

1 **Title:**

2 The Gastrointestinal Exertional Heat Stroke Paradigm: Pathophysiology, Assessment,  
3 Severity, Aetiology and Nutritional Countermeasures

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19 All authors declare that there is no conflict of interest regarding the publication of this paper

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22

23 **Abstract**

24 Exertional heat stroke (EHS) is a life-threatening medical condition involving  
25 thermoregulatory failure and is the most severe condition along a continuum of heat related  
26 illnesses. Current EHS policy guidance principally advocates a thermoregulatory management  
27 approach, despite growing recognition that gastrointestinal (GI) microbial translocation  
28 contributes to the pathophysiology. Contemporary research has focussed on understanding  
29 the relevance of GI barrier integrity and strategies to maintain it during periods of exertional-  
30 heat stress. GI barrier integrity can be assessed non-invasively using a variety of *in vivo*  
31 techniques, including *active* inert mixed-weight molecular probe recovery tests and *passive*  
32 biomarkers indicative of GI structural integrity loss or microbial translocation. Strenuous  
33 exercise is well-characterised to disrupt GI barrier integrity, and aspects of this response  
34 correlate with the corresponding magnitude of thermal strain. The aetiology of GI barrier  
35 integrity loss following exertional-heat stress is poorly understood, though may directly relate  
36 to localised hyperthermia, splanchnic hypoperfusion mediated ischemic injury, and  
37 alternations in several neuroendocrine-immune responses. Nutritional countermeasures to  
38 maintain GI barrier integrity following exertional-heat stress provide a promising approach to  
39 mitigate EHS. The focus of this review is to evaluate: (1) the GI paradigm of exertional heat  
40 stroke; (2) techniques to assess GI barrier integrity; (3) typical GI barrier integrity responses to  
41 exertional-heat stress; (4) the aetiology of GI barrier integrity loss following exertional-heat  
42 stress; and (5) nutritional countermeasures to maintain GI barrier integrity in response to  
43 exertional-heat stress.

44

45 **Abbreviations**

46	BC	Bovine Colostrum
47	Caco-2	Human Colonic Carcinoma Cell Line
48	CFU	Colony Forming Units
49	CHO	Carbohydrate
50	CHS	Classic Heat Stroke
51	DSAT	Dual-Sugar Absorption Test
52	EHS	Exertional Heat Stroke
53	GI	Gastrointestinal
54	I-BABP	Ileal Bile-Acid Binding Protein
55	I-FABP	Intestinal Fatty Acid Binding Protein
56	IFN	Interferon
57	IGF-1	Insulin-Like Growth Factor-1
58	I-HSP	Intracellular Heat Shock Protein
59	IL	Interleukin
60	kDa	Kilodalton
61	LBP	Lipopolysaccharide Binding Protein
62	LPS	Lipopolysaccharide
63	L/R	Lactulose-to-Rhamnose Ratio
64	MOF	Multiple Organ Failure
65	MSAT	Multi-Sugar Absorption Test
66	MT	Microbial Translocation
67	NO	Nitric Oxide
68	NO <sup>3</sup>	Nitrate
69	NO <sup>2</sup>	Nitrite
70	NOS	Nitric Oxide Synthase
71	NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
72	PAMPs	Pathogen Associated-Molecular Patterns
73	PCT	Procalcitonin
74	RDA	Recommended Daily Allowance
75	RES	Reticuloendothelial system

76	RH	Relative Humidity
77	SAPS	Simplified Acute Physiology Score
78	sCD14	Soluble Cluster of Differentiation 14
79	SIRS	Systemic Inflammatory Response Syndrome
80	S/E	Sucralose-to-Erythritol Ratio
81	S/R	Sucrose-to-Rhamnose Ratio
82	T <sub>core</sub>	Core Body Temperature
83	TJ	Tight Junction
84	TLR	Toll-Like Receptor
85	TNF	Tumour Necrosis Factor
86	VO <sub>2max</sub>	Maximal Oxygen Uptake
87	Watt <sub>max</sub>	Maximal Power (wattage) Output
88	ZnC	Zinc Carnosine
89		

90 **Introduction**

91 Exertional heat stroke (EHS) is a life-threatening medical condition involving  
92 thermoregulatory failure, which is the most severe condition along a continuum of heat-  
93 related illnesses [1]. Although anecdotal records from biblical times have documented  
94 mortality from EHS [2-3], the condition still has no universal medical definition [4]. Instead,  
95 the most popular definitions broadly outline characteristic patient symptoms at time of clinical  
96 admission [5]. These principally include: (1) a core body temperature ( $T_{\text{core}}$ ) above 40°C; (2)  
97 severe central nervous system disturbance (e.g. delirium, seizures, coma); and (3) multiple  
98 organ injury. Whilst classic heat stroke (CHS) primarily impacts incapacitated individuals (e.g.  
99 elderly, infants, chronic illness) whose thermoregulatory responses are unable to compensate  
100 for increased ambient temperatures [6], EHS sporadically impacts individuals (e.g. athletes,  
101 military personnel, firefighters) engaged in arduous physical activity [7]. Indeed, the primary  
102 cause of EHS is prolonged metabolic heat production, whilst exposure to high ambient  
103 temperature is less important than in CHS cases, despite further compromising  
104 thermoregulation [8].

105 The incidence of EHS has been frequently surveyed within high-risk populations since  
106 the beginning of the 20<sup>th</sup> century [3], though issues surrounding misdiagnosis (e.g. with less  
107 severe heat illness events) has generally limited accurate classification [9-10]. Over the last  
108 two-decades, the annual incidence of EHS has remained relatively stable within both athletic  
109 [11] and military [12] settings. Indeed, prevailing EHS incidence rates are reported to be *circa*:  
110 0.1-1.5 cases per 10,000 US high school athletes per season [13-14]; 0.5-20 cases per 10,000  
111 entrants during warm weather endurance races [15-17]; and 2-8 cases per 10,000 person  
112 years in both the United Kingdom [18] and United States [12, 19] armed forces. Given global  
113 predications of increased ambient surface temperature, coupled with a greater frequency,  
114 duration and intensity of extreme weather events, the risk of EHS is likely to increase [20].  
115 Whilst timely medical intervention (e.g. whole-body cooling) can help prevent direct mortality  
116 from EHS [21], many affected individuals still experience long-term health complications  
117 because of residual organ damage. These health-complications include: heat intolerance [22],  
118 neurological impairment [23], chronic kidney disease [24] and cardiovascular disease [25]. The  
119 burden of EHS not only relates to the health of the impacted patients, but can also result in  
120 reduced occupational effectiveness [26-27], significant medical/legal expenses [28-29], and in

121 some instances high-profile media criticism [30-31] to the patients governing body or  
122 employer. In consideration of these issues, numerous published consensus documents have  
123 provided occupational guidance on effective management of EHS (e.g. [32-35]). However,  
124 these documents predominately focus on a thermoregulatory approach to disease  
125 management (e.g. cooling, heat acclimation). A gastrointestinal paradigm of EHS  
126 pathophysiology (also known as “endotoxemia” or “heat sepsis”) is starting to receive more  
127 extensive recognition as a secondary pathway for EHS management [36-37], though  
128 consensus documents are present unavaliable.

129         The gastrointestinal (GI) tract, is an organ extending between the stomach to the  
130 colon. It is the human body’s longest mucosal interface (250-400 m<sup>2</sup>) forming a selectively  
131 permeable barrier to the external environment. The GI microbiota is a collection of  
132 microorganisms that colonise the GI tract and have co-evolved inside humans to provide  
133 various mutually beneficial functions [38]. The GI microbiota has an estimated size *circa* 10<sup>14</sup>  
134 cells, between 1- to 10-fold greater than the total number of cells within the human body [39].  
135 Alongside a predominant role in the absorption of dietary nutrients, a second vital function of  
136 the GI tract is to prevent the translocation of immunomodulatory GI microbial products (e.g.  
137 endotoxin, flagellin, bacterial DNA) into the systemic circulation [40]. To achieve this role, the  
138 structure of the GI tracts forms a multi-layered physical and immunological barrier. The  
139 physical barrier comprises a monolayer of epithelial cells interconnected by tight junction (TJ)  
140 protein complexes, and is reinforced by a mucosal lining secreted by goblet cells. The  
141 immunological barrier comprises crypt paneth cells within the epithelial monolayer that  
142 secrete antimicrobial proteins, and gut associated lymphoid tissue within the *lamina propria*  
143 that stimulate multiple effector immune responses. In healthy individuals, the GI tract is  
144 largely effective in preventing GI microbial translocation (MT) into the systemic circulation  
145 [40], though several reports have hypothesised a fundamental role of GI MT within the  
146 pathophysiology of EHS [36-37]. The focus of this review is to evaluate: (1) the GI paradigm of  
147 EHS; (2) GI barrier integrity assessment techniques; (3) typical GI barrier integrity responses  
148 to exertional-heat stress; (4) the aetiology of GI barrier integrity loss; and (5) nutritional  
149 countermeasures to support GI barrier integrity during exertional-heat stress.

150

151 **The GI Exertional Heat Stroke Paradigm**

152 The GI EHS paradigm was first introduced as a novel pathophysiology concept in the  
153 early 1990s [41] and was integrated into conventional EHS medical classifications in 2002 [5].  
154 The broad scientific basis of the GI EHS paradigm centres on the notion that sustained  
155 exertional-heat strain initiates damage to multiple layers of the GI barrier, which consequently  
156 permits GI MT into the systemic circulation. To counter this response, the liver's  
157 reticuloendothelial system (RES) provides the first line of GI microbial detoxification (e.g.  
158 kupffer cells and hepatocytes) through the portal circulation. However, this confers only a  
159 limited capacity for microbial neutralization before microbial leakage into the systemic  
160 circulation occurs [42]. Alternatively, GI MT might bypass the RES altogether, instead  
161 translocating directly through the mesenteric lymph nodes into the systemic circulation [43].  
162 In the systemic circulation MT products are neutralized through multiple host-binding  
163 pathways, including: natural antibodies (e.g. immunoglobulin G and M), leukocyte granular  
164 proteins (e.g. bactericidal permeability increasing protein, lactoferrin, lysozyme) and high-  
165 density lipoproteins [42]. In EHS patients, it appears that microbial detoxification capabilities  
166 might also be reduced, via the combined effects of RES dysfunction at  $T_{core}$  above 41-42°C [44]  
167 and immune antibody suppression, as demonstrated following strenuous exercise [45]. Failure  
168 of GI microbial detoxification mechanisms permits binding of unique GI pathogen associated-  
169 molecular patterns (PAMP) to toll-like receptors (TLR) located on cell surface membranes [46].  
170 TLR activation initiates a cascade of intracellular events that culminate in the production of  
171 pro-inflammatory cytokines (e.g. interleukin [IL] 1- $\beta$ , IL-2, IL-6, IL-8, tumour-necrosis factor  
172 [TNF]- $\alpha$ ), which are counterregulated by the production of anti-inflammatory cytokines (e.g.  
173 IL-1ra, IL-4, sIL-6r, IL-10, sTNFr). Downstream of this systemic inflammatory response  
174 syndrome (SIRS), a complex interplay of responses can culminate in haemorrhagic shock,  
175 disseminated intravascular coagulation (DIC), multiple organ failure (MOF) and possibly death  
176 [47]. The GI EHS paradigm is considered to be the primary cause of EHS in cases where  $T_{core}$   
177 remains below the threshold ( $\sim$ 42-44°C) of heat cytotoxicity [48]. A simplified schematic of  
178 the GI EHS paradigm is shown in Figure 1. Interested readers are referred to several detailed  
179 reviews on this topic [1, 36-37].

180

181 [Insert Figure 1 Here]

182 To date, direct pathophysiological investigation into the GI EHS paradigm has been  
183 limited, which is surprising given the substantial morbidity/mortality associated with the  
184 disease. The best available evidence is reliant on animal experimental models of CHS or  
185 opportunistic monitoring of human EHS patients. In a pioneering study, prior antibiotic  
186 administration in a canine CHS model (peak  $T_{core} = \sim 43.5^{\circ}\text{C}$ ) both suppressed GI microbial stool  
187 concentration and increased survival rate (71% versus 20%), indirectly suggesting the  
188 importance of inhibited GI MT [49]. In a seminal series of studies using a primate CHS model  
189 (peak  $T_{core} = \sim 43.5^{\circ}\text{C}$ ), plasma endotoxin concentrations were found to increase in parallel with  
190  $T_{core}$  (50-52), but prior antibiotic [50-51] or corticosteroid [52] treatment attenuated this  
191 effect. Importantly, 100% of prior- treated animals survived, in comparison with less than 30%  
192 of control animals. However, once hyperthermia was above the intensity to evoke heat  
193 cytotoxicity (peak  $T_{core} = \sim 44.5^{\circ}\text{C}$ ), mortality rates were 100% irrespective of pharmaceutical  
194 intervention. This suggests that the GI EHS paradigm is probably most relevant in cases when  
195  $T_{core}$  remains below  $\sim 42\text{-}43^{\circ}\text{C}$  [48]. Several studies have confirmed these findings in similar  
196 rodent CHS models (peak  $T_{core} = \sim 43.5^{\circ}\text{C}$ ), whereby prior corticosteroid injection inhibited GI  
197 MT and increased survival rate [53-55], whilst indomethacin injection enhanced gross  
198 morphological GI haemorrhage and suppressed survival rate [56].

199 Direct endotoxin injection into rodents before sub-lethal CHS (peak  $T_{core} = \sim 42\text{-}43^{\circ}\text{C}$ )  
200 unexpectedly killed 40% of animals (versus 0% in controls; [57]) and/or increased multiple-  
201 organ injury [58]. In the only animal models of EHS (peak  $T_{core} = 40.5\text{-}42.5^{\circ}\text{C}$ ), significant  
202 histopathological damage to all GI segments [59], in addition to GI epithelial injury [59-60] and  
203 systemic inflammation [61], were observed. However, in comparison to CHS models with a  
204 similar clinical endpoint (peak  $T_{core} = \sim 42\text{-}42.5^{\circ}\text{C}$ ), the magnitude of GI barrier integrity loss was  
205 reduced during EHS, though this was likely attributable to a  $\sim 50\%$  lower thermal area [60]. No  
206 published animal EHS research has yet evaluated the role of GI MT on EHS pathophysiology.  
207 However, recent data show the pattern of cytokine response during EHS is largely inconsistent  
208 with typical GI microbial PAMP recognition (e.g. minimal  $\text{TNF-}\alpha/\text{IL-1}\beta$  response; [60]. With this  
209 in mind, it is plausible intracellular cytokine production initiated following multiple organ  
210 injury (e.g. skeletal muscle; [61]) performs a greater role in EHS pathophysiology than



211 previously proposed in GI EHS consensus documents [37, 47].

