

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 ³	Nitrate
69	NO ²	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 _{core}	Core Body Temperature
83	TJ	Tight Junction
84	TLR	Toll-Like Receptor
85	TNF	Tumour Necrosis Factor
86	VO _{2max}	Maximal Oxygen Uptake
87	Watt _{max}	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_{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 20th 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 m²) 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* 10¹⁴
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- β , IL-2, IL-6, IL-8, tumour-necrosis factor
172 [TNF]- α), 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 (~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 ~ 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 γ ($r = 0.63$) 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 β , 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 β -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 (α -rhamnose [164 kDa]
261 or β -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, ⁵¹Cr-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 (α -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 ≥ 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 ± 0.010 vs. 0.026 ± 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 $T_{core} = 38.1^\circ\text{C}$ 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 ± 0.010) remained statistically indifferent to the temperate condition,
388 despite greater T_{core} elevations (e.g. peak $T_{core} = 39.6^\circ\text{C}$ [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_{max}) 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_{2max}) in temperate conditions [108, 119, 122], 18
401 repeated 400 metre supramaximal track sprints (120% VO_{2max}) 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 = <10³, ileum 10³-10⁷, colon= 10¹²- 10¹⁴) [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_{max}) 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_{2max}) in temperate environments has typically shown little effect on I-FABP
418 concentrations [128-130], but moderate-to-high intensity exercise (60-120% VO_{2max}) 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 (≤ 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 β -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°C when
473 (measured at 0.5°C T_{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_{core} peak above 39.0°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_{core} had risen 2°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_{core} of 39.5°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 (Δ ; $r= 0.52$; $p = <0.001$),
540 but not the DSAT (5-hr urine only; $r= 0.30$; $p= 0.19$), or endotoxin (Δ ; $r= 0.14$; $p= 0.56$)
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- α , IL-1 β , IL-6, IFN-
569 γ), 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- α) 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- β 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⁻¹ glucose), compared with water,
611 on GI barrier integrity (utilising the DSAT) during 60-90 minutes of moderate intensity exercise
612 (70% VO_{2max}) [111, 122]. However, follow-up studies reported attenuated GI barrier integrity
613 loss (I-FABP and DSAT) with glucose ingestion (60 g·hour⁻¹) during two-hours moderate
614 intensity running (60% VO_{2max}) in the heat (35°C and 25% relative humidity (RH); [193]), and
615 with sucrose ingestion (40 g·hour⁻¹) prior/during a one-hour moderate intensity cycle (70%
616 watt_{max}) [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⁻¹ glucose; 1.2 and 0.6 g·min⁻¹
618 glucose plus fructose; 0.6 and 1.2 g·min⁻¹ 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_{max}) [130].
621 Similarly, ingestion of 60 g·hour⁻¹ 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_{2max} 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_{2max} 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⁻¹]
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⁻¹) 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⁻¹) 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 ~ 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°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⁻¹ of whey protein hydrolysate during a 2-hour moderate-intensity (60%
700 VO_{2max}) 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 g·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% VO_{2max}) [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 g·day⁻¹; [226] or high (7 days at 1.7
728 g·kg·day⁻¹ (circa ~120-150g); [152]) BC dosing on I-FABP concentrations following a fatiguing
729 run in the heat (35-40°C; 50% RH). Likewise, March et al. [105], using their earlier BC
730 supplementation protocol [225], found only minor (~10%) suppression of I-FABP
731 concentration and a non-significant blunting of circulating bacteroides DNA following a 1-
732 hour run (70% VO_{2max}) in the heat (30°C/60% RH).

733 Practical recommendations support a BC dose of 20 g·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 mg·day⁻¹) BC ingestion improved
737 resting GI permeability (DSAT ratio) in athletes during heavy training [227], but chronic high
738 dose (60 g·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 g·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 (NO₃), nitrite (NO₂), NO serial reduction
751 pathway [231]. Supplementation with NO precursors, including L-arginine [232], L-citrulline
752 and inorganic NO₃ [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_{max}). However, this intervention
768 did not reduce peak post-exercise I-FABP concentrations, or the urinary DSAT ratio.

769 Inorganic NO₃ supplementation has increased in athletic populations over the last
770 decade [241]. Its popularity is founded upon evidence showing NO₃ 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 NO₃ supplementation and exercise-induced GI barrier integrity
774 loss. One placebo controlled study found acute sodium NO₃ (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_{max}) [131].

777 Practical recommendations regarding the use of L-arginine, L-citrulline or inorganic
778 NO₃ 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 (45×10^9 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 (3×10^9 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 (45×10^{11} CFU.day⁻¹ *Lactobacillus Casei*)
811 was associated with an increased rise in endotoxin concentrations, compared with placebo,

812 following two hours moderate-intensity running (60% VO_{2max}) in the heat (34°C/32% RH)
813 [149]. Similarly, the daily ingestion of another single strain probiotic (35 x 10⁹ 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 10⁹ 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 10⁸ CFU *Lactobacillus Salivarius*) had no influence on DSAT responses,
820 (or faecal microbial composition), following two hours of moderate intensity running (60%
821 VO_{2max}) 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⁻¹ 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⁻¹ 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⁻¹), a constituent of
861 turmeric, blunted circulating I-FABP concentrations by ~30% after one-hour moderate
862 intensity running (65% VO_{2max}) 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⁻¹) to
885 prevent deficiencies, and to supplement with large oral doses (~75 mg·day⁻¹), 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⁻¹) 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⁻¹) attenuated a 3-fold rise in DSAT ratio by 70%
891 after short-duration (20 minutes) high-intensity running (80% VO_{2max}) [114]. This effect was
892 comparable to that observed with BC (20 g·day⁻¹ 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⁻¹ 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⁻¹) 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⁻¹) 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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995 **REFERENCES**

