adhering to a gluten-free diet in the belief that the diet reduced gastrointestinal symptoms and enhanced exercise performance.[129] However, such perceived improvements in symptoms and performance reported is not supported by a blinded controlled study in which no difference in gastrointestinal symptoms, intestinal injury or systemic cytokine responses to exercise was observed between the presence or absence of gluten.[46] It is possible FODMAP reduction that typically accompanies a gluten-free diet may be an efficacious strategy to manage exercise-induced gastrointestinal symptoms. A recent case study reported that a short-term low FODMAP diet (ie, reducing the FODMAP content from 81 to 7 g/d) abolished gastrointestinal symptoms during running and rest periods in a symptomatic multisport athlete.[130] There is substantial evidence to support the role of a low FODMAP diet in the management of gastrointestinal symptoms, similar to those experienced by runners, in individuals suffering from irritable bowel syndrome,[131] and a low FODMAP diet may be a promising strategy to reduce exercise-associated gastrointestinal disturbances.

11.4 | Avoidance of NSAIDs

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 ulcers, gastrointestinal bleeding, and abnormal defecation (eg, diarrhoea).[122,132] The administration of NSAIDs prior to exercise can markedly increase intestinal injury and permeability in response to exercise,[45,133,134] so avoidance of NSAIDs prior to exercise would be recommended to minimise exercise-associated gastrointestinal damage.

11.5 | Dietary supplementation

It has been proposed that certain dietary supplements (ie, anti-oxidants, glutamine, L-arginine, L-citrulline, bovine colostrum and probiotics) may contribute to the prevention and/or attenuate the different perturbed components of exercise-induced gastrointestinal syndrome. The rationale for such approaches includes the following. Because exercise-induced disturbances to intestinal integrity and endotoxaemia, especially in the reperfusion period after exercise, which may be mediated by free radicals, anti-oxidant supplementation may prevent further epithelial damage and ameliorate endotoxaemia.[57,66] L-citrulline and L-arginine are precursors for nitric oxide production, which is a potent vasodilator, potentially enhancing blood flow into the intestinal microvasculature reducing exercise-induced hypoperfusion and ischaemic.[135,136] Glutamine and bovine colostrum have been proposed to enhance the expression of heat shock proteins (ie, proteins that protect cellular membrane under period of stress), which may protect the intestinal enterocytes, reduce intestinal permeability, and attenuate the development of local inflammatory pathways.[47,56,63,137-140] However, due to heterogeneity methods across studies (ie, magnitude of exercise- and heat-stress, population, supplementation period and dose) and discrepancy in outcomes, the evidence for the use of singular dietary supplements in the prevention and management of exercise-induced gastrointestinal syndrome in human populations is not clear, and warrants further investigation.

The concept that probiotics might exert favourable effects on intestinal epithelial integrity has led to three cross-over and blinded controlled laboratory studies investigating the impact on probiotic

supplementation on markers of gastrointestinal integrity in response to exercise stress. 4 weeks of capsule form *Lactobacillus*, *Bifidobacterium* and *Streptococcus* (4.5×10^9 colony forming units (CFU)) supplementation did not alter exercise-induced perturbations to gastrointestinal integrity, endotoxaemia and cytokinaemia, compared with placebo, in response to running exercise to fatigue (approximately 35 minutes) at 80% of ventilatory threshold in the heat (35°C).[65] Similarly, 14 weeks of multi-species probiotics (10^{10} CFU/d) had no effect on exercise-induced cytokinaemia in response to 90 minutes of cycle ergometer exercise using an incremental high intensity protocol.[141] A more recent study observed that oral ingestion of a commercially available probiotic beverage containing *L.casei* (volume equivalent for $\times10^{11}$ CFU/d) for seven consecutive days before 2 hours of running at 60% VO_{2max} in hot ambient conditions (34.0°C) resulted in a substantially greater endotoxaemia and cytokinaemia during the recovery period, compared with placebo.[67] Thus, evidence that probiotic might be beneficial in preventing or attenuating exercise-induced gastrointestinal syndrome is limited, and may actually contribute as an exacerbating factor.

For future prevention and management strategy research, it would be essential for experimental designs to consider and determine all relevant integrity and functional markers, comprising a comprehensive symptom assessment, and include a significant amount of exercise stress (eg, ≥2 hours at ≥60% VO_{2max} or equivalent), with potential consideration of including heat stress, such as an ambient temperature ≥30°C and/or hypohydration (eg, ≥3% acute body mass loss and plasma osmolality ≥300 mOsmol/kg), which are common external factors associated with exercise participation known to exacerbate gastrointestinal issues. It is also important to note that previous research in prevention and management strategies has focused on healthy trained population. To date, no research on exercise-induced gastrointestinal syndrome prevention and management strategies has been conducted in populations with gastrointestinal diseases/disorders, which clearly warrants investigation.

12 | CONCLUSION

Exercise-induced gastrointestinal syndrome has the ability to create acute disturbances in the health of the gastrointestinal tract due to multiple physiological changes associated with hypoperfusion and ischaemia, epithelial injury, impaired barrier function, impaired nutrient absorption, altered gastric and intestinal motility, endotoxaemia, local and systemic inflammation. These exercise-associated changes to gastrointestinal integrity and function amplify in accordance with the intensity and duration of exercise, and can be exacerbated by running in hot ambient conditions. Gastrointestinal symptoms are a common outcome, which can be modest and transient in nature, or more clinically severe and prolonged. Whether the syndrome is associated with the development of chronic disease acutely or after repeated insults remains unclear, but is of concern and requires more research. Considering exercise-induced gastrointestinal syndrome is multifactorial in origin, assessing gastrointestinal barrier integrity and functional responses during and/or after exercise in those individuals presenting symptoms and/or health implications is key to establishing the potential underlying mechanism(s) and biomarkers to recognise them on an individual basis, subsequently informing and tailoring preventive and management strategies.

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AUTHORSHIP

Guarantor of the article: R.J.S. Costa

Author contribution: RC, RS and CK undertook the systematic review (search, screening, eligibility, and data extraction as primary and secondary reviewer) of the acute exercise impact arm. RC, RS, CK and PG undertook the systematic review of the gastrointestinal diseases/disorders arm. All authors contributed to the preparation and review of the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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