212 In humans, the role of GI barrier integrity in the pathophysiology of EHS is a relatively  
213 recent area of research; which has been established on historical evidence of severe GI  
214 symptoms, ulceration and haemorrhage in military EHS fatalities [62-64]. Evidence supporting  
215 the present GI EHS model was first reported by Graber et al. [65], who observed endotoxin  
216 translocation into the systemic circulation and symptomology of experimental endotoxin  
217 shock in a single EHS case report. More substantial evidence was collated in the 1990s, from  
218 EHS patients (peak  $T_{core} = \sim 42^{\circ}\text{C}$ ) who had been on religious pilgrimage to Mecca [66]. The  
219 plasma endotoxin concentration increased  $\sim 1000$ -fold more than in healthy controls ( $8.6$   
220  $\text{ng}\cdot\text{ml}^{-1}$  vs  $9 \text{ pg}\cdot\text{ml}^{-1}$ ). In this study, weak correlations were reported between endotoxin and  
221 SIRS responses (e.g.  $\text{TNF-}\alpha$   $r = 0.46$ ;  $\text{IL-1}\beta$   $r = 0.47$ ), whilst in a follow-up study that did not  
222 monitor endotoxin responses, IL-6 concentration weakly correlated ( $r = 0.52$ ) with the disease  
223 Simplified Acute Physiology Score (SAPS; [67]). In support, IL-2 ( $r = 0.56$ ), IL-6 ( $r = 0.57$ ) and IFN-  
224  $\gamma$  ( $r = 0.63$ ) concentrations weakly correlated with the SAPS in a cohort of military EHS (peak  
225  $T_{core} = \sim 41.5^{\circ}\text{C}$ ) patients, though the SAPS did not correlate with the time-course of any other  
226 cytokine monitored (IL-1 $\beta$ , IL-2ra IL-4, IL-8, IL-10;  $\text{TNF-}\alpha$ ) [68]. Likewise, IL-6 and sTNFR, but  
227 not IL-1ra and C reactive protein, predicted survival in a later cohort of EHS patients (peak  $T_{core}$   
228  $= \sim 41.5^{\circ}\text{C}$ ) on Mecca pilgrimage [69]. Whilst none of these studies directly monitored GI MT  
229 responses, sub-clinical exertional-heat stress ( $T_{core} = < 40^{\circ}\text{C}$ ) experiments have reported  
230 similar patterns of endotoxin translocation and SIRS kinetics in some [70-71], but not all cases  
231 [72-73].

232 A key limitation of previous research has been the exclusive reliance of endotoxin to  
233 assess GI MT. There is evidence blood samples may be cross-contaminated during collection  
234 or analysis, for example one EHS case study reported the presence of  $\beta$ -glucan (a fungal cell  
235 wall component) in blood which was unlikely to be of GI origin [74]. Variations in sample  
236 contamination might explain EHS induced endotoxemia independent of GI MT [74]. Future  
237 research should focus on determining the sensitivity/specificity of GI barrier/MT biomarkers  
238 on EHS outcome. One potentially relevant novel biomarker is procalcitonin (PCT), a pro-  
239 inflammatory acute phase reactant, which offers strong sensitivity/specificity in diagnosing  
240 acute bacterial infections [75]. In EHS patients, PCT measured 2 hours following intensive care

241 unit admission was able to predict Acute Physiology and Chronic Health Evaluation (APACHE)  
242 II score ( $r = 0.59$ ) and had an odds-ratio of 2.98 for predicting disease mortality [76].  
243 Furthermore, in CHS patients, PCT concentrations were significantly greater in fatal versus  
244 non-fatal cases [77-78].

### 245 **Assessment of GI Barrier Integrity**

246 Various techniques are available for the *in vivo* assessment of GI barrier integrity.  
247 These techniques can be broadly categorised as either: (1) *active* tests involving the oral  
248 ingestion and extracellular recovery of water-soluble non-metabolizable inert molecular  
249 probes; (2) *passive* tests involving monitoring blood biomarkers indicative of GI barrier  
250 integrity; and (3) *microbial translocation* (MT) tests involving monitoring blood biomarkers  
251 indicative of the passage of GI microbial products across the GI barrier secondary to integrity  
252 loss (Table 1 [40]).

253

254 [Insert Table 1 Here]

255

256 The Dual Sugar Absorption Test (DSAT) is presently promoted as the gold-standard  
257 *active* GI function test [79], which has received almost exclusive application with the field of  
258 exercise science [80-82]. This test involves co-ingestion of both a large disaccharide (e.g.  
259 lactulose [342 kDa] or cellobiose [342 kDa] ~5 grams) that only transverses the GI tract  
260 paracellularly upon barrier integrity loss, and a small monosaccharide ( $\alpha$ -rhamnose [164 kDa]  
261 or  $\beta$ -mannitol [182 kDa] ~1-2 grams) that freely transverses the GI tract transcellularly  
262 independent of barrier integrity [83]. In the five hour period post-ingestion the excretion of  
263 both sugars are measured in urine and are believed to be equally affected by non-mucosal  
264 factors, such as gastric emptying and renal clearance [84]. The urinary ratio of lactulose-to-  
265 rhamnose (L/R) relative to the ingested dose is the clinical endpoint of this test. Recently, the  
266 DSAT has been validated in serum/plasma with improved sensitivity over a time-courses  
267 ranging between 60-150 minutes [85-88], and with comparable reliability to traditional  
268 urinary assessment [89]. Unfortunately, the DSAT has several practical limitations, most

269 notably: a requirement to perform basal/exercise tests on separate days and a lack of  
270 universal test standardisation (e.g. pre-trial controls, sugar dose, ingestion timing, biofluid  
271 timing) [84]. Furthermore, based on the degradation of lactulose in the large intestine, the  
272 test only provides information regarding small GI barrier function, with further sugar probes  
273 (i.e. multi-sugar absorption test; MSAT) required to assess gastroduodenal (e.g.  
274 sucrose/rhamnose; S/R) and large intestinal (e.g. sucralose/erythritol; S/E) barrier function  
275 [82]. Whilst routine implementation of the MSAT would be desirable, hyperosmolar stress  
276 utilising recommended sugar dosages will confound the test result. In attempt to overcome this  
277 issue, validation of a low dose (1 gram lactulose, sucrose, sucralose; 0.5 grams L-rhamnose,  
278 erythritol) MSAT protocol has recently been favourable evaluated against the traditional dose  
279 (5 grams lactulose, 2 grams L-rhamnose) DSAT protocol [87,90]. Polyethylene glycols (PEG;  
280 100-4000 kDa) are a less-common, though a validated alternative to the MSAT for whole-GI  
281 barrier integrity assessment [91]. An advantage of PEG assessment is the ability to provide  
282 information on the size based permeability of molecules able to transverse the GI barrier.  
283 However, this method does require additional lifestyle controls, as PEGs can be found in  
284 various commercial/dietary products (e.g. toothpaste, soft drinks) [82]. The application of  
285 single molecular probes tests (e.g. non-metabolizable sugars, <sup>51</sup>Cr-EDTA, Iohexol, Blue #1 Dye)  
286 cannot be recommended in exercise-settings given the confounding influence of non-mucosal  
287 factors [84].

288         Several *passive* blood-based biomarkers of GI barrier integrity are available, which can  
289 assess epithelial injury to specific regions of GI tract, TJ breakdown and MT [40]. Epithelial  
290 injury to the duodenum and jejunum can be evaluated via intestinal fatty-acid binding protein  
291 (I-FABP); and to the ilium via ileal bile-acid binding protein (I-BABP). These cytosolic proteins  
292 are involved in lipid metabolism, though offer strong diagnostic specificity/sensitivity in  
293 detecting GI barrier integrity loss [92], given their tissue specificity and transient 11 minute  
294 half-life [93]. Alternative biomarkers of GI epithelial/transmural injury include: alpha-  
295 glutathione s-transferase ( $\alpha$ -GST), diamine oxidase (DAO) and smooth muscle protein 22  
296 (SM22); however a lack of tissue specificity limits their application in settings (e.g. exercise)  
297 where multiple-organ injury is commonplace [40, 94]. There is presently no available  
298 biomarker of large intestinal epithelial injury. To assess TJ breakdown, zonulin, a pre-cursor  
299 protein to haptoglobin, has received most widespread attention, given its recognised role in

300 disassembling GI TJs [95]. However, the two commercial assays presently available for this  
301 biomarker are susceptible to cross-reactivity (e.g. for complement protein C3). Consequently  
302 data collected with this technique should be interpreted with caution until the methods have  
303 been validated [96]. Claudin-3, is a non-tissue specific, highly expressed GI TJ protein, which is  
304 an emerging biomarker for TJ breakdown. Preliminary data has shown claudin-3  
305 concentrations are elevated in clinical conditions where GI TJ damage has been confirmed  
306 histologically [97]. The test-retest reliability of I-FABP and claudin-3 was recently considered  
307 acceptable when assessed both at rest and following exertional-heat stress [89]. All GI  
308 epithelial injury/TJ breakdown biomarkers can be assayed in plasma/serum by ELISA, whilst  
309 future developments in auto-analysers and validation of capillary blood and urine samples  
310 have potential to make assessment simpler in the future.

311         The definition of MT was traditionally founded on the translocation of live bacteria  
312 from the GI lumen into the mesenteric lymph. However, given practical constraints of  
313 mesenteric lymph biopsy in healthy humans, this definition has been extended to include the  
314 detection of microbial products/fragments in blood [98]. To determine GI MT, measurement  
315 of endotoxin, a form of lipopolysaccharide (LPS) located on the outer membrane of gram-  
316 negative bacteria, has been widespread [80]. Endotoxin is detectable within the  
317 portal/systemic circulations following bacterial cleavage during both cell lysis and division,  
318 with assessment widely undertaken using the chromogenic limulus amoebocyte lysate (LAL)  
319 assay. Whilst popular, there are major flaws to endotoxin assessment, as it is prone to false-  
320 positive (e.g. from exogenous contamination, cross-reactivity) and false-negative (e.g. from  
321 hepatic clearance, immune neutralization) results [99]. Two indirect surrogate biomarkers for  
322 endotoxin exposure that can be quantified by ELISA are the acute phase proteins:  
323 lipopolysaccharide binding-protein (LBP; [100]) and soluble-CD14 (sCD14-ST; [100]). Whilst  
324 the roles of these biomarkers have been characterised during life-threatening septic shock  
325 [101], evidence regarding their time-course, sensitivity and specificity in predicting transient  
326 GI MT following exertional-heat stress is sparse [80]. D-lactate is a secondary enantiomer of  
327 L-lactate, hypothesised as a biomarker of GI MT given that the enzyme D-lactate  
328 dehydrogenase is specific to bacteria [102]. That said, human cells do produce small-quantities  
329 of D-lactate through secondary methylglyoxal metabolism [102]. Whilst D-lactate has been  
330 shown to predict GI MT in animal models of gut trauma [103-104], its low-molecular weight

331 (0.09 kDa) might permit false-positive results through transcellular translocation following  
332 production within the GI tract. Bacterial DNA (bactDNA) is a stable bacterial component, which  
333 through targeting phyla with high GI specificity offers potential as an improved MT biomarker  
334 [105]. Whilst a universal analytical procedure is currently lacking (e.g. target primers,  
335 positive/negative controls), one major advantage of bactDNA over endotoxin assessment, is  
336 an apparent lack of rapid hepatic clearance [46]. As the GI microbiota is dominated ( $\geq 90\%$ ) by  
337 two bacterial phyla *Firmicutes* and *Bacteroidetes*, which comprise only a minor proportion (0-  
338 10%) of the whole blood/plasma microbiota [106], developing methodologies that target  
339 these specific gene regions are likely to provide high GI specificity. Pioneering studies have  
340 shown total 16S DNA to offer good reliability at rest and post exertional-heat stress, however  
341 *Bacteroides* DNA (the dominant *Bacteroidetes* bacterial genus) offered poor reliability at both  
342 time points [89].

#### 343 **Severity of GI Barrier Integrity loss following Exertional-Heat Stress**

344 Numerous research models have characterised the influence of exertional-heat stress  
345 on GI barrier integrity. This research has primarily monitored small intestinal integrity using  
346 the DSAT, though attempts have been made to quantify gastroduodenal and large intestinal  
347 integrity using the MSAT [80]. Over the last decade, several passive GI integrity and/or MT  
348 biomarkers have become commonplace as an alternative to, or for use in combination with  
349 the DSAT. Generally, I-FABP has been monitored to assess GI epithelial integrity, and  
350 endotoxin to assess GI MT. The exercise models assessed are disparate, ranging from 45  
351 minutes brisk walking [107] to a 230-km ultramarathon [71]. That said, most studies comprise  
352 1-2 hours of continuous, submaximal (60-70%  $VO_{2max}$ ) running or cycling. Given the  
353 hypothesised relevance of GI barrier integrity within the pathophysiology of EHS, the impact  
354 of exercise-induced thermal strain (e.g.  $T_{core}$ ) on GI barrier integrity has been a specific topic  
355 of investigation [81]. In comparison to acute exercise-interventions, few studies have  
356 attempted to evaluate the effect of either chronic exercise training or multi-day occupational  
357 performance (e.g. sports competition, military/firefighting operation) on GI barrier integrity.  
358 Such exercise models would appear particularly relevant to EHS incidence, given that many  
359 documented EHS risk factors (e.g. prior heat exposure, skeletal muscle injury) relate to multi-  
360 day exercise [37]. Review tables are provided to summarise the effects of acute exercise on:  
361 DSAT (Table 2); I-FABP (Table 3); and MT (Table 4).

362            Seminal research using the DSAT, investigated the effects of one hour's treadmill  
363 running in temperate conditions on GI barrier integrity [108]. These authors found the DSAT  
364 ratio increased relative to both the magnitude of metabolic (60, 80 and 100%  $VO_{2max}$ ) and  
365 thermal (38.0, 38.7 and 39.6°C  $T_{core}$  peak) strain [108]. Later studies monitoring GI barrier  
366 integrity following exercise in temperate conditions corroborated this seminal finding, with  
367 low-to-moderate intensity (~40-60%  $VO_{2max}$ ) exercise having little influence on DSAT results  
368 compared with rest [e.g. 109-111]; whereas moderate-to-high intensity (~70-120%  $VO_{2max}$ )  
369 exercise of durations  $\geq 20$  minutes increase permeability by 100-250% [e.g. 86, 88, 112-116].  
370 Unfortunately, the present data does not allow more specific conclusions to be drawn, given  
371 large intra-study variability in absolute DSAT ratios, which can be attributed to modifications  
372 in the DSAT procedure (e.g. sugar probe type/dose/timing, analytical protocol) and/or a  
373 frequent lack of basal GI permeability correction (Table 2). That said, individual studies  
374 highlight the importance of particular aspects of the exercise stimulus on GI barrier integrity,  
375 with increased DSAT ratios after matched interventions comparing: running and cycling [117];  
376 permissive dehydration versus rehydration [118-119]; and following ingestion of non-steroidal  
377 anti-inflammatory drugs (NSAID) [120-124]. To date, only two published studies have directly  
378 compared the influence of ambient temperature on GI barrier permeability [115, 125]. In  
379 conflict with *a priori* hypotheses, the first of these studies found two hours of moderate  
380 intensity (60%  $VO_{2max}$ ) treadmill running in temperate (22°C/44% relative humidity [RH])  
381 versus mild hyperthermic (30°C/35% RH) conditions resulted in comparable DSAT responses  
382 ( $0.025 \pm 0.010$  vs.  $0.026 \pm 0.008$  [125]). However, these results were perhaps not entirely  
383 surprising given that  $T_{core}$  responses showed minimal divergence between the two  
384 environmental conditions (e.g. peak  $T_{core}$  = 38.1°C vs. 38.4°C [125]). A follow-up trial on the  
385 same subjects compared the results of the temperate exercise condition (22°C/44% RH) with  
386 a third trial conducted in a more severe hyperthermic (35°C/26% RH) environment [115]. The  
387 DSAT data ( $0.032 \pm 0.010$ ) remained statistically indifferent to the temperate condition,  
388 despite greater  $T_{core}$  elevations (e.g. peak  $T_{core}$  = 39.6°C [115]). These null findings might be  
389 interpreted with caution, as there was poor analytical reproducibility of sugar concentrations  
390 (duplicate sample coefficient of variation = 13.8%) and no basal DSAT correction.