- 996 1. Leon, L.R. and Helwig, B.G., 2010. Heat stroke: role of the systemic inflammatory
997 response. *Journal of applied physiology*, 109(6), pp.1980-1988.
- 998 2. Casa, D.J., Armstrong, L.E., Carter, R., Lopez, R., Mcdermott, B. and Scriber, K., 2010.
999 Historical perspectives on medical care for heat stroke, part 1: ancient times through the
1000 nineteenth century: a review of the literature. *Athletic training and sports health care*, 2(3),
1001 pp.132-138.
- 1002 3. Casa, D.J., Armstrong, L.E., Carter, R., Lopez, R., Mcdermott, B. and Scriber, K., 2010.
1003 Historical perspectives on medical care for heat stroke, part 2: 1850 through the present: a
1004 review of the literature. *Athletic Training and Sports Health Care*, 2(4), pp.178-190.
- 1005 4. Laitano, O., Leon, L.R., Roberts, W.O. and Sawka, M.N., 2019. Controversies in exertional
1006 heat stroke diagnosis, prevention, and treatment. *Journal of Applied Physiology*, 127(5),
1007 pp.1338-1348.
- 1008 5. Bouchama, A. and Knochel, J.P., 2002. Heat stroke. *New England journal of*
1009 *medicine*, 346(25), pp.1978-1988.
- 1010 6. Kravchenko, J., Abernethy, A.P., Fawzy, M. and Lyerly, H.K., 2013. Minimization of
1011 heatwave morbidity and mortality. *American journal of preventive medicine*, 44(3), pp.274-
1012 282.
- 1013 7. Epstein, Y. and Yanovich, R., 2019. Heatstroke. *New England Journal of Medicine*, 380(25),
1014 pp.2449-2459.
- 1015 8. Cramer, M.N. and Jay, O., 2016. Biophysical aspects of human thermoregulation during
1016 heat stress. *Autonomic Neuroscience*, 196, pp.3-13.
- 1017 9. DeGroot, D.W., Mok, G. and Hathaway, N.E., 2017. International Classification of Disease
1018 coding of exertional heat illness in US Army Soldiers. *Military medicine*, 182(9-10), pp.e1946-
1019 e1950.
- 1020 10. Stacey, M.J., Parsons, I.T., Woods, D.R., Taylor, P.N., Ross, D. and Brett, S.J., 2015.
1021 Susceptibility to exertional heat illness and hospitalisation risk in UK military personnel. *BMJ*
1022 *open sport & exercise medicine*, 1(1), p.e000055.
- 1023 11. Kerr, Z.Y., Casa, D.J., Marshall, S.W. and Comstock, R.D., 2013. Epidemiology of exertional
1024 heat illness among US high school athletes. *American journal of preventive medicine*, 44(1),
1025 pp.8-14.
- 1026 12. Military Health System. Available online:
1027 <https://health.mil/News/Articles/2019/04/01/Update-Heat-Illness> (Accessed on:
1028 20/01/2020)
- 1029 13. Yeargin, S.W., Kerr, Z.Y., Casa, D.J., Djoko, A., Hayden, R., Parsons, J.T. and Dompier, T.P.,
1030 2016. Epidemiology of Exertional Heat Illnesses in Youth, High School, and College
1031 Football. *Medicine and science in sports and exercise*, 48(8), pp.1523-1529.

- 1032 14. Yeargin, S.W., Dompier, T.P., Casa, D.J., Hirschhorn, R.M. and Kerr, Z.Y., 2019.
1033 Epidemiology of Exertional Heat Illnesses in National Collegiate Athletic Association Athletes
1034 During the 2009–2010 Through 2014–2015 Academic Years. *Journal of athletic*
1035 *training*, 54(1), pp.55-63.
- 1036 15. DeMartini, J.K., Casa, D.J., Belval, L.N., Crago, A., Davis, R.J., Jardine, J.J. and Stearns, R.L.,
1037 2014. Environmental conditions and the occurrence of exertional heat illnesses and
1038 exertional heat stroke at the Falmouth Road Race. *Journal of athletic training*, 49(4), pp.478-
1039 485.
- 1040 16. Divine, J.G., Daggy, M.W., Dixon, E.E., LeBlanc, D.P., Okragly, R.A. and Hasselfeld, K.A.,
1041 2018. Case Series of Exertional Heat Stroke in Runners During Early Spring: 2014 to 2016
1042 Cincinnati Flying Pig Marathon. *Current sports medicine reports*, 17(5), pp.151-158.
- 1043 17. Hosokawa, Y., Adams, W.M., Belval, L.N., Davis, R.J., Huggins, R.A., Jardine, J.F., Katch,
1044 R.K., Stearns, R.L. and Casa, D.J., 2018. Exertional heat illness incidence and on-site medical
1045 team preparedness in warm weather. *International journal of biometeorology*, 62(7),
1046 pp.1147-1153.
- 1047 18. Stacey, M.J., Brett, S., Woods, D., Jackson, S. and Ross, D., 2016. Case ascertainment of
1048 heat illness in the British Army: evidence of under-reporting from analysis of Medical and
1049 Command notifications, 2009–2013. *Journal of the Royal Army Medical Corps*, 162(6),
1050 pp.428-433.
- 1051 19. Nelson, D.A., Deuster, P.A., O'Connor, F.G. and Kurina, L.M., 2018. Timing and predictors
1052 of mild and severe heat illness among new military enlistees. *Medicine and science in sports*
1053 *and exercise*, 50(8), p.1603.
- 1054 20. Lucas, R.A., Epstein, Y. and Kjellstrom, T., 2014. Excessive occupational heat exposure: a
1055 significant ergonomic challenge and health risk for current and future workers. *Extreme*
1056 *physiology and medicine*, 3, pp.14-14.
- 1057 21. Belval, L.N., Casa, D.J., Adams, W.M., Chiampas, G.T., Holschen, J.C., Hosokawa, Y.,
1058 Jardine, J., Kane, S.F., Labotz, M., Lemieux, R.S. and McClaine, K.B., 2018. Consensus
1059 statement-prehospital care of exertional heat stroke. *Prehospital Emergency Care*, 22(3),
1060 pp.392-397.
- 1061 22. Hosokawa, Y., Stearns, R.L. and Casa, D.J., 2019. Is Heat Intolerance State or
1062 Trait?. *Sports Medicine*, 49(3), pp.365-370.
- 1063 23. Royburt, M., Epstein, Y., Solomon, Z. and Shemer, J., 1993. Long-term psychological and
1064 physiological effects of heat stroke. *Physiology & behavior*, 54(2), pp.265-267.
- 1065 24. Wang, J.C., Chien, W.C., Chu, P., Chung, C.H., Lin, C.Y. and Tsai, S.H., 2019. The
1066 association between heat stroke and subsequent cardiovascular diseases. *PloS one*, 14(2),
1067 p.e0211386.
- 1068 25. Wallace, R.F., Kriebel, D., Punnett, L., Wegman, D.H. and Amoroso, P.J., 2007. Prior heat
1069 illness hospitalization and risk of early death. *Environmental research*, 104(2), pp.290-295.

- 1070 26. Epstein, Y., Druyan, A. and Heled, Y., 2012. Heat injury prevention—a military
1071 perspective. *The Journal of Strength & Conditioning Research*, 26, pp.S82-S86.
- 1072 27. Mitchell, K.M., Chevront, S.N., King, M.A., Mayer, T.A., Leon, L.R. and Kenefick, R.W.,
1073 2019. Use of the heat tolerance test to assess recovery from exertional heat
1074 stroke. *Temperature*, 6(2), pp.106-119.
- 1075 28. Bonauto, D., Anderson, R., Rauser, E. and Burke, B., 2007. Occupational heat illness in
1076 Washington State, 1995–2005. *American journal of industrial medicine*, 50(12), pp.940-950.
- 1077 29. DeGroot, D.W., Kenefick, R.W. and Sawka, M.N., 2015. Impact of arm immersion cooling
1078 during ranger training on exertional heat illness and treatment costs. *Military
1079 medicine*, 180(11), pp.1178-1183.
- 1080 30. Porter, A.M., 2000. The death of a British officer-cadet from heat illness. *The
1081 Lancet*, 355(9203), pp.569-571.
- 1082 31. Stacey, M., Woods, D., Ross, D. and Wilson, D., 2014. Heat illness in military populations:
1083 asking the right questions for research. *Journal of the Royal Army Medical Corps*, 160(2),
1084 pp.121-124.
- 1085 32. Armstrong, L.E., Casa, D.J., Millard-Stafford, M., Moran, D.S., Pyne, S.W. and Roberts,
1086 W.O., 2007. American College of Sports Medicine position stand. Exertional heat illness
1087 during training and competition. *Medicine and science in sports and exercise*, 39(3), pp.556-
1088 572.
- 1089 33. Casa, D.J., DeMartini, J.K., Bergeron, M.F., Csillan, D., Eichner, E.R., Lopez, R.M., Ferrara,
1090 M.S., Miller, K.C., O'Connor, F., Sawka, M.N. and Yeargin, S.W., 2015. National Athletic
1091 Trainers' Association position statement: exertional heat illnesses. *Journal of athletic
1092 training*, 50(9), pp.986-1000.
- 1093 34. Altman, J., Stern, E., Stern, M., Prine, B., Smith, K.B. and Smith, M.S., 2019. Current
1094 paradigms in the prehospital care of exertional heat illness: A review. *Current Orthopaedic
1095 Practice*.
- 1096 35. Ministry of Defence. Available online:
1097 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/793094/JSP_539_Part_2_V3.1_Updated_04-19_.pdf (Accessed 20/01/2020)
1098
- 1099 36. Armstrong, L.E., Lee, E.C. and Armstrong, E.M., 2018. Interactions of Gut Microbiota,
1100 Endotoxemia, Immune Function, and Diet in Exertional Heatstroke. *Journal of Sports
1101 Medicine*, 2018.
- 1102 37. Lim, C.L., 2018. Heat sepsis precedes heat toxicity in the pathophysiology of heat
1103 stroke—a new paradigm on an ancient disease. *Antioxidants*, 7(11), p.149.
- 1104 38. Thursby, E. and Juge, N., 2017. Introduction to the human gut microbiota. *Biochemical
1105 Journal*, 474(11), pp.1823-1836.