391            In comparison with the extensive literature examining the acute effect of exercise on  
392 small GI integrity using the DSAT, few studies have assessed the influence of exercise or

393 exertional-heat stress on either gastroduodenal or large GI barrier integrity utilising the MSAT  
394 [80]. In the only published evidence where the MSAT was applied with reference probe co-  
395 administration [82], both gastroduodenal (S/R; [124]) and large intestinal (S/E; [86]) integrity  
396 were unaltered following one hour of moderate intensity cycling (70% watt<sub>max</sub>) in temperate  
397 conditions (~22°C), which was sufficiently intense to induce detectable small intestinal barrier  
398 integrity loss using the DSAT. Similarly, gastroduodenal integrity, measured using a single  
399 sugar-probe (sucrose) has been shown to be unaltered following one hour of moderate  
400 intensity treadmill running (40-80% VO<sub>2max</sub>) in temperate conditions [108, 119, 122], 18  
401 repeated 400 metre supramaximal track sprints (120% VO<sub>2max</sub>) in temperate conditions [88]  
402 and a ~33 minute exercise capacity trial at 80% ventilatory threshold in the heat (35°C/40%  
403 RH [126]). No further studies have measured large intestinal integrity following acute exercise  
404 using a single sugar-probe (sucralose). There is a clear gap in the literature regarding the  
405 influence of exertional-heat stress on large intestinal integrity, which warrants future  
406 investigation given the greater microbiota concentration in this segment of the GI tract (e.g.  
407 duodenum = <10<sup>3</sup>, ileum 10<sup>3</sup>-10<sup>7</sup>, colon= 10<sup>12</sup>- 10<sup>14</sup>) [166].

408

409 [Insert Table 2 Here]

410

411 Application of I-FABP as a biomarker of small-intestinal (duodenal and jejunal)  
412 epithelial injury was first applied in exercise settings during a series of studies conducted in  
413 the Netherlands, which demonstrated peak concentrations (~50-100% increase) immediately  
414 following termination of a one-hour moderate-intensity (70% Watt<sub>max</sub>) cycle [86, 124, 127]. I-  
415 FABP responses showed weak correlations with I-BABP (i.e. ileum injury) and the DSAT [86],  
416 suggestive of inconsistent injury across the small intestine. Since then, low intensity exercise  
417 (~50% VO<sub>2max</sub>) in temperate environments has typically shown little effect on I-FABP  
418 concentrations [128-130], but moderate-to-high intensity exercise (60-120% VO<sub>2max</sub>) elevates  
419 concentrations by 50-250% [88, 125, 131-133]. Where measured, I-FABP responses quickly  
420 recover within 1-2 hours of exercise termination, irrespective of the intensity/duration of the  
421 protocol [125, 131]. Like DSAT results, I-FABP responses are elevated in otherwise matched

422 exercise-interventions comparing: hypoxic ( $F_{iO_2} = 0.14$ ) versus normoxic environments [128,  
423 134]; permissive dehydration versus rehydration [135]; and post NSAID ingestion [124]. In  
424 comparison, since initial investigation [86], no studies have monitored the magnitude and  
425 time-course of I-BABP responses following exercise. Several studies have attempted to  
426 elucidate the influence of ambient temperature on GI epithelial injury [115, 125, 133, 136-  
427 137]. Compared with modest increases in I-FABP (127%) following two hours of moderate  
428 intensity cycling (60%  $VO_{2max}$ ) in temperate (22°C/44% RH) conditions (peak  $T_{core}$  38.1°C),  
429 performance of matched exercise in both mild (30°C/35% RH [115]) and severe heat stress  
430 conditions (35°C/26% RH; [125]) vastly enhanced peak  $T_{core}$  (38.4°C and 39.6°C) and  
431 percentage change in I-FABP (184% and 432%) responses, respectively. Furthermore, a  
432 moderate correlation ( $r = 0.63$ ) was shown between peak  $T_{core}$  and I-FABP concentration in  
433 these studies. Ingestion of cold (7°C) relative to temperate (22°C) water during two hours  
434 moderate intensity cycling (60%  $VO_{2max}$ ) in the heat, blunted the rise in both  $T_{core}$  (38.4 vs  
435 38.8°C) and I-FABP (~400% vs 500%) concentration [137], though whether these responses  
436 are directly related is questionable. These conclusions were recently substantiated following  
437 one hour of low intensity (50-70%  $watt_{max}$ ) cycling, where I-FABP concentration increased  
438 following performance in a hot (35°C/53% RH; 140%), but not temperate (20°C/55% RH; 29%)  
439 ambient environment [133]. Importantly, these observations have been directly attributed to  
440 the influence of ambient temperature on whole-body thermal strain, given that when relative  
441 exercise-intensity is matched ( $VO_{2max}$ ,  $T_{core}$ , heart rate), the influence of ambient heat stress  
442 (20 vs. 30°C) on I-FABP responses is abolished [136]. One study reported GI TJ breakdown  
443 (claudin-3) to increase to a similar extent following one hour of running in a temperate  
444 (22°C/62% RH) versus hot (33°C/50% RH) ambient environment [138], suggestive that TJ  
445 breakdown is insensitive to thermal stress. Alternatively, I-FABP and claudin-3 responses  
446 positively correlated ( $r = 0.41$ ) following an 80-minute brisk walk (6  $km \cdot h^{-1}$ /7% incline) in the  
447 heat (35°C/30% RH) [89].

448

449 [Insert Table 3 Here]

450



451 Endotoxin is a traditionally popular biomarker of GI MT and was the first technique  
452 utilised to assess GI barrier integrity in exercise settings. Seminal research monitoring  
453 endotoxin concentrations following exercise, found concentrations to increase transiently to  
454 magnitudes comparable to clinical sepsis patients ( $\sim 50\text{-}500\text{ pg}\cdot\text{ml}^{-1}$ ) when measured following  
455 competitive ultra-endurance events [80]. These included: an ultra-triathlon [139], a 90 km  
456 ultra-marathon [140], a 100-mile cycle race [141] and a 42.2 km marathon [142]. More  
457 recently, only minor increases in endotoxin concentrations have been shown following  
458 comparable duration competitive ultra-endurance races [71, 144-145], whilst moderate  
459 intensity exercise ( $\leq 2$  hours; 50-70%  $\text{VO}_{2\text{max}}$ ) performed in a temperate environment generally  
460 does not influence circulating endotoxin concentrations [132-133, 138, 143]. These discrepant  
461 results may be due to cross-contamination from  $\beta$ -glucan during early research, which  
462 following development of more robust endotoxin assays is now less of an issue [144]. It  
463 appears a presently undefined threshold of GI barrier integrity loss is required to induce  
464 endotoxemia following exercise, given that endotoxin concentrations are often unchanged  
465 from rest irrespective despite concurrent rises in DSAT or I-FABP concentrations [116, 125,  
466 132]. When endotoxin is assessed from systemic blood samples, hepatic/immune  
467 detoxification might lead to false-negative results, and in exercise settings access to portal  
468 blood is rarely feasible. Given the large range in absolute endotoxin concentrations reported  
469 between studies (Table 4), several recent attempts have been made to measure MT with  
470 alternative biomarkers, though results are equally inconsistent [131, 146-148]. Thermal stress  
471 appears to enhance endotoxin translocation above matched exercise performed in temperate  
472 conditions. In an early study, endotoxin concentrations increased linearly above  $38.5^\circ\text{C}$  when  
473 (measured at  $0.5^\circ\text{C}$   $T_{\text{core}}$  increments), during uncompensable ( $40^\circ\text{C}/30\%$  RH) treadmill walking  
474 ( $4\text{ km}\cdot\text{h}^{-1}$ ) [146]. Likewise, a follow-up study found one hour of moderate intensity treadmill  
475 running ( $70\%$   $\text{VO}_{2\text{max}}$ ) only increased endotoxin concentrations in hot ( $33^\circ\text{C}/50\%$  RH; 54%), but  
476 not temperate ( $22^\circ\text{C}/62\%$  RH) conditions [138]. In a series of studies monitoring endotoxin  
477 concentrations following two hours moderate intensity treadmill running ( $60\%$   $\text{VO}_{2\text{max}}$ ),  
478 concentrations were found to increase by  $4\text{-}10\text{ pg}\cdot\text{ml}^{-1}$  irrespective of the thermal  
479 environment ( $22\text{-}35^\circ\text{C}$ ; [115, 125, 149]. Numerous other studies have measured endotoxin  
480 concentrations following exertional-heat stress, though large intra-study variability in  
481 absolute concentration make it impossible to make precise recommendations regarding the  
482 typical magnitude of response (Table 4). In studies where endotoxin concentrations do

483 increase following exertional-heat stress, responses peak immediately upon trial termination  
484 [138, 150].

485 [Insert Table 4 Here]

486           Whilst many studies have monitored GI barrier integrity responses following acute  
487 exertional-heat stress, relatively few studies have monitored GI barrier integrity following  
488 chronic (multi-day) exertional-heat stress. Where chronic exercise studies have been  
489 undertaken, they predominately focus on the influence of structured heat acclimation on GI  
490 barrier integrity. In an early study, involving seven days fixed-intensity heat acclimation (100  
491 minutes walking at  $6.3 \text{ km}\cdot\text{h}^{-1}$  in  $46.5^\circ\text{C}/20\% \text{ RH}$ ), endotoxin concentrations remained stable  
492 both at rest and following exertional-heat stress, despite  $T_{\text{core}}$  peak above  $39.0^\circ\text{C}$  [143].  
493 Utilising a variation of this experimental design, five consecutive days treadmill running at  
494 lactate threshold pace in the heat ( $40^\circ\text{C}/40\% \text{ RH}$ ) until  $T_{\text{core}}$  had risen  $2^\circ\text{C}$  above rest, evoked  
495 comparable post-exercise I-FABP and endotoxin responses compared to day-one [72].  
496 Likewise, 10 days of fixed-intensity heat acclimation (one hour running at  $50\% \text{ VO}_{2\text{max}}$  in  
497  $40^\circ\text{C}/25\% \text{ RH}$ ), had no influence on post-exercise I-FABP concentration compared to day one  
498 [128]. In a recent study, neither seven nor thirteen days isothermic heat-acclimation (90  
499 minutes to sustain  $T_{\text{core}} \sim 38.5^\circ\text{C}$ ) blunted the rise in endotoxin concentration following 45  
500 minutes low intensity ( $40\% \text{ watt}_{\text{max}}$ ) cycling in the heat ( $40^\circ\text{C}/50\% \text{ RH}$ ), despite large  
501 reductions in thermal strain [151]. In a non-heat acclimation study, 14 days of 20% increased  
502 training versus standard load, led to a reduction in resting endotoxin concentration (35%), but  
503 did not influence peak concentrations following a  $70\% \text{ VO}_{2\text{max}}$  treadmill run ( $35^\circ\text{C}/40\% \text{ RH}$ )  
504 until a  $T_{\text{core}}$  of  $39.5^\circ\text{C}$  was attained [150]. The influence of aerobic fitness has been shown to  
505 both increase (I-FABP; [152]) and reduce (endotoxin; [146]) GI barrier integrity loss following  
506 exertional heat stress that evoked comparable thermal strain between groups. Future research,  
507 using well-designed and adequately powered studies coupled with sensitive biomarkers, is  
508 required to determine the influence of heat acclimation on GI barrier integrity. As well as  
509 ensuring an appropriate sample size, an exertional-heat stress protocol that evokes high  
510 physiological strain should be used, using study participants that possess the same physiological  
511 characteristics as the target population.

512

513 **Aetiology of GI Barrier Integrity Loss following Exertional-Heat Stress**

514 The aetiology of exertional-heat stroke induced GI barrier loss appears multifactorial  
515 and is incompletely understood. The best supported explanations relate to: hyperthermia-  
516 mediated dysregulation of GI TJs [153]; splanchnic hypoperfusion-mediated ischemia-  
517 reperfusion injury [82, 155]; and alternations in several complex neuroendocrine-immune  
518 related interactions [156].

519 Increased tissue metabolic rate during strenuous exercise, and/or environmental heat  
520 stress, can evoke uncompensable heat strain on the body as thermoregulatory cooling  
521 responses (e.g. sweating and increased skin perfusion) become overwhelmed [157]. Within  
522 the GI tract, exertional-heat stress results in a relatively uniform rise in tissue temperature  
523 across both the small and large intestinal segments (though this rise is lower in the stomach),  
524 which can be predicted from  $T_{core}$  assessment in the distal colon [158]. This will weaken the  
525 GI barrier by morphologically disrupting the enterocyte structure and opening TJ complexes  
526 [153]. Cell culture models have consistently shown temperature elevations from 1.3°C to  
527 rapidly disrupt the GI barrier in a dose/duration dependant manner [159]. Rodent studies  
528 support these conclusions, with evidence of both histopathological GI damage and increased  
529 GI permeability following passive heating >40°C [154]. Nevertheless, the mechanistic  
530 pathways directly linking hyperthermia to GI barrier integrity loss have been poorly  
531 characterised. The available evidence suggests that heat stress positively regulates the GI  
532 barrier through sodium-dependant glucose cotransporter/tyrosine kinase pathways [160] and  
533 negatively through the myosin light-chain kinase/protein kinase-c pathways [161]. Ethical  
534 constraints have prevented laboratory GI barrier integrity assessment following severe  
535 hyperthermia (>40°C) in humans. However, a systematic review including available data up  
536 until September 2016 reported strong correlations ( $r= 0.79$ ) between peak  $T_{core}$  and GI barrier  
537 integrity loss (5-hr urine DSAT only) when all available  $T_{core}$  assessment techniques were  
538 included [81]. Data presented in tables 2-4 show a weak correlation between peak post-  
539 exercise  $T_{core}$  (rectal, gastrointestinal or oesophageal) with peak I-FABP ( $\Delta$ ;  $r= 0.52$ ;  $p = <0.001$ ),  
540 but not the DSAT (5-hr urine only;  $r= 0.30$ ;  $p= 0.19$ ), or endotoxin ( $\Delta$ ;  $r= 0.14$ ;  $p= 0.56$ )  
541 concentration (note: studies without  $T_{core}$  assessment were excluded).

542 Splanchnic vascular beds receive ~20% of total resting cardiac output but consume  
543 only 10-20% of the available oxygen [162]. Consequently, blood flow during strenuous  
544 exercise can be safely redistributed from splanchnic organs to skeletal muscle to maintain  
545 aerobic metabolism, and to skin to assist thermoregulation [157]. Hypoperfusion of splanchnic  
546 vascular beds, measured using doppler ultrasonography, appears to be proportional to  
547 exercise intensity and duration [162]. Specifically, splanchnic blood flow declines by 30-60%  
548 following both 30 minutes of moderate-intensity (60-70%  $VO_{2max}$ ) and 1-2 hours of low-  
549 intensity exercise (40-50%  $VO_{2max}$ ) [163]. These responses appear amplified when exercise is  
550 performed in a warm environment [164]. A key downstream event following GI hypoperfusion  
551 is GI ischemia measured using gastric tonometry, which is also known to be suppressed  
552 following exercise in an intensity dependant manner [86, 165]. Localised GI hypoperfusion is  
553 considered to evoke secondary adenosine triphosphate depletion, acidosis, altered  
554 membrane ion pump activity and oxidative stress, all physiological responses that damage the  
555 GI barrier [154, 159, 167]. One limitation of this research is the inability of tonometry to  
556 measure large intestinal ischemia in exercising humans, especially as the largest microbial  
557 biomass is located in the distal GI segments [166]. The partial pressure of oxygen across the  
558 GI tract displays a proximal-to-distance gradient [168], which might have clinical  
559 manifestations on MT given that the integrity of the large intestine is considered less  
560 susceptible to ischemic injury [82]. Contrary to previous beliefs, the influence of splanchnic  
561 reperfusion following exertional-heat stress appears to be an unlikely mechanism of GI barrier  
562 integrity loss [82]. Indeed, one study found plasma I-FABP concentrations correlated with  
563 splanchnic (stomach) hypoperfusion during moderate intensity exercise ( $r= 0.59$ ), though  
564 following post-exercise intestinal reperfusion, I-FABP concentrations began to recover within  
565 the first 10 minutes [86].

566 Inflammatory cytokines comprise a large family of intercellular pleiotropic signalling  
567 molecules that perform many regulatory functions, and are primarily involved in innate  
568 immunity [169]. Strenuous exercise induces strong pro-inflammatory (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IFN-  
569  $\gamma$ ), followed by anti-inflammatory (IL-1ra, IL-4, IL-10) responses throughout numerous cells  
570 and tissues across the body [170]. The specific biological roles of individual cytokines are  
571 incompletely understood and are likely context dependant. That said, several pro-  
572 inflammatory cytokines released post-exercise (e.g. TNF- $\alpha$ ) appear to disrupt GI barrier

573 integrity [153]. Potential regulatory mechanisms might include: direct modulation of several  
574 cell signalling pathways that regulate TJ protein complex stability [171-173]; and the indirect  
575 pyrogenic modulation of body temperature where local hyperthermia damages the GI barrier  
576 [174-175]. With EHS cases, pro-inflammatory cytokines are produced upon immune activation  
577 (e.g. nuclear factor kappa- $\beta$  transcription) following binding between MT products and toll-  
578 like receptors located on cell surface membranes [156]. This response appears to operate  
579 through a positive feedback loop that may further promote GI MT, cytokine production, and  
580 potentially culminate in fatal septic shock [176].

581

## 582 **Nutritional Countermeasures**

583 Nutritional countermeasures could modulate key cellular pathways involved in  
584 mitigating exertional-heat stress induced GI barrier integrity loss. Diet regimens and nutrition  
585 supplements with evidence they can influence GI barrier integrity following exercise and/or  
586 exertional-heat stress will be reviewed. The mechanistic basis of each nutritional intervention,  
587 evidence of improved GI barrier function following exercise and practical recommendations  
588 are presented.

## 589 **Carbohydrate**

590 Carbohydrates (CHO) are the main macronutrient of western diets and are an essential  
591 energy substrate in sustained moderate and high intensity exercise. The physiological  
592 response to CHO ingestion is highly dependant upon its biochemical formula, where high  
593 glycaemic index CHO (e.g. glucose, maltose) have rapid bioavailability, and low glycaemic  
594 index CHO (e.g. fructose, galactose) have delayed bioavailability. The volume, tonicity and  
595 osmolality of CHO is equally influential. In healthy resting humans, ingestion of a single CHO-  
596 rich meal (55-70% of total kilo-calories) evokes equivocal (endotoxin [177-179] or slightly  
597 improved (I-FABP; [180-181]) GI barrier integrity postprandially. However, rodent  
598 experimental models of acute GI distress indicate that oral ingestion of maltodextrin [182] or  
599 sucrose [183] favourably influence GI barrier integrity. Mechanisms of action at the whole-  
600 body level are likely multifactorial, including regulation of the GI microbiota [184] and an  
601 elevation of splanchnic perfusion [185]. Nevertheless, *in vivo* and *in vitro* studies indicate that

602 high glucose exposure might reduce GI TJ stability through an abnormal redistribution of  
603 several TJ proteins [186]. Compared with ingestion of a single CHO-rich meal, ingestion of a  
604 single fat-rich meal results in acute GI MT [178-179, 187].

605 The ingestion of CHO pre-, during and post-exercise in athletic populations is widely  
606 recommended to improve exercise performance [188], accelerate recovery [189] and  
607 maintain immune function [190]. In comparison, the influence of CHO on GI barrier integrity  
608 has received less attention, despite being associated with the onset of GI complaints [191] and  
609 increased splanchnic perfusion [192]. Contrary to proposed hypotheses, preliminary research  
610 found no influence of CHO beverage ingestion (30-60 g·hour<sup>-1</sup> glucose), compared with water,  
611 on GI barrier integrity (utilising the DSAT) during 60-90 minutes of moderate intensity exercise  
612 (70% VO<sub>2max</sub>) [111, 122]. However, follow-up studies reported attenuated GI barrier integrity  
613 loss (I-FABP and DSAT) with glucose ingestion (60 g·hour<sup>-1</sup>) during two-hours moderate  
614 intensity running (60% VO<sub>2max</sub>) in the heat (35°C and 25% relative humidity (RH); [193]), and  
615 with sucrose ingestion (40 g·hour<sup>-1</sup>) prior/during a one-hour moderate intensity cycle (70%  
616 watt<sub>max</sub>) [131]. However, neither intervention ameliorated the severity of GI MT. Formulations  
617 of single- and multi-transportable CHO mixtures (i.e. 1.8 g·min<sup>-1</sup> glucose; 1.2 and 0.6 g·min<sup>-1</sup>  
618 glucose plus fructose; 0.6 and 1.2 g·min<sup>-1</sup> glucose plus sucrose) all tended to (interaction effect  
619  $p = 0.10$ ) reduce I-FABP concentrations (area under the curve at 30 minute intervals) to a  
620 similar extent relative to water during three hours of low-intensity cycling (50% Watt<sub>max</sub>) [130].  
621 Similarly, ingestion of 60 g·hour<sup>-1</sup> of either potato flesh puree or carbohydrate gel (2:1  
622 maltodextrin/fructose) were able to completely attenuate the rise in I-FABP observed  
623 throughout a 2.5 hour mixed-intensity cycle (2 hours 60% VO<sub>2max</sub> then a 20 km time trial in  
624 temperate conditions) [181]. To date, only one study has reported an adverse effect of CHO  
625 ingestion during exercise (1 hour 70% VO<sub>2max</sub> running in 35°C and 12-20% RH) on GI barrier  
626 integrity, with ingestion of a multi-transportable CHO gel (18 g maltodextrin and 9 g fructose)  
627 20-minutes into exercise shown to increase GI barrier integrity (I-FABP and endotoxin) loss  
628 relative to a placebo [194]. Surprisingly, in the placebo condition exertional-heat stress had  
629 no influence on GI barrier integrity, whilst in the CHO condition the magnitude of GI integrity  
630 loss was minimal. Currently little is known about the influence of pre-exercise CHO availability  
631 on GI barrier integrity. One study reported that 48-hour low (20% CHO, 65% fat) versus high  
632 (60% CHO, 25% fat) CHO-diet had no influence on GI MT after a laboratory duathlon [195];

633 whilst a similar study reported no influence of a 24 hour low or high FODMAP diet on GI barrier  
634 integrity (I-FABP, LBP, sCD14-ST) following 2 hours of exertional-heat stress [147].

635 Practical recommendations for CHO ingestion on GI barrier integrity are unable to be  
636 established at present, given the large variation in findings from seemingly comparable  
637 studies. This lack of consistency cannot be attributed to differences in prandial state,  
638 exercise intensity, CHO type/dose or participant demographic. In general, the application of  
639 traditional sports nutrition guidelines for CHO ingestion do not appear to adversely influence  
640 GI barrier integrity, and more likely would appear to offer favourable benefits. Future work  
641 is required to determine the most effective CHO formulations for fueling exercise and  
642 maintaining GI barrier integrity. Factors that may be important include: the carbohydrate  
643 source (e.g. potato, maize), dextrose equivalence, osmolarity, sugar profile and delivery  
644 format (e.g. drink, gel, energy chew, or bar). The impact of pre-exercise CHO status (e.g. low  
645 carbohydrate training, or fasted training) may also influence the GI barrier response to  
646 feeding. The strategy of gut-training (i.e. multiple exercise sessions with high [90 g·hour<sup>-1</sup>]  
647 CHO intake) to improve CHO tolerance during exercise does not appear to strengthen the GI  
648 barrier [191].

## 649 **Glutamine**

650 Glutamine is the most abundant amino acid in human tissue and plasma, where it  
651 performs numerous important regulatory functions. It is a *conditionally essential* nutrient  
652 during states of catabolic stress (e.g. starvation, trauma and severe infection), and is the major  
653 energy substrate of GI enterocytes. The use of L-glutamine supplementation to support GI  
654 barrier function has received extensive examination [196]. Benefits have repeatedly been  
655 shown in humans following large intravenous L-glutamine infusions (~0.2-0.5 g·kg·day<sup>-1</sup>) in  
656 patients with critical illness indicative of glutamine deficiency, including severe burns [197-  
657 198], post-infectious irritable bowel syndrome [199], and major abdominal trauma [200]. In  
658 comparison, benefits are less prominent with low dose oral ingestion (<0.2 g·kg·day<sup>-1</sup>) in  
659 chronic GI diseases patients, whom are unlikely to be glutamine deficient and/or exposed to  
660 acute stress [201-202]. Mechanisms of action appear multifactorial including: increased  
661 epithelial cell proliferation [203]; upregulation of cytoprotective intracellular heat shock  
662 protein (I-HSP) expression [204]; modulation of inflammatory signalling pathways [205];

663 increased vasodilating factors (e.g. nitric oxide); GI microbiota regulation [206]; enhanced GI  
664 glutathione status [207]; and improvement in TJ stability through increased expression of  
665 multiple TJ proteins [208-209].

666         Supplementation with L-glutamine is not presently endorsed by sports nutrition  
667 guidelines, on the basis of weak evidence demonstrating improved immune function [190] or  
668 exercise-performance [210]. Early research investigating the effect of L-glutamine  
669 supplementation on exercise-induced GI permeability (assessed with DSAT), found no  
670 additional benefit of co-administering L-glutamine ( $0.018 \text{ g}\cdot\text{kg}^{-1} \text{ BM}$ ) with CHO ( $0.18 \text{ g}\cdot\text{kg}^{-1}\text{BM}$ )  
671 every 10 minutes during a one-hour moderate-intensity run ( $70\% \text{ VO}_{2\text{max}}$ ), in comparison to  
672 CHO alone [122]. Unfortunately, L-Glutamine was not assessed in isolation and the total dose  
673 consumed was only *circa* 8-12 g. Since then, researchers have changed their focus from low  
674 dose L-glutamine supplementation to maintain circulating concentrations, to provision of large  
675 oral doses to saturate the GI tissue prior to exercise. Both chronic ( $3 \times 0.3 \text{ g}\cdot\text{kg}\cdot\text{FFM}^{-1}$  for seven  
676 days; [211]) and acute ( $0.9 \text{ g}\cdot\text{kg}\cdot\text{FFM}^{-1}$  two-hours pre-exercise [116]) L-glutamine ingestion  
677 raised circulating concentrations by  $\sim 2.5$ -fold (suggestive of GI saturation) and attenuated the  
678 rise in the GI permeability (DSAT ratio) from basal conditions following a one-hour moderate-  
679 intensity run ( $70\% \text{ VO}_{2\text{max}}$ ) in the heat ( $30^{\circ}\text{C}/12\text{-}20\% \text{ RH}$ ). Using an identical experimental-  
680 design, it was subsequently shown that L-glutamine doses of 0.25, 0.5 and  $0.9 \text{ g}\cdot\text{kg}\cdot\text{FFM}^{-1}$   
681 suppressed the post exertional-heat stress rise in serum I-FABP concentration ( $\sim 0\text{-}20\%$ ) and  
682 DSAT ratio ( $\sim 25\text{-}40\%$ ). Although the authors reported a dose-dependent effect on GI barrier  
683 integrity [212], statistical significance testing was not undertaken, with these conclusions  
684 drawn from magnitude based inference analysis. Recently, ingestion of  $0.9 \text{ g}\cdot\text{kg}\cdot\text{FFM}^{-1}$  of L-  
685 glutamine one hour prior to a 20 km cycling time trial in the heat ( $35^{\circ}\text{C}$ ,  $50\% \text{ RH}$ ) blunted the  
686 rise in circulating post-exercise I-FABP, although this studies conclusions were drawn from a  
687 linear mixed methods Bayesian statistical approach [213].

688         Practical recommendations support the use of a single L-glutamine dose ( $0.90$   
689  $\text{ g}\cdot\text{kg}\cdot\text{FFM}^{-1}$ ) two-hours pre-exercise to protect GI barrier integrity. Given the requirement to  
690 only ingest a single acute-dose in the hours prior to exertional-heat stress, the  
691 supplementation protocol has clear real-world application in terms of both implementation  
692 logistics and expense. Further work is required to confirm these findings following more



693 severe exertional-heat stress protocols and extending analysis to include secondary markers  
694 of GI MT. The oral tolerance and safety of such large L-glutamine doses requires clinical  
695 assessment as it is above general guidelines (5-10 g) for sports supplements [214]. Likewise,  
696 a limitation of all previous research has been the performance of trials in the fasted state,  
697 whereby positive findings are potentially attributable to improvement in post-prandial  
698 splanchnic perfusion, rather than any benefits directly related to L-glutamine. Indeed,  
699 ingesting 15 g·20 min<sup>-1</sup> of whey protein hydrolysate during a 2-hour moderate-intensity (60%  
700 VO<sub>2max</sub>) run in the heat (35°C/30% RH) has also been shown to be highly effective in  
701 maintaining GI barrier integrity [193]. Future research should focus on determining if  
702 specific amino acid mixtures are as effective, or can even outperform L-glutamine alone, for  
703 maintaining GI barrier integrity.

#### 704 **Bovine Colostrum**

705 Bovine colostrum (BC) is the milk produced by cows during the first 24-48 hours post-  
706 partum, and its composition markedly differs from milk produced later in lactation [215]. In  
707 humans, colostrum provides many health benefits to the neonate, including rapid tissue  
708 development and immune defence [216]. BC contains a variety of growth factors (e.g. insulin-  
709 like growth factor-1; IGF-1) and immunomodulatory components (e.g. immunoglobulins,  
710 cytokines) at higher concentrations than human colostrum [217]. The use of a BC nutritional  
711 supplement (liquid and powder) to maintain GI barrier function in healthy adults has been  
712 shown to reduce GI permeability post NSAID administration [218], and can blunt systemic  
713 elevations in endotoxin following critical illness [219]. These findings are supported by *in vitro*  
714 studies on Caco-2 cells, where BC blunted GI cell apoptosis and increased epithelial resistance  
715 during heat exposure [113, 220]. Mechanisms of action include: increased epithelial cell  
716 proliferation [113, 221], upregulation of cytoprotective I-HSP expression [114] and improved  
717 TJ stability through a reduction in phosphorylated tyrosine concentrations of occludin and  
718 claudin-1 [114].

719 Supplementation with BC has increased in athletic populations in response to recent  
720 evidence of enhanced muscle growth rates [222], blunted exercise-associated  
721 immunosuppression [223] and improved exercise performance [224]. More recent  
722 investigations have assessed the influence of BC on exercise-induced GI damage. In a series

723 of experiments, 14 days of BC ( $20 \text{ g}\cdot\text{day}^{-1}$ ) halved the 3-fold rise in urinary DSAT ratio and  
724 circulating I-FABP concentrations following short-duration (20 minutes) high-intensity  
725 running ( $80\% \text{ VO}_{2\text{max}}$ ) [113, 114, 225]. Whilst these results show promise, such benefits  
726 appear attenuated by more demanding exercise protocols. Two comparable studies  
727 reported no effect of either a moderate (14 days at  $20 \text{ g}\cdot\text{day}^{-1}$ ; [226] or high (7 days at  $1.7$   
728  $\text{g}\cdot\text{kg}\cdot\text{day}^{-1}$  (circa  $\sim 120\text{-}150\text{g}$ ); [152]) BC dosing on I-FABP concentrations following a fatiguing  
729 run in the heat ( $35\text{-}40^\circ\text{C}$ ;  $50\% \text{ RH}$ ). Likewise, March et al. [105], using their earlier BC  
730 supplementation protocol [225], found only minor ( $\sim 10\%$ ) suppression of I-FABP  
731 concentration and a non-significant blunting of circulating bacteroides DNA following a 1-  
732 hour run ( $70\% \text{ VO}_{2\text{max}}$ ) in the heat ( $30^\circ\text{C}/60\% \text{ RH}$ ).