- 1106 39. Sender, R., Fuchs, S. and Milo, R., 2016. Revised estimates for the number of human and
1107 bacteria cells in the body. *PLoS biology*, 14(8), p.e1002533.
- 1108 40. Wells, J.M., Brummer, R.J., Derrien, M., MacDonald, T.T., Troost, F., Cani, P.D.,
1109 Theodorou, V., Dekker, J., Méheust, A., De Vos, W.M. and Mercenier, A., 2016. Homeostasis
1110 of the gut barrier and potential biomarkers. *American Journal of Physiology-Gastrointestinal
1111 and Liver Physiology*, 312(3), pp.G171-G193.
- 1112 41. Moseley, P.L. and Gisolfi, C.V., 1993. New frontiers in thermoregulation and
1113 exercise. *Sports medicine*, 16(3), pp.163-167.
- 1114 42. Munford, R.S., 2005. Invited review: detoxifying endotoxin: time, place and
1115 person. *Journal of endotoxin research*, 11(2), pp.69-84.
- 1116 43. Deitch, E.A., 2012. Gut-origin sepsis: evolution of a concept. *The Surgeon*, 10(6), pp.350-
1117 356.
- 1118 44. Gathiram, P., Gaffin, S.L., Brock-Utne, J.G. and Wells, M.T., 1987. Time course of
1119 endotoxemia and cardiovascular changes in heat-stressed primates. *Aviation, space, and
1120 environmental medicine*, 58(11), pp.1071-1074.
- 1121 45. Nieman, D.C. and Nehlsen-Cannarella, S.L., 1991. The effects of acute and chronic
1122 exercise on immunoglobulins. *Sports Medicine*, 11(3), pp.183-201.
- 1123 46. Fukui, H., 2016. Endotoxin and other microbial translocation markers in the blood: A clue
1124 to understand leaky gut syndrome. *Cell Mol Med*, 2, p.3.
- 1125 47. Heled, Y., Fleischmann, C. and Epstein, Y., 2013. Cytokines and their role in hyperthermia
1126 and heat stroke. *Journal of basic and clinical physiology and pharmacology*, 24(2), pp.85-96.
- 1127 48. Lim, C.L. and Mackinnon, L.T., 2006. The roles of exercise-induced immune system
1128 disturbances in the pathology of heat stroke. *Sports Medicine*, 36(1), pp.39-64.
- 1129 49. Bynum, G., Brown, J., Dubose, D., Marsili, M., Leav, I., Pistole, T.G., Hamlet, M., LeMaire,
1130 M. and Caleb, B., 1979. Increased survival in experimental dog heatstroke after reduction of
1131 gut flora. *Aviation, space, and environmental medicine*, 50(8), pp.816-819.
- 1132 50. Gathiram, P., Wells, M.T., Brock-Utne, J.G., Wessels, B.C. and Gaffin, S.L., 1987.
1133 Prevention of endotoxaemia by non-absorbable antibiotics in heat stress. *Journal of clinical
1134 pathology*, 40(11), pp.1364-1368.
- 1135 51. Gathiram, P., Wells, M.T., Brock-Utne, J.G. and Gaffin, S.L., 1987. Antilipopolsaccharide
1136 improves survival in primates subjected to heat stroke. *Circulatory shock*, 23(3), pp.157-164.
- 1137 52. Gathiram, P., Wells, M.T., Brock-Utne, J.G. and Gaffin, S.L., 1988. Prophylactic
1138 corticosteroid increases survival in experimental heat stroke in primates. *Aviation, space,
1139 and environmental medicine*, 59(4), pp.352-355.
- 1140 53. Lim, C.L., Wilson, G., Brown, L., Coombes, J.S. and Mackinnon, L.T., 2007. Pre-existing
1141 inflammatory state compromises heat tolerance in rats exposed to heat stress. *American*

- 1142 *Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 292(1), pp.R186-
1143 R194.
- 1144 54. Yang, T.H., Shih, M.F., Wen, Y.S., Ho, W.Y., Leu, K.L., Wang, M.Y. and Liu, C.C., 2010.
1145 Attenuation of circulatory shock and cerebral ischemia injury in heat stroke by combination
1146 treatment with dexamethasone and hydroxyethyl starch. *Experimental & translational*
1147 *stroke medicine*, 2(1), p.19.
- 1148 55. Liu, C.C., Shih, M.F., Wen, Y.S., Lai, Y.H. and Yang, T.H., 2014. Dexamethasone improves
1149 heat stroke-induced multiorgan dysfunction and damage in rats. *International journal of*
1150 *molecular sciences*, 15(11), pp.21299-21313.
- 1151 56. Audet, G.N., Dineen, S.M., Stewart, D.A., Plamper, M.L., Pathmasiri, W.W., McRitchie,
1152 S.L., Sumner, S.J. and Leon, L.R., 2017. Pretreatment with indomethacin results in increased
1153 heat stroke severity during recovery in a rodent model of heat stroke. *Journal of Applied*
1154 *Physiology*, 123(3), pp.544-557.
- 1155 57. Caputa, M., Dokladny, K. and Kurowicka, B., 2000. Endotoxaemia does not limit heat
1156 tolerance in rats: the role of plasma lipoproteins. *European journal of applied*
1157 *physiology*, 82(1-2), pp.142-150.
- 1158 58. Lin, X.J., Li, Y.J., Li, Z.L., Zou, F. and Lin, M.T., 2009. Pre-existing lipopolysaccharide may
1159 increase the risk of heatstroke in rats. *The American journal of the medical sciences*, 337(4),
1160 pp.265-270.
- 1161 59. King, M.A., Leon, L.R., Mustico, D.L., Haines, J.M. and Clanton, T.L., 2015. Biomarkers of
1162 multiorgan injury in a preclinical model of exertional heat stroke. *Journal of Applied*
1163 *Physiology*, 118(10), pp.1207-1220.
- 1164 60. Lin, Y. and Zhang, Y., 2019. Renoprotective effect of oral rehydration solution III in
1165 exertional heatstroke rats. *Renal failure*, 41(1), pp.190-196.
- 1166 61. King, M.A., Leon, L.R., Morse, D.A. and Clanton, T.L., 2016. Unique cytokine and
1167 chemokine responses to exertional heat stroke in mice. *Journal of Applied*
1168 *Physiology*, 122(2), pp.296-306.
- 1169 62. Malamud, N., Haymaker, W. and Custer, R.P., 1946. Heat Stroke. A Clinico-Pathologic
1170 Study of 125 Fatal Cases. *Military surgeon*, 99(5), pp.397-449.
- 1171 63. Shibolet, S., Coll, R., Gilat, T. and Sohar, E., 1967. Heatstroke: its clinical picture and
1172 mechanism in 36 cases. *Quarterly Journal of Medicine*, 36(144), pp.525-48.
- 1173 64. Chao, T.C., Sinniah, R. and Pakiam, J.E., 1981. Acute heat stroke deaths. *Pathology*, 13(1),
1174 pp.145-156.
- 1175 65. Graber, C.D., Reinhold, R.B., Breman, J.G., Harley, R.A. and Hennigar, G.R., 1971. Fatal
1176 heat stroke: Circulating endotoxin and gram-negative sepsis as complications. *Jama*, 216(7),
1177 pp.1195-1196.

- 1178 66. Bouchama, A., Parhar, R.S., el-Yazigi, A., Sheth, K. and al-Sedairy, S., 1991. Endotoxemia
1179 and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. *Journal of*
1180 *applied physiology (Bethesda, Md.: 1985)*, 70(6), pp.2640-2644.
- 1181 67. Bouchama, A., Al-Sedairy, S., Siddiqui, S., Shail, E. and Bezeig, M., 1993. Elevated
1182 pyrogenic cytokines in heatstroke. *Chest*, 104(5), pp.1498-1502.
- 1183 68. Lu, K.C., Wang, J.Y., Lin, S.H., Chu, P. and Lin, Y.F., 2004. Role of circulating cytokines and
1184 chemokines in exertional heatstroke. *Critical care medicine*, 32(2), pp.399-403.
- 1185 69. Hashim, I.A., Al-Zeer, A., Al-Shohaib, S., Al-Ahwal, M. and Shenkin, A., 1997. Cytokine
1186 changes in patients with heatstroke during pilgrimage to Makkah. *Mediators of*
1187 *inflammation*, 6(2), pp.135-139.
- 1188 70. Camus, G., Nys, M., Poortmans, J.R., Venneman, I., Monfils, T., Deby-Dupont, G.,
1189 Juchmes-Ferir, A., Deby, C., Lamy, M. and Duchateau, J., 1998. Endotoxaemia, production of
1190 tumour necrosis factor α and polymorphonuclear neutrophil activation following strenuous
1191 exercise in humans. *European journal of applied physiology and occupational*
1192 *physiology*, 79(1), pp.62-68.
- 1193 71. Gill, S.K., Teixeira, A., Rama, L., Prestes, J., Rosado, F., Hankey, J., Scheer, V., Hemmings,
1194 K., Ansley-Robson, P. and Costa, R.J., 2015. Circulatory endotoxin concentration and cytokine
1195 profile in response to exertional-heat stress during a multi-stage ultra-marathon
1196 competition. *Exercise immunology review*, 21, p.114.
- 1197 72. Barberio, M.D., Elmer, D.J., Laird, R.H., Lee, K.A., Gladden, B. and Pascoe, D.D., 2015.
1198 Systemic LPS and inflammatory response during consecutive days of exercise in
1199 heat. *International journal of sports medicine*, 36(03), pp.262-270.
- 1200 73. Ng, Q.Y., Lee, K.W., Byrne, C., Ho, T.F. and Lim, C.L., 2008. Plasma Endotoxin and Immune
1201 Responses During a 21-km Road Race Under a Warm and Humid Environment. *Ann Acad*
1202 *Med Singapore*, 37, pp.307-14.
- 1203 74. Aibiki, M., Ohtsubo, S., Nishiyama, T., Maekawa, S., Oka, H., Dote, K. and Shirakawa, Y.,
1204 2005. Elevated serum beta-D-glucan level and depressed neutrophil phagocytosis in a
1205 heatstroke patient. *Resuscitation*, 65(1), pp.115-117.
- 1206 75. Wacker, C., Prkno, A., Brunkhorst, F.M. and Schlattmann, P., 2013. Procalcitonin as a
1207 diagnostic marker for sepsis: a systematic review and meta-analysis. *The Lancet infectious*
1208 *diseases*, 13(5), pp.426-435.
- 1209 76. Tong, H.S., Liu, Y.S., Wen, Q., Tang, Y.Q., Yuan, F.F. and Su, L., 2012. Serum procalcitonin
1210 predicting mortality in exertional heatstroke. *Emerg Med J*, 29(2), pp.113-117.
- 1211 77. Hausfater, P., Hurtado, M., Pease, S., Juillien, G., Lvovschi, V.E., Salehabadi, S., Lidove, O.,
1212 Wolff, M., Bernard, M., Chollet-Martin, S. and Riou, B., 2008. Is procalcitonin a marker of
1213 critical illness in heatstroke?. *Intensive care medicine*, 34(8), pp.1377-1383.