733 Practical recommendations support a BC dose of  $20 \text{ g}\cdot\text{day}^{-1}$  for 14 days to protect the  
734 GI tract during moderately demanding exercise, though little-to-no benefits appear likely  
735 during more intense exercise. Two days of BC supplementation with the same daily dose  
736 offered no protective benefits [144]. Chronic low dose ( $500 \text{ mg}\cdot\text{day}^{-1}$ ) BC ingestion improved  
737 resting GI permeability (DSAT ratio) in athletes during heavy training [227], but chronic high  
738 dose ( $60 \text{ g}\cdot\text{day}^{-1}$ ) BC ingestion appeared to increase GI permeability [228]. Further work is  
739 required to determine the optimal time-course and BC dose to support GI barrier function.  
740 As there are large inter-manufacturer variations in BC formulations, future research should  
741 include accurate characterisation of the bioactive components in intervention trials, as  
742 these components are likely to have a significant bearing on study findings [229]. No studies  
743 have successfully measured the influence of BC on secondary GI MT post-exercise. BC  
744 appears to be well-tolerated in healthy individuals in doses up to  $60 \text{ g}\cdot\text{day}^{-1}$  over several  
745 weeks, and although IGF-1 is on the World Anti-Doping Agency banned substance list, it is  
746 unlikely BC can result a positive doping control [230].

## 747 **Nitric Oxide**

748 The free radicle gas, Nitric Oxide (NO), performs multiple signalling roles in the body.  
749 Synthesis occurs through two complementary pathways: the NO synthase (NOS) dependant L-  
750 arginine pathway; and the NOS independent nitrate ( $\text{NO}_3$ ), nitrite ( $\text{NO}_2$ ), NO serial reduction  
751 pathway [231]. Supplementation with NO precursors, including L-arginine [232], L-citrulline  
752 and inorganic  $\text{NO}_3$  [233], are all capable of upregulating NO bioavailability across the

753 splanchnic organs. Rodent models show this increase in NO blunts GI histopathological  
754 damage and subsequent MT following NSAID ingestion [234], small bowel obstruction [235]  
755 and experimentally induced ischemic-reperfusion injury [236-237]. The vasodilatory role of  
756 NO in maintaining GI microcirculation appears to be one of the main mechanisms [82], with  
757 enhanced antioxidant scavenging [238], constrained neutrophil activation [239] and increased  
758 GI TJ protein expression [240] as complementary pathways.

759           No guidelines exist for L-arginine or L-citrulline supplementation in athletic populations  
760 [241], and consensus documents do not support its use to improve oxygen uptake kinetics or  
761 exercise performance [242]. Only two studies have investigated the influence of nitric oxide  
762 precursors on exercise-induced GI barrier integrity loss. A rodent study found addition of 2%  
763 L-arginine to the standard diet (over seven days) prevented a rise in GI barrier loss relative to  
764 the control following ~1-hour forced running to fatigue in the heat (34°C) [243]. Similarly in  
765 humans, Van Wijck et al. [127] found acute L-citrulline supplementation (10g given 30 minutes  
766 pre-exercise) successfully maintained splanchnic perfusion and blunted the rise in systemic I-  
767 FABP during one hour of moderate intensity cycling (70% watt<sub>max</sub>). However, this intervention  
768 did not reduce peak post-exercise I-FABP concentrations, or the urinary DSAT ratio.

769           Inorganic NO<sub>3</sub> supplementation has increased in athletic populations over the last  
770 decade [241]. Its popularity is founded upon evidence showing NO<sub>3</sub> supplementation (~ 8  
771 mmol, acutely and chronically) reduces the oxygen cost of exercise, enhances muscle  
772 efficiency and improves prolonged aerobic performance (10-40 minutes) [244]. There is  
773 limited evidence addressing NO<sub>3</sub> supplementation and exercise-induced GI barrier integrity  
774 loss. One placebo controlled study found acute sodium NO<sub>3</sub> (800 mg given 2.5 hours pre-  
775 exercise), did not attenuate the rise in circulating I-FABP or LBP concentration concentration  
776 following 1-hour of moderate intensity cycling (70% watt<sub>max</sub>) [131].

777           Practical recommendations regarding the use of L-arginine, L-citrulline or inorganic  
778 NO<sub>3</sub> to protect the GI tract during exercise are inconclusive. Further work is required to  
779 substantiate present findings and to verify any benefits over a range of exercise protocols.  
780 Likewise, evidence is required to confirm whether benefits are observed in highly-trained  
781 populations (who tend not to respond to NO supplementation), and to determine which NO

782 precursors provide the most effective GI protection. A further practical consideration is the  
783 apparent impaired thermoregulation associated with reduced cutaneous vasodilation, which  
784 might disrupt the GI barrier especially when exercising in the heat [245-246].

## 785 **Probiotics**

786 Probiotics are live microorganisms considered to regulate the GI microbiota, which  
787 might confer health benefits when consumed in adequate quantities [247]. They are found in  
788 low concentrations across various food sources (e.g. non-pasteurised dairy products), and  
789 regular consumption has been recommended in patients with GI conditions since the early  
790 1900s [247]. More recently, probiotic supplementation to support GI barrier function has  
791 received extensive examination. Whilst positive barrier effects are reported in ~50% of human  
792 studies, these are not universal, and may reflect the large variations in dose and strains  
793 administered [248-249]. Inconclusive effects are also reported *in vitro* on GI cellular apoptosis  
794 and epithelial integrity when Caco-2 cells are cultured with probiotics prior to insult [250-251].  
795 Mechanisms of action are incompletely understood, but are believed to include: inhibition of  
796 pathogenic bacterial overgrowth; competition with pathogenic bacteria for binding sites on  
797 mucins and/or epithelial cells; increased mucosal immunoglobulin and antimicrobial proteins  
798 secretion; increased epithelial cell proliferation; upregulated I-HSP concentrations;  
799 suppressed local GI inflammation; and increased TJ stability through upregulation of GI TJ  
800 protein expression (for review see: [252]).

801 Probiotic supplementation is increasingly popular in athletic populations, despite  
802 inconsistent effects of their use for either maintaining immune health or improving exercise  
803 performance [253]. With respect to GI barrier integrity, four weeks daily consumption of a  
804 multi-strain probiotic ( $45 \times 10^9$  colony forming units [CFU]; from three strains) blunted DSAT  
805 ratios (8%) and circulating endotoxin concentrations (~12%) following a ~35-minute  
806 fatiguing run (80% ventilatory threshold) in the heat (35°C/40% RH) [261]. A follow-up study  
807 reported daily ingestion of a similar multi-strain probiotic ( $3 \times 10^9$  CFU; from nine strains)  
808 for a period of twelve weeks approximately halved basal endotoxin concentrations  
809 immediately prior to and 6-days following an ultra-triathlon [254]. In contrast, seven days  
810 high-dose single strain probiotic supplementation ( $45 \times 10^{11}$  CFU.day<sup>-1</sup> *Lactobacillus Casei*)  
811 was associated with an increased rise in endotoxin concentrations, compared with placebo,

812 following two hours moderate-intensity running (60% VO<sub>2max</sub>) in the heat (34°C/32% RH)  
813 [149]. Similarly, the daily ingestion of another single strain probiotic (35 x 10<sup>9</sup> CFU  
814 *Bifidobacterium longum*) had no effect on resting endotoxin concentrations following six  
815 weeks of pre-season training in collegiate swimmers [255]. Likewise, four weeks daily  
816 supplementation with a multi-strain probiotic (25 x 10<sup>9</sup> CFU; from five strains) had no  
817 influence on either DSAT, I-FABP or sCD14 responses following a simulated 42.2 km  
818 marathon in temperate conditions [148]. Finally, four weeks supplementation with a single  
819 strain probiotic (2 x 10<sup>8</sup> CFU *Lactobacillus Salivarius*) had no influence on DSAT responses,  
820 (or faecal microbial composition), following two hours of moderate intensity running (60%  
821 VO<sub>2max</sub>) in temperate conditions [256]. It is unlikely the final two studies were sufficiently  
822 powered to detect any influence of probiotic supplementation of GI barrier integrity.

823           The present data indicate that probiotic supplementation has little for supporting GI  
824 barrier integrity in response to exercise. It is not possible to elucidate whether inconsistent  
825 responses are attributable to the specific probiotic strain, duration of supplementation or  
826 another factor. Future research is required to develop probiotic supplementation regimes and  
827 will need to address factors such as strain(s), timing and dose. It will also be necessary to verify  
828 potential efficacy using relevant exercise (heat stress) protocols. Global metabolomics  
829 approaches have linked exercise-induced GI barrier function loss with alterations in GI  
830 microbiota composition during a four-day military arctic training exercise (51 km ski march;  
831 [257]), and such methodologies should be applied when developing probiotic supplements to  
832 support GI barrier integrity. Probiotic use is considered safe in healthy populations, when  
833 consumed acutely and chronically [253].

## 834 **Polyphenols**

835           Polyphenols are natural compounds that defend plants against damage from radiation  
836 and pathogens. Over 8000 polyphenols have been identified, which are classified into four  
837 major groups: flavonoids; phenolic acids; stilbenes; and lignans. Quercetin is the most  
838 abundant dietary flavonoid polyphenol [258], and in rodents' supplementation has been  
839 shown to maintain GI barrier integrity [259]. However, *in vitro* evidence from human Caco-2  
840 cells is less conclusive, with quercetin shown to both improve [260-261] and impair [262-263]  
841 GI barrier integrity in response to heat stress. Proposed mechanisms in favourable studies

842 include modulation of vasodilatory factors (e.g. NO [263]), elevated antioxidant scavenging  
843 [265] and improved TJ stability through upregulation of several TJ proteins [266]. Proposed  
844 mechanisms in non-favourable studies relate to reduced cytoprotective I-HSP expression  
845 [267] and TJ stability through disruption in occludin TJ protein localisation [262]. Both positive  
846 and negative responses have been comparatively reported when Caco-2 cells are  
847 supplemented *in vitro* with additional polyphenols [264, 266]. Human studies assessing  
848 polyphenol supplementation efficacy on GI barrier integrity are lacking [264], and where *in*  
849 *vitro* studies administer physiologically relevant polyphenol doses the effects have been  
850 negligible [268].

851 Polyphenol supplementation is increasingly popular in athletic populations [269]. This  
852 is founded upon moderate evidence of enhanced skeletal muscle recovery from micro-  
853 damage [270], blunted exercise-associated immunosuppression [271] and in some cases  
854 improved (1-3%) endurance exercise performance [272]. With respect to polyphenol  
855 supplementation and exercise-induced GI barrier integrity, the effect of daily quercetin  
856 supplementation (2 g·day<sup>-1</sup> one hour pre-exercise) on GI permeability following the first and  
857 seventh days of a standardised isothermic walking (100 minutes; 1.8 m·s<sup>-1</sup> in 46°C/20% RH)  
858 heat acclimation regime was assessed [143]. On both days, quercetin ingestion stimulated a  
859 ~two-fold rise in urinary lactulose and plasma endotoxin compared with a placebo condition.  
860 More promisingly, supplementation with curcumin (3 days of 0.5 g·day<sup>-1</sup>), a constituent of  
861 turmeric, blunted circulating I-FABP concentrations by ~30% after one-hour moderate  
862 intensity running (65% VO<sub>2max</sub>) in the heat (37°C/25% RH; [273]).

863 There are no practical recommendations supporting polyphenol use to protect the GI  
864 tract during strenuous exercise. Despite promising *in vitro* observations, more work is required  
865 to determine the optimal formulation, time-course and polyphenol dose to support GI barrier  
866 function across different exercise-modalities. No studies have successfully measured the  
867 effect of polyphenols on secondary GI MT post-exercise and clearly future studies should  
868 attempt to control for dietary polyphenol intake.

## 869 **Zinc-Carnosine**

870 Zinc-Carnosine (ZnC) is a pharmaceutical chelate of zinc and L-carnosine [274]. It is  
871 widely used in Japan to treat gastric ulcers [275], and more recently has been marketed in  
872 Europe to support GI health [276]. Zinc is an essential trace element and a co-factor in  
873 numerous tissue regenerative and immunomodulatory enzymatic reactions [277], whilst L-  
874 carnosine is a cytoplasmic dipeptide of beta-alanine and L-histidine [278]. Daily ZnC ingestion  
875 improves GI barrier integrity in healthy humans following chronic GI barrier damaging NSAID  
876 ingestion [276, 279]. These protective benefits are reported to be synergistic compared with  
877 consuming either ingredient individually [280]. *In vitro* studies of rat intestinal and human  
878 Caco-2 cells support these reports, where ZnC blunts GI cellular apoptosis [281-282] and  
879 increases epithelial electrical resistance [114] upon damage, in a dose-dependent fashion.  
880 Mechanisms of action appear multifactorial, including increased: epithelial cell proliferation  
881 [276]; I-HSP concentrations [114]; antioxidant activity [283]; and stability of TJs through  
882 blunting phosphorylated occludin and claudin-1 expression [114].

883 No guidelines exist concerning ZnC supplementation in athletic populations. Athletes  
884 are recommended to ensure sufficient dietary zinc ingestion (EU RDA = 10 mg·day<sup>-1</sup>) to  
885 prevent deficiencies, and to supplement with large oral doses (~75 mg·day<sup>-1</sup>), when suffering  
886 from acute upper respiratory tract infection to accelerate recovery [190]. Though L-Carnosine  
887 supplementation is uncommon, supplementing β-alanine (~65 mg·kg·day<sup>-1</sup>) the rate-limiting  
888 precursor for muscle L-carnosine synthesis, has been shown to increase muscle carnosine  
889 stores [283]. To date, only one study has investigated the influence of ZnC on exercise-induced  
890 GI damage. Fourteen days of ZnC (75 mg·day<sup>-1</sup>) attenuated a 3-fold rise in DSAT ratio by 70%  
891 after short-duration (20 minutes) high-intensity running (80% VO<sub>2max</sub>) [114]. This effect was  
892 comparable to that observed with BC (20 g·day<sup>-1</sup> for 14 days) in the same study, and when the  
893 two-treatments were combined the benefits appeared synergistic (85% reduction DSAT ratio).  
894 Furthermore, the combination of ZnC and BC blunted the exercise-induced increase in DSAT  
895 ratio by 30% after only two-days, whilst no protection was offered by either ingredient alone  
896 at this point [114].

897 Practical recommendations support ZnC use at a dose of 75 mg·day<sup>-1</sup> for 14 days to  
898 protect the GI tract during moderately demanding exercise. Further work is needed to  
899 substantiate existing findings and verify the potential benefits of ZnC during more strenuous

900 exercise. No studies have successfully measured the influence of ZnC on secondary GI MT  
901 post-exercise. Research is required to determine the optimal time-course and dose of ZnC to  
902 support GI barrier function with chronic and acute supplementation. Larger doses of ZnC  
903 (150 mg·day<sup>-1</sup>) appear well-tolerated in GI disease patients in the short-term [285], and  
904 dose-dependent *in vitro* evidence suggests this might offer greater protection [280]. Co-  
905 ingestion of copper with zinc (1:10 ratio or 2 mg·day<sup>-1</sup>) appears to prevent zinc inhibiting  
906 copper absorption [190].

### 907 **Limitations and Future Directions**

908 Investigation of nutritional countermeasures that support GI barrier integrity during  
909 strenuous exercise is an important and expanding area of research. Preliminary observations  
910 indicate some diet regimens and dietary supplements could benefit exercising populations.  
911 Optimal supplementation strategies should be safe, well-tolerated, practical (e.g.  
912 affordable/low mass), fast acting and effective in a wide range of scenarios (e.g. exercise  
913 intensity/duration, population). It is also important that they are without secondary adverse  
914 responses, especially those relating to skeletal muscle adaptation, thermoregulation,  
915 immune function, bone health etc. Whilst there are numerous examples of well-conducted  
916 studies reporting beneficial effects from diet regimens and individual supplements on GI  
917 barrier integrity, it is currently not possible to provide definitive guidance. In part this is due  
918 to limitations and variations in study designs and in some instances incomplete  
919 characterisation of the bioactive nutrients.