- 1214 78. Yang, Q., Liu, W., Yu, J., Jiang, J., Xu, T. and Zhou, Y., 2019. Effect of prealbumin level on
1215 mortality in heatstroke patients. *Experimental and therapeutic medicine*, 17(4), pp.3053-
1216 3060.
- 1217 79. Galipeau, H.J. and Verdu, E.F., 2016. The complex task of measuring intestinal
1218 permeability in basic and clinical science. *Neurogastroenterology & Motility*, 28(7), pp.957-
1219 965.
- 1220 80. Costa, R.J.S., Snipe, R.M.J., Kitic, C.M. and Gibson, P.R., 2017. Systematic review:
1221 exercise-induced gastrointestinal syndrome—implications for health and intestinal
1222 disease. *Alimentary pharmacology & therapeutics*, 46(3), pp.246-265.
- 1223 81. Pires, W., Veneroso, C.E., Wanner, S.P., Pacheco, D.A.S., Vaz, G.C., Amorim, F.T., Tonoli,
1224 C., Soares, D.D. and Coimbra, C.C., 2017. Association Between Exercise-Induced
1225 Hyperthermia and Intestinal Permeability: A Systematic Review. *Sports medicine (Auckland,*
1226 *NZ)*, 47(7), pp.1389-1403.
- 1227 82. van Wijck, K., Lenaerts, K., Grootjans, J., Wijnands, K.A., Poeze, M., Van Loon, L.J.,
1228 Dejong, C.H. and Buurman, W.A., 2012. Physiology and pathophysiology of splanchnic
1229 hypoperfusion and intestinal injury during exercise: strategies for evaluation and
1230 prevention. *American journal of physiology-gastrointestinal and liver physiology*, 303(2),
1231 pp.G155-G168.
- 1232 83. Menzies, I.S., Zuckerman, M.J., Nukajam, W.S., Somasundaram, S.G., Murphy, B., Jenkins,
1233 A.P., Crane, R.S. and Gregory, G.G., 1999. Geography of intestinal permeability and
1234 absorption. *Gut*, 44(4), pp.483-489.
- 1235 84. Bjarnason, I., Macpherson, A. and Hollander, D., 1995. Intestinal permeability: an
1236 overview. *Gastroenterology*, 108(5), pp.1566-1581.
- 1237 85. Fleming, S.C., Duncan, A., Russell, R.I. and Laker, M.F., 1996. Measurement of sugar
1238 probes in serum: an alternative to urine measurement in intestinal permeability
1239 testing. *Clinical chemistry*, 42(3), pp.445-448.
- 1240 86. van Wijck, K., Lenaerts, K., Van Loon, L.J., Peters, W.H., Buurman, W.A. and Dejong, C.H.,
1241 2011. Exercise-induced splanchnic hypoperfusion results in gut dysfunction in healthy
1242 men. *PLoS one*, 6(7), p.e22366.
- 1243 87. van Wijck, K., van Eijk, H.M., Buurman, W.A., Dejong, C.H. and Lenaerts, K., 2011. Novel
1244 analytical approach to a multi-sugar whole gut permeability assay. *Journal of*
1245 *Chromatography B*, 879(26), pp.2794-2801.
- 1246 88. Pugh, J.N., Impey, S.G., Doran, D.A., Fleming, S.C., Morton, J.P. and Close, G.L., 2017.
1247 Acute high-intensity interval running increases markers of gastrointestinal damage and
1248 permeability but not gastrointestinal symptoms. *Applied Physiology, Nutrition, and*
1249 *Metabolism*, 42(9), pp.941-947.
- 1250 89. Ogden, H.B., Fallowfield, J.L., Child, R.B., Davison, G., Fleming, S.C., Edinburgh, R.M.,
1251 Delves, S.K., Millyard, M., Westwood, C.S. and Layden, J.D., 2020. Reliability of

- 1252 **Gastrointestinal Barrier Integrity and Microbial Translocation Biomarkers at Rest and**
1253 **Following Exertional Heat Stress. *Physiological Reports*,**
- 1254 90. van Wijck, K., Verlinden, T.J., van Eijk, H.M., Dekker, J., Buurman, W.A., Dejong, C.H. and
1255 Lenaerts, K., 2013. Novel multi-sugar assay for site-specific gastrointestinal permeability
1256 analysis: a randomized controlled crossover trial. *Clinical nutrition*, 32(2), pp.245-251
- 1257 91. van Wijck, K., Bessems, B.A., van Eijk, H.M.H., Buurman, W.A., Dejong, C.H.C. and
1258 Lenaerts, K., 2012. Polyethylene glycol versus dual sugar assay for gastrointestinal
1259 permeability analysis: is it time to choose?. *Clinical and experimental gastroenterology*, 5,
1260 pp.139-50.
- 1261 92. Sun, D.L., Cen, Y.Y., Li, S.M., Li, W.M., Lu, Q.P. and Xu, P.Y., 2016. Accuracy of the serum
1262 intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-
1263 analysis. *Scientific reports*, 6, pp.34371-34371.
- 1264 93. van de Poll, M.C., Derikx, J.P., Buurman, W.A., Peters, W.H., Roelofs, H.M., Wigmore, S.J.
1265 and Dejong, C.H., 2007. Liver manipulation causes hepatocyte injury and precedes systemic
1266 inflammation in patients undergoing liver resection. *World journal of surgery*, 31(10),
1267 pp.2033-2038.
- 1268 94. Montagnana, M., Danese, E. and Lippi, G., 2018. Biochemical markers of acute intestinal
1269 ischemia: possibilities and limitations. *Annals of translational medicine*, 6(17), p.341.
- 1270 95. Sturgeon, C. and Fasano, A., 2016. Zonulin, a regulator of epithelial and endothelial
1271 barrier functions, and its involvement in chronic inflammatory diseases. *Tissue barriers*, 4(4),
1272 p.e1251384.
- 1273 96. Ajamian, M., Steer, D., Rosella, G. and Gibson, P.R., 2019. Serum zonulin as a marker of
1274 intestinal mucosal barrier function: May not be what it seems. *PloS one*, 14(1), p.e0210728.
- 1275 97. Thuijls, G., Derikx, J.P., de Haan, J.J., Grootjans, J., de Bruïne, A., Masclee, A.A.,
1276 Heineman, E. and Buurman, W.A., 2010. Urine-based detection of intestinal tight junction
1277 loss. *Journal of clinical gastroenterology*, 44(1), pp.e14-e19.
- 1278 98. Nagpal, R. and Yadav, H., 2017. Bacterial translocation from the gut to the distant organs:
1279 an overview. *Annals of Nutrition and Metabolism*, 71, pp.11-16.
- 1280 99. Gnauck, A., Lentle, R.G. and Kruger, M.C., 2016. Chasing a ghost?—Issues with the
1281 determination of circulating levels of endotoxin in human blood. *Critical reviews in clinical*
1282 *laboratory sciences*, 53(3), pp.197-215.
- 1283 100. Mussap, M., Noto, A., Fravega, M. and Fanos, V., 2011. Soluble CD14 subtype presepsin
1284 (sCD14-ST) and lipopolysaccharide binding protein (LBP) in neonatal sepsis: new clinical and
1285 analytical perspectives for two old biomarkers. *The Journal of Maternal-Fetal & Neonatal*
1286 *Medicine*, 24(sup2), pp.12-14.
- 1287 101. Mierzchala, M., Krzystek-Korpacka, M., Gamian, A. and Durek, G., 2011. Quantitative
1288 indices of dynamics in concentrations of lipopolysaccharide-binding protein (LBP) as

- 1289 prognostic factors in severe sepsis/septic shock patients—comparison with CRP and
1290 procalcitonin. *Clinical biochemistry*, 44(5-6), pp.357-363.
- 1291 102. Ewaschuk, J.B., Naylor, J.M. and Zello, G.A., 2005. D-lactate in human and ruminant
1292 metabolism. *The Journal of nutrition*, 135(7), pp.1619-1625.
- 1293 103. Sun, X.Q., Fu, X.B., Zhang, R., Lu, Y., Deng, Q., Jiang, X.G. and Sheng, Z.Y., 2001.
1294 Relationship between plasma D (-)-lactate and intestinal damage after severe injuries in
1295 rats. *World journal of gastroenterology*, 7(4), pp.555-558.
- 1296 104. Sobhian, B., Kröpfl, A., Hölzenbein, T., Khadem, A., Redl, H. and Bahrami, S., 2012.
1297 Increased circulating D-lactate levels predict risk of mortality after hemorrhage and surgical
1298 trauma in baboons. *Shock*, 37(5), pp.473-477.
- 1299 105. March, D.S., Jones, A.W., Thatcher, R. and Davison, G., 2019. The effect of bovine
1300 colostrum supplementation on intestinal injury and circulating intestinal bacterial DNA
1301 following exercise in the heat. *European journal of nutrition*, 58(4), pp.1441-1451.
- 1302 106. Païssé, S., Valle, C., Servant, F., Courtney, M., Burcelin, R., Amar, J. and Lelouvier, B.,
1303 2016. Comprehensive description of blood microbiome from healthy donors assessed by 16
1304 S targeted metagenomic sequencing. *Transfusion*, 56(5), pp.1138-1147
- 1305 107. Nieman, D., Kay, C., Rathore, A., Grace, M., Strauch, R., Stephan, E., Sakaguchi, C. and
1306 Lila, M., 2018. Increased Plasma Levels of Gut-Derived Phenolics Linked to Walking and
1307 Running Following Two Weeks of Flavonoid Supplementation. *Nutrients*, 10(11), p.1718.
- 1308 108. Pals, K.L., Chang, R.T., Ryan, A.J. and Gisolfi, C.V., 1997. Effect of running intensity on
1309 intestinal permeability. *Journal of Applied Physiology*, 82(2), pp.571-576.
- 1310 109. JanssenDuijghuijsen, L.M., Keijer, J., Mensink, M., Lenaerts, K., Ridder, L., Nierkens, S.,
1311 Kartaram, S.W., Verschuren, M.C., Pieters, R.H., Bas, R. and Witkamp, R.F., 2017. Adaptation
1312 of exercise-induced stress in well-trained healthy young men. *Experimental*
1313 *physiology*, 102(1), pp.86-99.
- 1314 110. van Nieuwenhoven, 1999. The effect of physical exercise on parameters of
1315 gastrointestinal function. *Neurogastroenterology & Motility*, 11(6), pp.431-439.
- 1316 111. van Nieuwenhoven, M.A., Brummer, R.J. and Brouns, F.J.P.H., 2000. Gastrointestinal
1317 function during exercise: comparison of water, sports drink, and sports drink with
1318 caffeine. *Journal of applied physiology*, 89(3), pp.1079-1085.
- 1319 112. van Nieuwenhoven, M.A., Brouns, F. and Brummer, R.J.M., 2004. Gastrointestinal
1320 profile of symptomatic athletes at rest and during physical exercise. *European journal of*
1321 *applied physiology*, 91(4), pp.429-434.
- 1322 113. Marchbank, T., Davison, G., Oakes, J.R., Ghatei, M.A., Patterson, M., Moyer, M.P. and
1323 Playford, R.J., 2010. The nutraceutical bovine colostrum truncates the increase in gut
1324 permeability caused by heavy exercise in athletes. *American Journal of Physiology-*
1325 *Gastrointestinal and Liver Physiology*, 300(3), pp.G477-G484.

- 1326 114. Davison, G., Marchbank, T., March, D.S., Thatcher, R. and Playford, R.J., 2016. Zinc
1327 carnosine works with bovine colostrum in truncating heavy exercise-induced increase in gut
1328 permeability in healthy volunteers. *The American journal of clinical nutrition*, 104(2), pp.526-
1329 536.
- 1330 115. Snipe, R.M., Khoo, A., Kitic, C.M., Gibson, P.R. and Costa, R.J., 2018. The impact of
1331 exertional-heat stress on gastrointestinal integrity, gastrointestinal symptoms, systemic
1332 endotoxin and cytokine profile. *European journal of applied physiology*, 118(2), pp.389-400.
- 1333 116. Zuhl, M., Dokladny, K., Mermier, C., Schneider, S., Salgado, R. and Moseley, P., 2015.
1334 The effects of acute oral glutamine supplementation on exercise-induced gastrointestinal
1335 permeability and heat shock protein expression in peripheral blood mononuclear cells. *Cell
1336 Stress and Chaperones*, 20(1), pp.85-93.
- 1337 117. van Nieuwenhoven, M.A., Brouns, F. and Brummer, R.J.M., 2004. Gastrointestinal
1338 profile of symptomatic athletes at rest and during physical exercise. *European journal of
1339 applied physiology*, 91(4), pp.429-434.
- 1340 118. van Nieuwenhoven, M.A., Vriens, B.E.P.J., Brummer, R.J. and Brouns, F.J.P.H., 2000.
1341 Effect of dehydration on gastrointestinal function at rest and during exercise in
1342 humans. *European journal of applied physiology*, 83(6), pp.578-584.
- 1343 119. Lambert, G.P., Lang, J., Bull, A., Pfeifer, P.C., Eckerson, J., Moore, G., Lanspa, S. and
1344 O'Brien, J., 2008. Fluid restriction during running increases GI permeability. *International
1345 journal of sports medicine*, 29(03), pp.194-198.
- 1346 120. Ryan, A.J., Chang, R.T. and Gisolfi, C.V., 1996. Gastrointestinal permeability following
1347 aspirin intake and prolonged running. *Medicine and science in sports and exercise*, 28(6),
1348 pp.698-705.
- 1349 121. Lambert, G.P., Boylan, M., Laventure, J.P., Bull, A. and Lanspa, S., 2007. Effect of aspirin
1350 and ibuprofen on GI permeability during exercise. *International journal of sports
1351 medicine*, 28(09), pp.722-726.
- 1352 122. Lambert, G.P., Broussard, L.J., Mason, B.L., Mauermann, W.J. and Gisolfi, C.V., 2001.
1353 Gastrointestinal permeability during exercise: effects of aspirin and energy-containing
1354 beverages. *Journal of Applied Physiology*, 90(6), pp.2075-2080.
- 1355 123. Smetanka, R.D., Lambert, C.P., Murray, R., Eddy, D., Horn, M. and Gisolfi, C.V., 1999.
1356 Intestinal permeability in runners in the 1996 Chicago marathon. *International Journal of
1357 Sport Nutrition and Exercise Metabolism*, 9(4), pp.426-433.
- 1358 124. van Wijck, K., Lenaerts, K., Van Bijnen, A.A., Boonen, B., Van Loon, L.J., Dejong, C.H. and
1359 Buurman, W.A., 2012. Aggravation of exercise-induced intestinal injury by Ibuprofen in
1360 athletes. *Med Sci Sports Exerc*, 44(12), pp.2257-2262.
- 1361 125. Snipe, R.M., Khoo, A., Kitic, C.M., Gibson, P.R. and Costa, R.J., 2018. The impact of mild
1362 heat stress during prolonged running on gastrointestinal integrity, gastrointestinal