920 Future research should address diet regimens/nutritional supplements that satisfy the  
921 above requirements when tested in the most demanding scenarios (e.g. high  
922 intensity/prolonged exertional-heat stress). It would appear very worthwhile to assess the  
923 synergy between ingredients that maintain GI integrity, especially if they are thought to act via  
924 different biochemical pathways. Further supplements that warrant future exploration include:  
925 omega-3 polyunsaturated fatty acids [286]; vitamin C [287]; vitamin E [287]; vitamin D [288]  
926 and prebiotics [289]. Research should target specific populations (e.g. gender, training status,  
927 heat-acclimated, GI disease), exercise modalities (especially prolonged duration),  
928 supplementation timings (e.g. repeat dosing, delayed/post-exercise ingestion) and monitor  
929 the continued efficacy of supplementation following chronic application. Of note, future



930 research is warranted to determine the most damaging exercise protocol on GI barrier, which  
931 possibly involves a combination of prolonged/intense exercise performed in the heat.

932 From a methodological perspective, it is recommended that future studies assess a  
933 battery of relevant GI barrier integrity markers (e.g. DSAT, plus I-FABP/I-BABP/claudin-3, plus  
934 endotoxin/LBP/sCD14/bactDNA) and monitor alterations in the proposed mechanistic  
935 pathways (e.g. splanchnic perfusion, I-HSPs) underpinning any functional benefits. Key  
936 extraneous variables should be controlled, including: prandial state [180]; hydration status  
937 [135]; beverage temperature [137]; prior NSAID ingestion [121]; habitual diet and supplement  
938 use.

### 939 **Conclusions**

940 EHS is a life-threatening disease involving thermoregulatory failure, which sporadically  
941 arises in otherwise healthy individuals following performance of strenuous exercise or  
942 occupationally arduous tasks. Current EHS management policy primarily takes a  
943 thermoregulatory management approach despite evidence of MT following loss of GI barrier  
944 integrity being an important process in the disease pathophysiology. A range of techniques  
945 are available to assess GI barrier integrity *in vivo*, and a battery approach monitoring multiple  
946 measures in both field and research settings is recommended. The severity of GI barrier  
947 integrity loss following exertional-heat stress appears to be intensity and duration-  
948 dependant, with thermoregulatory strain being an additional risk factor. Considerations for  
949 the specific GI barrier integrity assessment technique must be made when interpreting  
950 individual studies conclusions, whereby I-FABP responses typically provided the greatest  
951 sensitivity. The specific aetiology of exertional-heat stress induced GI barrier integrity loss is  
952 poorly defined, but likely relates to the direct effects of localised hyperthermia, ischemia-  
953 reperfusion injury and neuroendocrine-immune alterations.

954 A range of nutritional countermeasures have been shown to positively affect GI  
955 barrier integrity following strenuous exercise and exercise-heat stress. However, despite  
956 rapid advancements in this field, definitive recommendations cannot be provided due to the  
957 heterogeneity of experimental designs. Nevertheless, promising effects have been  
958 associated with following general sports nutrition CHO supplementation guidelines during

959 exercise ( $30\text{-}100\text{ g}\cdot\text{h}^{-1}$  liquid multi-transportable CHO), and acute L-glutamine ingestion two  
960 hours pre-exercise ( $0.25\text{-}0.9\text{ g}\cdot\text{kg}\cdot\text{FFM}^{-1}$ ). Benefits from BC, and probiotics likely relate to the  
961 specific supplement formulation, and hence require further investigation. Despite a sound  
962 rationale for the use of NO precursors and polyphenols to limit exercise-induced GI barrier  
963 integrity loss, substantive supporting evidence is currently absent. ZnC requires further  
964 verification, where short-term (1-3 days) high-dose supplementation appears an attractive  
965 consideration. Further well-controlled research in nascent areas could elucidate potential  
966 treatment options for exercise-induced GI barrier integrity loss.

967

968 **Declarations**

969 **Ethical Approval and Consent to Participate**

970 Not Applicable

971

972 **Consent for Publication**

973 Not Applicable

974

975 **Availability of Data and Materials**

976 Not Applicable

977

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979 The authors declare that they have no competing interests

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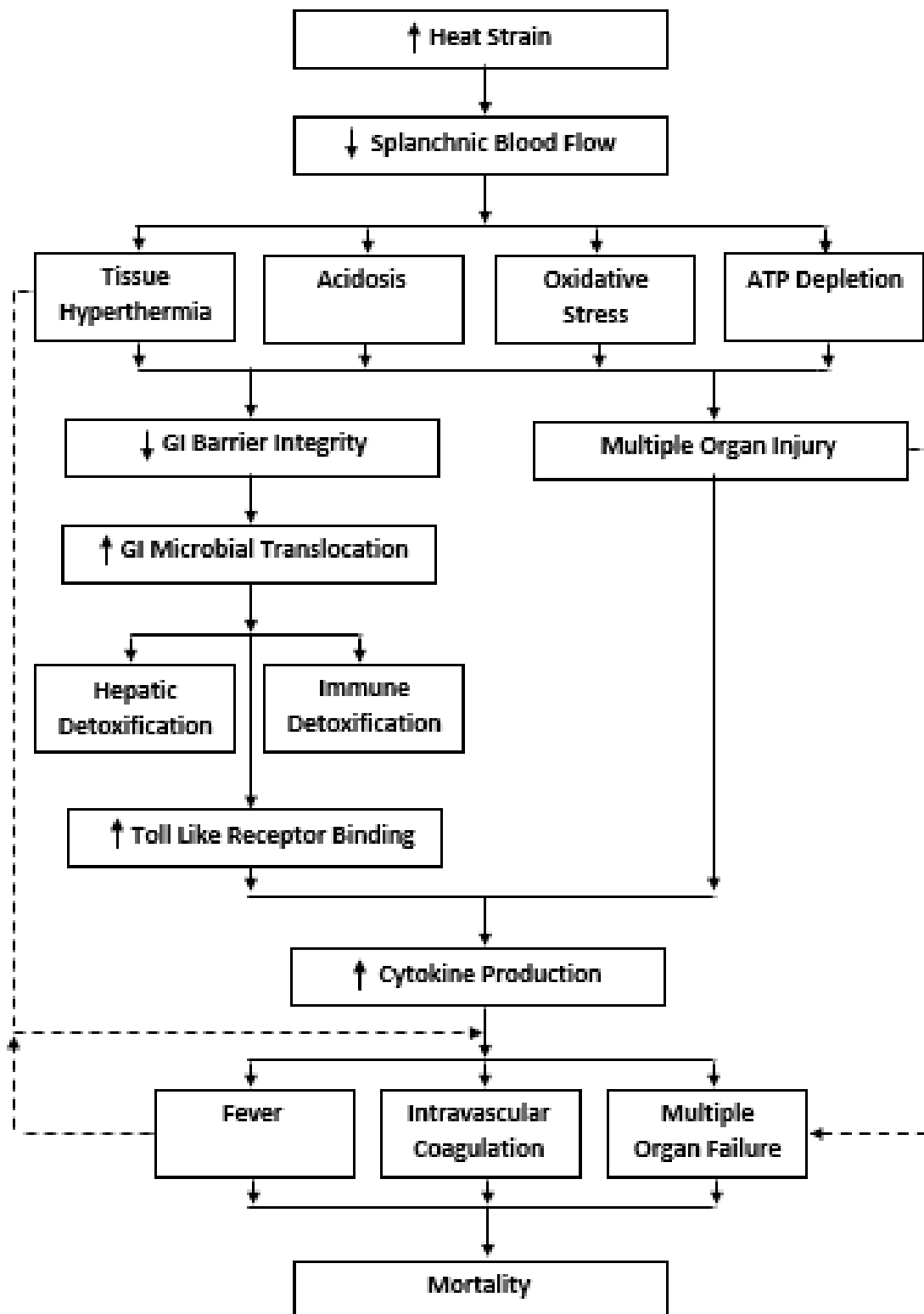
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1955 **Figure 1.** The gastrointestinal paradigm of exertional heat stroke

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**Table 1.** Overview of *In Vivo* techniques to assess GI Barrier Integrity

Technique	Sample	Method	Site	Limitations
<b>Active Techniques</b>				
Dual-Sugar Absorption Test (DSAT)	Urine or blood	HPLC (+) MS	Small GI Integrity	Gold-standard. High reliability. Time-consuming (5 hr urine, >2.5 hour blood). No standard protocol with exercise. Well-studied.
Multi-Sugar Absorption Test (MSAT)	Urine or blood	HLPC (+) MS	Entire GI Integrity	Gold-Standard. Segmental GI integrity. Time-consuming (5 hr urine, >2.5 hour blood). No standard protocol with exercise. Few studies.
Polyethylene Glycol (PEG) Absorption Test	Urine	HLPC (+) MS	Entire GI Integrity	Validated against MSAT. Can include multiple weight PEGs (e.g. 100, 400, 1000, 4000 kDa). Time-consuming (5 hr urine). Few studies.
<b>Passive Techniques</b>				
Intestinal Fatty Acid Binding Protein (I-FABP)	Urine or Blood	ELISA	Epithelial injury	Tissue specific (duodenum and jejunum). Short half-life (11 minutes). Weak correlations with DSAT. Well-studied.
Ileal Bile-Acid Binding Protein (I-BABP)	Urine or Blood	ELISA	Epithelial injury	Tissue specific (ileum). Few studies. Weak correlations with I-FABP. Few studies.
Diamine Oxidase (DAO), $\alpha$ -Glutathione s-Transferase ( $\alpha$ -GST), Smooth Muscle 22 (SM22)	Blood	ELISA	Epithelial injury	Non-tissue specific. Few studies.
Claudin-3 (CLDN3)	Urine or Blood	ELISA	TJ Integrity	Non-tissue specific. Few studies.
Zonulin	Blood or Faeces	ELISA	TJ Integrity	Non-tissue specific. Assay cross-reactivity (complement C3). Moderate studies.
Endotoxin (LPS)	Blood	LAL assay	MT	Tissue specific. Sample contamination causes false-positives. Hepatic removal and receptor binding cause false-negatives. Well-studied.
LPS Binding Protein (LBP)	Blood	ELISA	MT	Tissue specific. Lower risk of false-positives than endotoxin. Indirect marker of endotoxin exposure. Influenced by hepatic production. Long half-life (12-14 hours). Few studies.
Soluble-CD14 (sCD14-ST)	Blood	ELISA	MT	Tissue specific. Lower risk of false positives than endotoxin. Influenced by hepatic production and monocytes shedding. Few studies.
D-lactate	Blood	ELISA	MT	Predominately tissue specific. Economical and time efficient assessment. Potentially influenced by methylglyoxal metabolism. Few studies.
16s Bacterial rDNA (bactDNA)	Blood	Real-time PCR assay	MT	Tissue specific. Novel. Lower risk of false-positives than endotoxin. Potential for regional integrity assessment. Few studies.

1958 Abbreviations: HPLC, high performance liquid chromatography; MS, mass spectrometry;  
 1959 ELISA, enzyme-linked immunosorbent assay; LAL, limulus amoebocyte lysate assay; PCR,  
 1960 polymerase chain reaction



**Table 2.** Influence of acute exercise-(heat) stress on small-intestine DSAT responses

Author	Subjects	Exercise Protocol	Peak T <sub>Core</sub> (°C)	Mean HR (bpm)	Biofluid, DSAT L/R or L/M (timepoint)
van Nieuwenhoven et al. [110]	10 male (MT)	90 minutes cycling at 70% Watt <sub>max</sub> (fasted) in T <sub>amb</sub> 19°C (RH = N/A)	N/A	N/A	Urine L/R (5hr): 0.007 <sup>s</sup>
van Nieuwenhoven et al. [118]	10 male (MT)	90 minutes cycling at 70% Watt <sub>max</sub> (fasted) in T <sub>amb</sub> 19°C (RH = N/A)	38.8	N/A	Urine L/R (5hr): 0.008 <sup>nb, c</sup>
Nieman et al. [107]	20 male and female (UT)	45 minutes walking uphill (5% grade) at 60% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	132	Urine L/R (5hr): 0.009 <sup>nb, c</sup>
Smetanka et al. [123]	8 male (HT)	Chicago marathon (42.2 km) in T <sub>amb</sub> (fed) 22°C (48% RH)	N/A	N/A	Urine L/R (5hr): 0.020 <sup>ns</sup>
Shing et al. [126]	10 male (HT)	~33 minutes running to fatigue at 80% VE (fed) in T <sub>amb</sub> 35°C (40% RH)	39.4	172	Urine L/R (5hr): 0.022 <sup>nb, c</sup>
Janssen-Duijghuijsen et al. [109]	11 male (HT)	90 minutes cycling at 50% watt <sub>max</sub> (fed) in T <sub>amb</sub> not reported following a <i>sleep-low</i> glycogen depletion regime	N/A	N/A	Urine L/R (5hr): ~0.022 <sup>ns</sup> Plasma L/R (1hr): ~0.110 <sup>s</sup>
Snipe et al. [115, 125]	6 male and 4 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 22°C (44% RH)	38.5	~150	Urine L/R (5hr): 0.025 <sup>nb</sup>
Snipe et al. [125]	6 male and 4 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 30°C (25% RH)	38.6	~155	Urine L/R (5hr): 0.026 <sup>nb</sup>
van Wijck et al. [127]	10 male (MT)	60 minutes cycling at 70% watt <sub>max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/R (2hr): 0.027 <sup>nb, c</sup>
Snipe and Costa [291]	13 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (25% RH)	38.8	~155	Urine L/R (5hr): 0.028 <sup>nb</sup>
Ryan et al. [120]	7 males (MT)	60 minutes running at 68% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/M (6hr): 0.029 <sup>ns</sup>
van Nieuwenhoven et al. [112]	9 male and 1 female (MT)	90 minutes cycling at 70% Watt <sub>max</sub> (fasted) in T <sub>amb</sub> 19°C (RH = N/A)	N/A	N/A	Urine L/R (5hr): 0.030 <sup>ns</sup>
van Wijck et al. [124]	9 male (MT)	60 minutes cycling at 70% watt <sub>max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/R (2hr): 0.030 <sup>s, c</sup>
Pugh et al. [88]	11 male (MT-HT)	18x 400 metre sprint at 120% VO <sub>2max</sub> (fed) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/R (2hr): 0.030 <sup>ns</sup> Serum L/R (2hr): ~0.051 <sup>s</sup>
Snipe and Costa [291]	11 male (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (25% RH)	39.1	~150	Urine L/R (5hr): 0.030 <sup>nb</sup>
Buchman et al. [290]	17 male and 2 female	Competitive Marathon (fed) in T <sub>amb</sub> 2°C with freezing rain	N/A	N/A	Urine L/R (6hr): 0.030 <sup>ns, c</sup>

<b>Snipe et al. (Part B) [115]</b>	6 male and 4 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (26% RH)	39.6	~170	Urine L/R (5hr): 0.032 <sup>nb</sup>
<b>Snipe et al. [193]</b>	6 male and 5 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (30% RH)	39.3	159	Urine L/R (5hr): 0.034 <sup>nb, c</sup>
<b>March et al. [225]</b>	9 male (MT)	20 minutes running at 80% VO <sub>2peak</sub> (fasted) in T <sub>amb</sub> 22°C (37% RH)	38.4	170	Urine L/R (5hr): 0.035 <sup>s, c</sup>
<b>Pals et al. (Part A) [108]</b>	5 male and 1 female (MT)	60 minutes running at 40% VO <sub>2peak</sub> (fasted) in T <sub>amb</sub> 22°C (50% RH)	38.0	N/A	Urine L/R (5hr): 0.036 <sup>ns</sup>
<b>Marchbank et al. [113]</b>	12 male (MT)	20 minutes running to fatigue at 80% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> not reported	38.3	N/A	Urine L/R (5hr): 0.038 <sup>s, c</sup>
<b>van Nieuwenhoven et al. [111]</b>	9 male and 1 female (MT)	90 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 19°C (RH = N/A)	N/A	N/A	Urine L/R (5hr): 0.040 <sup>s</sup>
<b>van Wijck et al. [86]</b>	6 male (HT)	60 minutes cycling at 70% watt <sub>max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/R (5hr): 0.040 <sup>ns</sup> Plasma L/R (2.4hr): 0.060 <sup>s</sup>
<b>Lambert et al. (Part A) [119]</b>	11 male and 9 female (MT)	60 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 22°C (48% RH)	38.5	N/A	Urine L/R (5hr): 0.049 <sup>ns, c</sup>
<b>Lambert et al. [122]</b>	13 male and 4 female (HT)	60 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 22°C (48% RH)	38.3	N/A	Urine L/R (5hr): 0.050 <sup>nb, c</sup>
<b>Zuhl et al. [211]</b>	4 male and 3 female (LT/MT)	60 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 30°C (12-20% RH)	39.4	N/A	Urine L/R (5hr): 0.060 <sup>nb, c</sup>
<b>Zuhl et al. [116]</b>	2 male and 5 female (LT/MT)	60 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 30°C (12-20% RH)	39.5	N/A	Urine L/R (5hr): 0.060 <sup>nb, c</sup>
<b>Lambert et al. (Part B) [119]</b>	11 male and 9 female (MT)	60 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 22°C (48% RH) without fluid ingestion	38.5	N/A	Urine L/R (5hr): 0.063 <sup>s, c</sup>
<b>Pals et al. (Part B) [108]</b>	5 male and 1 female (MT)	60 minutes running at 40% VO <sub>2peak</sub> (fasted) in T <sub>amb</sub> 22°C (50% RH)	38.7	N/A	Urine L/R (5hr): 0.064 <sup>ns</sup>
<b>Lambert et al. [121]</b>	8 male (MT)	60 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 22°C (48% RH)	38.3	N/A	Urine L/R (5hr): 0.065 <sup>nb, c</sup>
<b>Buchman et al. [287]</b>	15 male and female (LT-HT)	Road marathon (42.2 km) (fed) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/M (6hr): 0.070 <sup>ns, c</sup>
<b>Pugh et al. [212]</b>	10 male (MT)	60 minutes at 70% VO <sub>2max</sub> running (fasted) in T <sub>amb</sub> 30°C (4-45% RH)	38.5	82.5% of max	Serum L/R (2hr): ~0.080 <sup>s, c</sup>
<b>Pugh et al. [148]</b>	10 male and 2 female (MT)	42.4 km track marathon (247 ± 47 minutes; fed) in T <sub>amb</sub> 16-17°C (N/A RH)	N/A	~160	Serum L/R (1hr) 0.081 (37%) <sup>s, c</sup>

<b>Lambert et al. [292]</b>	12 female (LT-HT)	Hawaii Ironman (fed) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/R (5hr): 0.087 <sup>nb</sup>
<b>Davison et al. [114]</b>	8 male (MT/HT)	20 minutes running to fatigue at 80% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> not reported	39.3	~170	Urine L/R (5hr): 0.098 <sup>s, c</sup>
<b>Janssen-Duijghuijsen et al. [293]</b>	4 male and 6 female (LT)	60 minutes cycling at 70% watt <sub>max</sub> (fed) in T <sub>amb</sub> not reported	N/A	N/A	Plasma L/R (1hr): ~0.100 <sup>s</sup>
<b>Lambert et al. [292]</b>	29 male (LT-HT)	Hawaii Ironman (fed) in T <sub>amb</sub> not reported	N/A	N/A	Urine L/R (5hr): 0.105 <sup>nb</sup>
<b>Pals et al. (Part C) [108]</b>	5 male and 1 female (MT)	60 minutes running at 40% VO <sub>2peak</sub> (fasted) in T <sub>amb</sub> 22°C (50% RH)	39.6	N/A	Urine L/R (5hr): 0.107 <sup>s</sup>

1962 LT = Low-trained (35-49 ml·kg·min<sup>-1</sup> VO<sub>2max</sub>); MT = Moderate-trained (50-59 ml·kg·min<sup>-1</sup>  
1963 VO<sub>2max</sub>); HT = High-trained (60+ ml·kg·min<sup>-1</sup> VO<sub>2max</sub>). s = significant change post-exercise (p <  
1964 0.05); ns = non-significant change post-exercise (p >0.05); nb = no baseline resting data to  
1965 compare against; c = control/placebo trial of study  
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**Table 3.** Influence of acute exercise-(heat) stress on systemic I-FABP concentrations

Reference	Subjects	Exercise Protocol	Peak T <sub>Core</sub> (°C)	Mean HR (bpm)	FABP2 ( $\Delta$ pre-to-post exercise)
Janssen-Duijghuijsen et al. [109]	11 male (HT)	90 minutes cycling at 50% watt <sub>max</sub> (fed) in T <sub>amb</sub> not reported following a "sleep-low" glycogen depletion regime	N/A	N/A	~90 pg·ml <sup>-1</sup> (~65%) <sup>c</sup>
Kartaram et al. (Part A) [129]	15 male (MT)	60 minutes cycling at 50% watt <sub>max</sub> (fed) in T <sub>amb</sub> not reported	N/A	N/A	~50 pg·ml <sup>-1</sup> (~10%) <sup>ns</sup>
Lee and Thake (Part A) [128]	7 male (MT)	60 minutes cycling at 50% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 18°C (35% RH) on day one of temperate acclimation	37.9	133	28 pg·ml <sup>-1</sup> (8%) <sup>ns,c</sup>
Trommelen et al. [130]	10 male (HT)	180 minutes cycling at 50% watt <sub>max</sub> (fasted) in T <sub>amb</sub> 18-22°C (55-65% RH)	N/A	N/A	N/A pg·ml <sup>-1</sup> (20%) <sup>ns,c</sup>
Edinburgh et al. (Part A) [180]	12 male (MT)	60 minutes cycling at 50% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 18°C (35% RH)	N/A	N/A	70 pg·ml <sup>-1</sup> (34%) <sup>s</sup>
Edinburgh et al. (Part B) [180]	12 male (MT)	60 minutes cycling at 50% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 18°C (35% RH)	N/A	N/A	88 pg·ml <sup>-1</sup> (20%) <sup>s</sup>
Osborne et al. (Part A) [133]	8 male (MT-HT)	30 minutes cycling at 50/70% Watt <sub>max</sub> , then 30 minutes at 50% watt <sub>max</sub> (fasted) in T <sub>amb</sub> 20°C (55% RH)	38.5	139	138 pg·ml <sup>-1</sup> (29%) <sup>ns</sup>
Salvador et al. 2019 [181]	12 male (MT-HT)	120 minutes cycling at 60% VO <sub>2max</sub> (fed) then 30-40 minutes (20 km) time trial in T <sub>amb</sub> not reported	37.9	~168	N/A pg·ml <sup>-1</sup> (~50%) <sup>s,c</sup>
van Wijck et al. [127]	10 male (MT)	60 minutes cycling at 70% watt <sub>max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	N/A	153 pg·ml <sup>-1</sup> (72%) <sup>s</sup>
Nava et al. [294]	7 male and 4 female (LT-MT)	56 minutes mixed intensity (~55% VO <sub>2max</sub> ) discontinuous firefighting exercises (fed) in T <sub>amb</sub> 38°C (35% RH) on day one of two	38.7	~161	~160 pg·ml <sup>-1</sup> (23%) <sup>ns,c</sup>
Van Wijck et al. [124]	9 male (MT)	60 minutes cycling at 70% watt <sub>max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	N/A	179 pg·ml <sup>-1</sup> (61%) <sup>s</sup>
Lee et al. (Part C) [128]	7 male (MT)	60 minutes cycling at 50% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 18°C (35% RH) and FiO <sub>2</sub> = 0.14 on day one of hypoxic acclimation	38.2	149	193 pg·ml <sup>-1</sup> (43%) <sup>s,c</sup>
Lis et al. [295]	13 male and female (MT)	45 minutes cycling at 70% watt <sub>max</sub> and 15 min cycling time trial (fed) in 20°C (40% RH)	N/A	168	210 pg·ml <sup>-1</sup> (223%) <sup>s,c</sup>
Pugh et al. [148]	10 male (MT)	60 minutes at 70% VO <sub>2max</sub> running (fasted) in T <sub>amb</sub> 30°C (4-45% RH)	38.5	82.5% of HR max	250 pg·ml <sup>-1</sup> (71%) <sup>s,c</sup>
Snipe et al. (Part A) [115, 125]	6 male and 4 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 22°C (44% RH)	38.5	~150	274 pg·ml <sup>-1</sup> (127%) <sup>s</sup>
Sheahen et al. (Part A) [136]	12 male (MT)	45 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 20°C (40% RH)	38.2	165	281 pg·ml <sup>-1</sup> (49%) <sup>s</sup>

<b>Lee et al. (Part B) [128]</b>	7 male (MT)	60 minutes cycling at 50% $VO_{2max}$ (fed) in $T_{amb}$ 40°C (25% RH) on day one of heat acclimation	38.7	151	282 $pg\cdot ml^{-1}$ (76%) <sup>s,c</sup>
<b>Morrison et al. (Part B) [152]</b>	8 male (UT)	30 minutes cycling at 50% heart rate reserve (HRR), 30 minutes jogging at 80% HRR and 30 minute running time trial (fed) in $T_{amb}$ 30°C (50% RH)	38.6	N/A	283 $pg\cdot ml^{-1}$ (276%) <sup>s,c</sup>
<b>Barberio et al. [72]</b>	9 male (MT)	~24 minutes running at 78% $VO_{2max}$ (fed) in $T_{amb}$ 40°C (40% RH) prior to heat acclimation	39.0	N/A	297 $pg\cdot ml^{-1}$ (46%) <sup>s,c</sup>
<b>Hill et al. [134]</b>	10 male (MT)	60 minutes running at 65% $VO_{2max}$ (fasted) in $T_{amb}$ not reported	N/A	~170	300 $pg\cdot ml^{-1}$ (50%) <sup>ns,c</sup>
<b>van Wijck et al. [86]</b>	15 male (HT)	60 minutes cycling at 70% $watt_{max}$ (fasted) in $T_{amb}$ not reported	N/A	N/A	306 $pg\cdot ml^{-1}$ (61%) <sup>s</sup>
<b>Kashima et al. [296]</b>	5 male and 3 female (MT)	30 intermittent 20 second cycle sprints at 120% $watt_{max}$ , with 40 seconds recovery between each (fed) in 23°C (40% RH)	N/A	150	343 $pg\cdot ml^{-1}$ (266%) <sup>s</sup>
<b>Pugh et al. [88]</b>	11 male (MT-HT)	18x 400 metre sprint at 120% $VO_{2max}$ (fed) in $T_{amb}$ not reported	N/A	N/A	348 $pg\cdot ml^{-1}$ (72%) <sup>s</sup>
<b>March et al. [225]</b>	9 male (MT)	20 minutes running at 80% $VO_{2peak}$ (fasted) in $T_{amb}$ 22°C (37% RH)	38.4	170	350 $pg\cdot ml^{-1}$ (61%) <sup>s,c</sup>
<b>Janssen-Duijghuijsen et al. [293]</b>	4 male and 6 female (LT)	60 minutes cycling at 70% $watt_{max}$ (fed) in $T_{amb}$ not reported	N/A	N/A	~350 $pg\cdot ml^{-1}$ (~77%) <sup>s,c</sup>
<b>Sheahen et al. (Part B) [136]</b>	12 male (MT)	45 minutes running at 70% $VO_{2max}$ (fasted) in $T_{amb}$ 30°C (40% RH)	38.3	163	369 $pg\cdot ml^{-1}$ (63%) <sup>s</sup>
<b>Costa et al. [135]</b>	11 male (MT-HT)	120 minutes running at 70% $VO_{2max}$ (fed) in $T_{amb}$ 25°C (35% RH)	N/A	148	371 $pg\cdot ml^{-1}$ (86%) <sup>ns,c</sup>
<b>Osborne et al. [213]</b>	12 male (MT-HT)	33 minutes (20 km) cycling time trial (fasted) in 35°C (50% RH)	39	167	441 $pg\cdot ml^{-1}$ (83%) <sup>s,c</sup>
<b>Kartaram et al. (Part B) [129]</b>	15 male (MT)	60 minutes cycling at 70% $watt_{max}$ (fed) in $T_{amb}$ not reported	N/A	N/A	~500 $pg\cdot ml^{-1}$ (~66%) <sup>s</sup>
<b>Kartaram et al. (Part C) [129]</b>	15 male (MT)	60 minutes cycling at 85/55% $watt_{max}$ (fed) in $T_{amb}$ not reported	N/A	N/A	~500 $pg\cdot ml^{-1}$ (~66%) <sup>s</sup>
<b>McKenna et al. [226]</b>	10 male (MT)	46 minutes running at 95% VE threshold (fasted) in $T_{amb}$ 40°C (50% RH)	39.7	N/A	516 $pg\cdot ml^{-1}$ (52%) <sup>s,c</sup>
<b>Karhu et al. [132]</b>	17 male (MT-HT)	90 minutes running at 80% of best 10 km race time (fed) in $T_{amb}$ not reported	N/A	N/A	531 $pg\cdot ml^{-1}$ (151%) <sup>s</sup>
<b>Snipe and Costa [137]</b>	6 male and 6 female (MT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ 30°C (35% RH)	38.8	160	573 $pg\cdot ml^{-1}$ (184%) <sup>s,c</sup>
<b>Snipe et al. (Part B) [125]</b>	6 male and 4 female (MT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ 30°C (25% RH)	38.6	~155	~580 $pg\cdot ml^{-1}$ (184%)

<b>Hill et al. [134]</b>	10 male (MT)	60 minutes running at 65% $VO_{2max}$ (fasted) in $T_{amb}$ not reported ( $F_{iO_2} = 13.5\%$ )	N/A	~170	700 $pg \cdot ml^{-1}$ (168%) <sup>ns,c</sup>
<b>Osborne et al. (Part B) [133]</b>	8 Male (MT-HT)	30 minutes cycling at 50/70% $Watt_{max}$ , then 30 minutes at 50% $watt_{max}$ (fasted) in $T_{amb}$ 35°C (53% RH)	39.5	159	608 $pg \cdot ml^{-1}$ (140%) <sup>s</sup>
<b>Szymanski et al. [273]</b>	6 male and 2 female (LT/MT)	60 minutes running at 68% $VO_{2max}$ (fasted) in $T_{amb}$ 37°C (25% RH)	39.0	174	800 $pg \cdot ml^{-1}$ (87%) <sup>s,c</sup>
<b>Morrison et al. (Part A) [152]</b>	7 male (HT)	30 minutes cycling at 50% heart rate reserve (HRR), 30 minutes jogging at 80% HRR and 30 minute running time trial (fed) in $T_{amb}$ 30°C (50% RH)	38.6	N/A	806 $pg \cdot ml^{-1}$ (663%) <sup>s,c</sup>
<b>Snipe et al. [193]</b>	6 male and 5 female (MT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ 35°C (30% RH)	39.3	159	897 $pg \cdot ml^{-1}$ (288%) <sup>s,c</sup>
<b>Snipe et al. (Part B) [115]</b>	6 male and 4 female (MT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ 35°C (26% RH)	39.6	~170	1230 $pg \cdot ml^{-1}$ (432%) <sup>s</sup>
<b>Pugh et al. [148]</b>	10 male and 2 female (MT)	42.4 km track marathon ( $247 \pm 47$ minutes; fed) in $T_{amb}$ 16-17°C (N/A RH)	N/A	~160	1246 $pg \cdot ml^{-1}$ (371%) <sup>s,c</sup>
<b>March et al. [105]</b>	12 male (MT)	60 minutes running at 70% $VO_{2max}$ (fasted) in $T_{amb}$ 30°C (60% RH)	39.3	170	1263 $pg \cdot ml^{-1}$ (407%) <sup>s,c</sup>
<b>Snipe and Costa [291]</b>	11 male (MT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ 35°C (25% RH)	39.1	~150	1389 $pg \cdot ml^{-1}$ (479%) <sup>s</sup>
<b>Snipe et al. [291]</b>	13 female (MT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ 35°C (25% RH)	38.8	~155	1445 $pg \cdot ml^{-1}$ (479%) <sup>s</sup>
<b>Jonvik et al. [131]</b>	16 male (HT)	60 minutes cycling at 70% $watt_{max}$ (fasted) in $T_{amb}$ not reported	N/A	N/A	1745 $pg \cdot ml^{-1}$ (249%) <sup>s</sup>
<b>Gaskell et al. [147]</b>	10 male and 8 female (MT-HT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ 35°C (25% RH)	38.6	~151	1805 $pg \cdot ml^{-1}$ (710%) <sup>s,c</sup>