- 1363 symptoms, systemic endotoxin and cytokine profiles. *International journal of sports*
1364 *medicine*, 39(04), pp.255-263.
- 1365 126. Shing, C.M., Peake, J.M., Lim, C.L., Briskey, D., Walsh, N.P., Fortes, M.B., Ahuja, K.D. and
1366 Vitetta, L., 2014. Effects of probiotics supplementation on gastrointestinal permeability,
1367 inflammation and exercise performance in the heat. *European journal of applied*
1368 *physiology*, 114(1), pp.93-103.
- 1369 127. van Wijck, K., Wijnands, K.A., Meesters, D.M., Boonen, B., Van Loon, L.J., Buurman,
1370 W.A., Dejong, C.H., Lenaerts, K. and Poeze, M., 2014. L-citrulline improves splanchnic
1371 perfusion and reduces gut injury during exercise. *Medicine & Science in Sports &*
1372 *Exercise*, 46(11), pp.2039-2046.
- 1373 128. Lee, B.J. and Thake, C.D., 2017. Heat and Hypoxic Acclimation Increase Monocyte Heat
1374 Shock Protein 72 but Do Not Attenuate Inflammation following Hypoxic Exercise. *Frontiers in*
1375 *physiology*, 8, pp.811-811.
- 1376 129. Kartaram, S., Mensink, M., Teunis, M., Schoen, E., Witte, G., Duijghuijsen, L.J.,
1377 Verschuren, M., Mohrmann, K., M'Rabet, L., Knipping, K. and Wittink, H., 2019. Plasma
1378 citrulline concentration, a marker for intestinal functionality, reflects exercise intensity in
1379 healthy young men. *Clinical Nutrition*, 38(5), pp.2251-2258.
- 1380 130. Trommelen, J., Fuchs, C., Beelen, M., Lenaerts, K., Jeukendrup, A., Cermak, N. and Van
1381 Loon, L., 2017. Fructose and sucrose intake increase exogenous carbohydrate oxidation
1382 during exercise. *Nutrients*, 9(2), p.167.
- 1383 131. Jonvik, K.L., Lenaerts, K., Smeets, J.S., Kolkman, J.J., Van Loon, L.J. and Verdijk, L.B.,
1384 2019. Sucrose but Not Nitrate Ingestion Reduces Strenuous Cycling-induced Intestinal
1385 Injury. *Med. Sci. Sports Exerc*, 51, pp.436-444.
- 1386 132. Karhu, E., Forsgård, R.A., Alanko, L., Alfthan, H., Pussinen, P., Hämäläinen, E. and
1387 Korpela, R., 2017. Exercise and gastrointestinal symptoms: running-induced changes in
1388 intestinal permeability and markers of gastrointestinal function in asymptomatic and
1389 symptomatic runners. *European journal of applied physiology*, 117(12), pp.2519-2526.
- 1390 133. Osborne, J.O., Stewart, I.B., Beagley, K.W. and Minett, G.M., 2019. The effect of cycling
1391 in the heat on gastrointestinal-induced damage and neuromuscular fatigue. *European*
1392 *journal of applied physiology*, pp.1-12.
- 1393 134. Hill, G.W., Gillum, T.L., Lee, B.J., Romano, P.A., Schall, Z.J., Hamilton, A.M. and Kuennen,
1394 M.R., 2019. Prolonged treadmill running in normobaric hypoxia causes gastrointestinal
1395 barrier permeability and elevates circulating levels of pro-and anti-inflammatory
1396 cytokines. *Applied Physiology, Nutrition, and Metabolism*, (ja).
- 1397 135. Costa, R.J., Camoes-Costa, V., Snipe, R.M., Dixon, D., Russo, I. and Huschtscha, Z., 2019.
1398 Impact of exercise-induced hypohydration on gastrointestinal integrity, function, symptoms,
1399 and systemic endotoxin and inflammatory profile. *Journal of Applied Physiology*, 126(5),
1400 pp.1281-1291.

- 1401 136. Sheahan, B.L., Fell, J.W., Zadow, E.K., Hartley, T.F. and Kitic, C.M., 2018. Intestinal
1402 damage following short-duration exercise at the same relative intensity is similar in
1403 temperate and hot environments. *Applied physiology, nutrition, and metabolism*, 43(12),
1404 pp.1314-1320.
- 1405 137. Snipe, R.M. and Costa, R.J., 2018. Does the temperature of water ingested during
1406 exertional-heat stress influence gastrointestinal injury, symptoms, and systemic
1407 inflammatory profile?. *Journal of science and medicine in sport*, 21(8), pp.771-776.
- 1408 138. Yeh, Y.J., Law, L.Y.L. and Lim, C.L., 2013. Gastrointestinal response and endotoxemia
1409 during intense exercise in hot and cool environments. *European journal of applied
1410 physiology*, 113(6), pp.1575-1583.
- 1411 139. Bosenberg, A.T., Brock-Utne, J.G., Gaffin, S.L., Wells, M.T. and Blake, G.T., 1988.
1412 Strenuous exercise causes systemic endotoxemia. *Journal of Applied Physiology*, 65(1),
1413 pp.106-108.
- 1414 140. Brock-Utne, J.G., Gaffin, S.L., Wells, M.T., Gathiram, P., Sohar, E., James, M.F., Morrell,
1415 D.F. and Norman, R.J., 1988. Endotoxaemia in exhausted runners after a long-distance
1416 race. *South African Medical Journal/Suid-Afrikaanse Mediese Tydskrift*, 73(9), pp.533-536.
- 1417 141. Moore, G.E., Holbein, M.E. and Knochel, J.P., 1995. Exercise-associated collapse in
1418 cyclists is unrelated to endotoxemia. *Medicine and science in sports and exercise*, 27(9),
1419 pp.1238-1242.
- 1420 142. Camus, G., Nys, M., Poortmans, J.R., Venneman, I., Monfils, T., Deby-Dupont, G.,
1421 Juchmes-Ferir, A., Deby, C., Lamy, M. and Duchateau, J., 1998. Endotoxaemia, production of
1422 tumour necrosis factor α and polymorphonuclear neutrophil activation following strenuous
1423 exercise in humans. *European journal of applied physiology and occupational
1424 physiology*, 79(1), pp.62-68.
- 1425 143. Kuennen, M., Gillum, T., Dokladny, K., Bedrick, E., Schneider, S. and Moseley, P., 2011.
1426 Thermotolerance and heat acclimation may share a common mechanism in
1427 humans. *American Journal of Physiology-Regulatory, Integrative and Comparative
1428 Physiology*, 301(2), pp.R524-R533.
- 1429 144. Jeukendrup, A.E., Vet-Joop, K., Sturk, A., Stegen, J.H.J.C., Senden, J., Saris, W.H.M. and
1430 Wagenmakers, A.J.M., 2000. Relationship between gastro-intestinal complaints and
1431 endotoxaemia, cytokine release and the acute-phase reaction during and after a long-
1432 distance triathlon in highly trained men. *Clinical Science*, 98(1), pp.47-55.
- 1433 145. Gill, S.K., Hankey, J., Wright, A., Marczak, S., Hemming, K., Allerton, D.M., Ansley-
1434 Robson, P. and Costa, R.J.S., 2015. The impact of a 24-h ultra-marathon on circulatory
1435 endotoxin and cytokine profile. *International journal of sports medicine*, 36(08), pp.688-695.
- 1436 146. Selkirk, G.A., McLellan, T.M., Wright, H.E. and Rhind, S.G., 2008. Mild endotoxemia, NF-
1437 κ B translocation, and cytokine increase during exertional heat stress in trained and
1438 untrained individuals. *American Journal of Physiology-Regulatory, Integrative and
1439 Comparative Physiology*, 295(2), pp.R611-R623.