1981 LT = Low-trained (35-49  $ml \cdot kg \cdot min^{-1} VO_{2max}$ ); MT = Moderate-trained (50-59  $ml \cdot kg \cdot min^{-1}$   
1982  $VO_{2max}$ ); HT = High-trained (60+  $ml \cdot kg \cdot min^{-1} VO_{2max}$ ). s = significant change post-exercise ( $p <$   
1983 0.05); ns = non-significant change post-exercise ( $p > 0.05$ ); c = control/placebo trial of study

1984

1985

1986

1987

1988

1989

1990  
1991

**Table 4.** Influence of acute exercise-(heat) stress on systemic gastrointestinal microbial translocation responses

Reference	Subjects	Exercise Protocol	Peak T <sub>core</sub> (°C)	Mean HR (bpm)	Endotoxin (Δ pre-to-post exercise)
Antunes et al. [297]	19 male (MT)	56 ± 7 minutes cycling at 90% of first ventilatory threshold (fasted) in 22.1°C (55% RH)	N/A	<sup>141</sup>	-3 pg·ml <sup>-1</sup> (-3%) <sup>ns</sup>
Yeh et al. (Part B) [138]	15 male and 1 female (LT)	60 minutes running at 70% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 22°C (66% RH)	38.4	~145	-1.1 pg·ml <sup>-1</sup> (-10%) <sup>ns</sup>
Zuhl et al. [116]	2 male and 5 female (LT/MT)	60 minutes running at 70% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 30°C (12-20% RH)	39.5	N/A	-0.2 pg·ml <sup>-1</sup> (-7%) <sup>ns, c</sup>
Osborne et al. (Part A) [133]	8 Male (MT-HT)	30 minutes cycling at 50/70% Watt <sub>max</sub> , then 30 minutes at 50% watt <sub>max</sub> (fasted) in T <sub>amb</sub> 20°C (55% RH)	38.5	165	0.1 pg·ml <sup>-1</sup> (1%) <sup>ns, #</sup>
Osborne et al. (Part B) [133]	8 Male (MT-HT)	30 minutes cycling at 50/70% Watt <sub>max</sub> , then 30 minutes at 50% watt <sub>max</sub> (fasted) in T <sub>amb</sub> 35°C (53% RH)	39.5	182	0.2 pg·ml <sup>-1</sup> (1%) <sup>s, #</sup>
Karhu et al. [132]	17 males (MT-HT)	90 minutes running at 80% of best 10 km race time (fed) in T <sub>amb</sub> not reported	N/A	N/A	0.3 pg·ml <sup>-1</sup> (~ 1%) <sup>ns, c</sup>
Kuennen et al. [143]	8 male (MT)	100 minutes walking (6.3 km·h <sup>-1</sup> ) at 50% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> 46.5°C (20% RH)	39.3	N/A	~0.5 pg·ml <sup>-1</sup> (10%) <sup>ns, c</sup>
Ng et al. [73]	30 males (HT)	Half-marathon (fed) in T <sub>amb</sub> 27°C (84% RH)	40.7	172	0.6 pg·ml <sup>-1</sup> (32%) <sup>s</sup>
Jeukendrup et al. [144]	29 male and 1 female (HT)	Ironman (3.8 km swim; 185 km cycle; 42.2 km run) (fed) in T <sub>amb</sub> 9-32°C	N/A	N/A	1.7 pg·ml <sup>-1</sup> (666%) <sup>s</sup>
Guy et al. [298]	20 male (LT-MT)	10 minutes cycling at 50%, 60%, and 70% watt <sub>max</sub> , then 5 km (fasted) in T <sub>amb</sub> 35°C (70% RH)	38.9	160	2 pg·ml <sup>-1</sup> (9%) <sup>ns</sup>
Selkirk et al. (Part B) [126]	12 male (HT)	To fatigue (~122 minutes) uphill walk at 4.5 km·h <sup>-1</sup> (fasted) in T <sub>amb</sub> 40°C (30% RH)	39.7	156	~3 pg·ml <sup>-1</sup> (200%) <sup>s</sup>
Shing et al. [146]	10 male (HT)	~33 minutes running to fatigue at 80% VE (fed) in T <sub>amb</sub> 35°C (40% RH)	39.4	172	4 pg·ml <sup>-1</sup> (15%) <sup>s</sup>
Snipe et al. (Part A) [115, 125]	6 male and 4 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 22°C (44% RH)	38.5	~150	4.1 pg·ml <sup>-1</sup> (5%) <sup>ns</sup>
Yeh et al. (Part B) [138]	15 male and 1 female (LT)	60 minutes running at 70% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 33°C (50% RH)	39.3	~145	5 pg·ml <sup>-1</sup> (54%) <sup>s</sup>
Antunes et al. (Part B) [297]	19 male (MT)	45 ± 18 minutes cycling at midpoint between first and second ventilatory threshold (fasted) in 22.1°C (55% RH)	N/A	<sup>162</sup>	5 pg·ml <sup>-1</sup> (7%) <sup>ns</sup>

<b>Antunes et al. (Part C) [297]</b>	19 male (MT)	10 ± 9 minutes cycling at midpoint between second ventilatory threshold and maximal aerobic power (fasted) in 22.1°C (55% RH)	N/A	<sup>180</sup>	6 pg·ml <sup>-1</sup> (5%) <sup>ns</sup>
<b>Ashton et al. [286]</b>	10 males (LT)	VO <sub>2max</sub> test (~15 minutes)- on cycle ergometer (fasted) in T <sub>amb</sub> not reported	N/A	N/A	9.4 pg·ml <sup>-1</sup> (72%) <sup>s</sup>
<b>Snipe et al. (Part B) [115]</b>	6 male and 4 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (26% RH)	39.6	~170	9.8 pg·ml <sup>-1</sup> (11%) <sup>s</sup>
<b>Gill et al. [149]</b>	8 male (MT-HT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 32°C (34% RH)	38.6	165	10 pg·ml <sup>-1</sup> (4%) <sup>ns, c</sup>
<b>Snipe et al. [193]</b>	6 male and 5 female (MT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (30% RH)	39.3	159	10 pg·ml <sup>-1</sup> (N/A %) <sup>nb</sup>
<b>Selkirk et al. (Part A) [126]</b>	11 male (LT-MT)	To fatigue (~106 minutes) uphill walk at 4.5 km·h <sup>-1</sup> (fasted) in T <sub>amb</sub> 40°C (30% RH)	39.1	164	~10 pg·ml <sup>-1</sup> (300%) <sup>s</sup>
<b>Lim et al. (Part B) [150]</b>	9 male (HT)	To fatigue (time not given) at 70% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (40% RH)	39.5	N/A	13 pg·ml <sup>-1</sup> (92%) <sup>s, c</sup>
<b>Guy et al. [299]</b>	8 male (LT)	10 minutes cycling at 50%, 60%, and 70% watt <sub>max</sub> , then 5 km (fasted) in T <sub>amb</sub> 35°C (70% RH)	38.6	161	16 pg·ml <sup>-1</sup> (9%) <sup>ns, c, #</sup>
<b>Gill et al. [71]</b>	13 male and 6 female (HT)	Multistage ultra-marathon stage 1 (37 km) (fed) in T <sub>amb</sub> 32-40°C (32-40% RH)	N/A	N/A	40 pg·ml <sup>-1</sup> (14%) <sup>s</sup>
<b>Barberio et al. [72]</b>	9 male (MT)	~24 minutes running at 78% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 40°C (40% RH) prior to heat acclimation	39.0	N/A	40 pg·ml <sup>-1</sup> (57%) <sup>s, c</sup>
<b>Moss et al. [151]</b>	9 male (HT)	45 minutes cycling at 40% PPO (unstated prandial state) in T <sub>amb</sub> 40°C (50% RH) prior to heat acclimation	38.9	153	52 pg·ml <sup>-1</sup> (27%) <sup>s, c</sup>
<b>Costa et al. [135]</b>	11 male (MT-HT)	120 minutes running at 70% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 25°C (35% RH)	N/A	148	96 pg·ml <sup>-1</sup> (46%) <sup>ns, c, #</sup>
<b>Gill et al. [145]</b>	14 male and 3 female (HT)	24 hour ultramarathon (fed) in T <sub>amb</sub> 0-20°C (54-82% RH)	N/A	N/A	122 pg·ml <sup>-1</sup> (37%) <sup>s, #</sup>
<b>Machado et al. (Part A) [300]</b>	9 male (MT)	60 minutes running at 50% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> not reported	N/A	N/A	130 pg·ml <sup>-1</sup> (33%) <sup>ns, #</sup>
<b>Machado et al. (Part B) [300]</b>	9 male (MT)	60 minutes running at 50% VO <sub>2max</sub> (fasted) in T <sub>amb</sub> not reported (FIO <sub>2</sub> = 13.5%)	N/A	N/A	250 pg·ml <sup>-1</sup> (48%) <sup>s, #</sup>
<b>Gaskell et al. [147]</b>	10 male and 8 female (MT-HT)	120 minutes running at 60% VO <sub>2max</sub> (fed) in T <sub>amb</sub> 35°C (25% RH)	38.6	~151	LBP ~2 µg·ml <sup>-1</sup> (N/A%) <sup>ns, c</sup>
<b>Selkirk et al. (Part A) [146]</b>	11 male (HT)	To fatigue (~163 minutes) uphill walk at 4.5 km·h <sup>-1</sup> (fasted) in T <sub>amb</sub> 40°C (30% RH)	39.1	164	LBP ~0 µg·ml <sup>-1</sup> (0%) <sup>ns</sup>



<b>Moncada-Jiminez et al. [195]</b>	11 male (MT-HT)	135-minute laboratory duathlon at 71% $VO_{2max}$ (15km run and 30km cycle) (fasted) in $T_{amb}$ not reported	38.5	N/A	LBP $\sim 0.59 \mu\text{g}\cdot\text{ml}^{-1}$ (22%) <sup>s, c</sup>
<b>Selkirk et al. (Part B) [146]</b>	12 male (LT-MT)	To fatigue ( $\sim 106$ minutes) uphill walk at $4.5 \text{ km}\cdot\text{h}^{-1}$ (fasted) in $T_{amb}$ $40^\circ\text{C}$ (30% RH)	39.7	156	LBP $\sim 1.5 \mu\text{g}\cdot\text{ml}^{-1}$ (15%) <sup>s</sup>
<b>Jonvik et al. [131]</b>	16 male (HT)	60 minutes cycling at 70% $watt_{max}$ (fasted) in $T_{amb}$ not reported	N/A	N/A	LBP $1.6 \mu\text{g}\cdot\text{ml}^{-1}$ (13%) <sup>s</sup>
<b>Costa et al. [135]</b>	11 male (MT-HT)	120 minutes running at 70% $VO_{2max}$ (fed) in $T_{amb}$ $25^\circ\text{C}$ (35% RH)	N/A	148	sCD14-ST $0.05 \mu\text{g}\cdot\text{ml}^{-1}$ (N/A%) <sup>ns, c</sup>
<b>Gaskell et al. [147]</b>	10 male and 8 female (MT-HT)	120 minutes running at 60% $VO_{2max}$ (fed) in $T_{amb}$ $35^\circ\text{C}$ (25% RH)	38.6	$\sim 151$	sCD14-ST $0.1 \mu\text{g}\cdot\text{ml}^{-1}$ (N/A%) <sup>s, c</sup>
<b>Stuempfle et al. [301]</b>	15 male and 5 female (MT)	161-km ultramarathon ( $26.8 \pm 2.4$ hours; fed) in $T_{amb}$ $0-30^\circ\text{C}$ (N/A RH)	38.3	N/A	sCD14-ST $0.6 \mu\text{g}\cdot\text{ml}^{-1}$ (63%) <sup>s</sup>
<b>Pugh et al. [148]</b>	10 male and 2 female (MT)	42.4 km track marathon ( $4.1 \pm 0.8$ hours; fed) in $T_{amb}$ $16-17^\circ\text{C}$ (N/A RH)	N/A	$\sim 160$	sCD14-ST $5.4 \mu\text{g}\cdot\text{ml}^{-1}$ (164%) <sup>s, c</sup>

1992 LT = Low-trained ( $35-49 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1} VO_{2max}$ ); MT = Moderate-trained ( $50-59 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$   
1993  $VO_{2max}$ ); HT = High-trained ( $60+ \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1} VO_{2max}$ ). s = significant change post-exercise ( $p <$   
1994  $0.05$ ); ns = non-significant change post-exercise ( $p > 0.05$ ); nb = no baseline resting data to  
1995 compare with; c = control/placebo trial of study. # Where data have been converted from  
1996  $\text{EU}\cdot\text{ml}^{-1}$  to  $\text{pg}\cdot\text{ml}^{-1}$  through standard conversions ( $1 \text{ EU}\cdot\text{ml}^{-1} = 100 \text{ pg}\cdot\text{ml}^{-1}$ )

1997

1998

1999

2000

2001

2002

2003

2004

2005

2006

2007

2008  
2009

**Table 5.** Evidence basis of nutritional supplements to help protect exercise-induced GI barrier integrity loss

<b>Nutrient</b>	<b>Evidence</b>	<b>Dosing</b>	<b>Consensus and Limitations</b>
<b>Carbohydrate</b>	Cell: - - Clinical: + + - Exercise: + + +	30-108 g·kg·h <sup>-1</sup> liquid multi-transportable CHO.	Effects of pre- exercise CHO status or solid CHO ingestion unknown. Greater exploration on CHO timing and types required.
<b>L- Glutamine</b>	Cell: + + + - Clinical: + + - Exercise: + + +	0.25-0.9 g·kg·FFM. <sup>-1</sup> given 1-2 hours pre-exercise.	Dose ≥ 0.25g·kg·FFM <sup>-1</sup> appears favourable. High doses poorly tolerated in some individuals. No evidence during prolonged exercise or on MT.
<b>Bovine Colostrum</b>	Cell: + + + + Clinical: + + + Exercise: + +	20 g·day <sup>-1</sup> for 14 days pre-exercise	Potentially useful following less demanding exercise. No effects with short-term supplementation. Certain formulations might be more beneficial.
<b>Nitric Oxide</b>	Cell: + + Clinical: + + Exercise: - -	More evidence required	No benefits of L-citrulline or sodium nitrate. Nitrate ingestion might compromise thermoregulation with exercise in the heat. Only two human exercise studies.
<b>Probiotics</b>	Cell: + - Clinical: + + - - Exercise: + - -	More evidence required	Contrasting results between formulations. Multi-strain probiotics seem favourable. Negative responses have been reported. Further evidence required.
<b>Polyphenols</b>	Cell: + + - - Clinical: + - Exercise: + -	3 days of 0.5 g·day <sup>-1</sup> of curcumin. Quercetin not recommended	Contrasting results between formulations. Only two human exercise studies. Further evidence required.
<b>Zinc Carnosine</b>	Cell: + + + Clinical: + + Exercise: +	75 mg·day <sup>-1</sup> for ≥ 2 days	Unknown effects in severe exercise situations. A 150 mg·day <sup>-1</sup> dose warrants research. Only one human exercise study. Further evidence required.

2010