- 1440 147. Gaskell, S.K., Taylor, B., Muir, J. and Costa, R.J., 2019. Impact of 24-hour high and low
1441 fermentable oligo-di-mono-saccharide polyol diets on markers of exercise-induced
1442 gastrointestinal syndrome in response to exertional-heat stress. *Applied Physiology,*
1443 *Nutrition, and Metabolism*, (ja).
- 1444 148. Pugh, J.N., Sparks, A.S., Doran, D.A., Fleming, S.C., Langan-Evans, C., Kirk, B., Fearn, R.,
1445 Morton, J.P. and Close, G.L., 2019. Four weeks of probiotic supplementation reduces GI
1446 symptoms during a marathon race. *European journal of applied physiology*, 119(7), pp.1491-
1447 1501.
- 1448 149. Gill, S.K., Allerton, D.M., Ansley-Robson, P., Hemmings, K., Cox, M. and Costa, R.J., 2016.
1449 Does short-term high dose probiotic supplementation containing lactobacillus casei
1450 attenuate exertional-heat stress induced endotoxaemia and cytokinaemia?. *International*
1451 *journal of sport nutrition and exercise metabolism*, 26(3), pp.268-275.
- 1452 150. Lim, C.L., Pyne, D., Horn, P., Kalz, A., Saunders, P., Peake, J., Suzuki, K., Wilson, G. and
1453 Mackinnon, L.T., 2009. The effects of increased endurance training load on biomarkers of
1454 heat intolerance during intense exercise in the heat. *Applied Physiology, Nutrition, and*
1455 *Metabolism*, 34(4), pp.616-624.
- 1456 151. Moss, J.N., Bayne, F.M., Castelli, F., Naughton, M.R., Reeve, T.C., Trangmar, S.J.,
1457 Mackenzie, R.W. and Tyler, C.J., 2019. Short-term isothermic heat acclimation elicits
1458 beneficial adaptations but medium-term elicits a more complete adaptation. *European*
1459 *journal of applied physiology*, pp.1-12.
- 1460 152. Morrison, S.A., Cheung, S.S. and Cotter, J.D., 2014. Bovine colostrum, training status,
1461 and gastrointestinal permeability during exercise in the heat: a placebo-controlled double-
1462 blind study. *Applied Physiology, Nutrition, and Metabolism*, 39(9), pp.1070-1082.
- 1463 153. Dokladny, K., Zuhl, M.N. and Moseley, P.L., 2015. Intestinal epithelial barrier function
1464 and tight junction proteins with heat and exercise. *Journal of Applied Physiology*, 120(6),
1465 pp.692-701.
- 1466 154. Oliver, S.R., Phillips, N.A., Novosad, V.L., Bakos, M.P., Talbert, E.E. and Clanton, T.L.,
1467 2012. Hyperthermia induces injury to the intestinal mucosa in the mouse: evidence for an
1468 oxidative stress mechanism. *American Journal of Physiology-Regulatory, Integrative and*
1469 *Comparative Physiology*, 302(7), pp.R845-R853.
- 1470 155. Grootjans, J., Lenaerts, K., Buurman, W.A., Dejong, C.H. and Derikx, J.P., 2016. Life and
1471 death at the mucosal-luminal interface: New perspectives on human intestinal ischemia-
1472 reperfusion. *World journal of gastroenterology*, 22(9), p.2760.
- 1473 156. de Punder, K. and Pruijboom, L., 2015. Stress induces endotoxemia and low-grade
1474 inflammation by increasing barrier permeability. *Frontiers in immunology*, 6, p.223.
- 1475 157. Sawka, M.N., Leon, L.R., Montain, S.J. and Sonna, L.A., 2011. Integrated physiological
1476 mechanisms of exercise performance, adaptation, and maladaptation to heat
1477 stress. *Comprehensive Physiology*, 1(4), pp.1883-1928.

- 1478 158. Byrne, C. and Lim, C.L., 2007. The ingestible telemetric body core temperature sensor: a
1479 review of validity and exercise applications. *British journal of sports medicine*, 41(3), pp.126-
1480 133.
- 1481 159. Dokladny, K., Moseley, P.L. and Ma, T.Y., 2006. Physiologically relevant increase in
1482 temperature causes an increase in intestinal epithelial tight junction permeability. *American*
1483 *Journal of Physiology-Gastrointestinal and Liver Physiology*, 290(2), pp.G204-G212.
- 1484 160. Ikari, A., Nakano, M., Suketa, Y., Harada, H. and Takagi, K., 2005. Reorganization of ZO-1
1485 by sodium-dependent glucose transporter activation after heat stress in LLC-PK1
1486 cells. *Journal of cellular physiology*, 203(3), pp.471-478.
- 1487 161. Yang, P.C., He, S.H. and Zheng, P.Y., 2007. Investigation into the signal transduction
1488 pathway via which heat stress impairs intestinal epithelial barrier function. *Journal of*
1489 *gastroenterology and hepatology*, 22(11), pp.1823-1831.
- 1490 162. Ter Steege, R.W.F. and Kolkman, J.J., 2012. The pathophysiology and management of
1491 gastrointestinal symptoms during physical exercise, and the role of splanchnic blood
1492 flow. *Alimentary pharmacology & therapeutics*, 35(5), pp.516-528.
- 1493 163. Ahlborg, G.U.N.V.O.R., Weitzberg, E. and Lundberg, J., 1995. Metabolic and vascular
1494 effects of circulating endothelin-1 during moderately heavy prolonged exercise. *Journal of*
1495 *Applied Physiology*, 78(6), pp.2294-2300.
- 1496 164. Kenney, W.L. and Ho, C.W., 1995. Age alters regional distribution of blood flow during
1497 moderate-intensity exercise. *Journal of Applied Physiology*, 79(4), pp.1112-1119.
- 1498 165. Otte, J.A., Oostveen, E., Geelkerken, R.H., Groeneveld, A.J. and Kolkman, J.J., 2001.
1499 Exercise induces gastric ischemia in healthy volunteers: a tonometry study. *Journal of*
1500 *Applied Physiology*, 91(2), pp.866-871.
- 1501 166. Thursby, E. and Juge, N., 2017. Introduction to the human gut microbiota. *Biochemical*
1502 *Journal*, 474(11), pp.1823-1836.
- 1503 167. JanssenDuijghuisen, L.M., Grefte, S., de Boer, V.C., Zeper, L., van Dartel, D.A., van der
1504 Stelt, I., Bekkenkamp-Grovenstein, M., van Norren, K., Wichers, H.J. and Keijer, J., 2017.
1505 Mitochondrial ATP depletion disrupts Caco-2 monolayer integrity and internalizes claudin
1506 7. *Frontiers in physiology*, 8, p.794.
- 1507 168. Friedman, E.S., Bittinger, K., Esipova, T.V., Hou, L., Chau, L., Jiang, J., Mesaros, C., Lund,
1508 P.J., Liang, X., FitzGerald, G.A. and Goulian, M., 2018. Microbes vs. chemistry in the origin of
1509 the anaerobic gut lumen. *Proceedings of the National Academy of Sciences*, 115(16),
1510 pp.4170-4175.
- 1511 169. Turner, M.D., Nedjai, B., Hurst, T. and Pennington, D.J., 2014. Cytokines and
1512 chemokines: at the crossroads of cell signalling and inflammatory disease. *Biochimica et*
1513 *Biophysica Acta (BBA)-Molecular Cell Research*, 1843(11), pp.2563-2582.
- 1514 170. Suzuki, K., 2018. Cytokine response to exercise and its modulation. *Antioxidants*, 7(1),
1515 p.17.

- 1516 171. Al-Sadi, R., Guo, S., Dokladny, K., Smith, M.A., Ye, D., Kaza, A., Watterson, D.M. and Ma,
1517 T.Y., 2012. Mechanism of interleukin-1 β induced-increase in mouse intestinal permeability in
1518 vivo. *Journal of Interferon & Cytokine Research*, 32(10), pp.474-484.
- 1519 172. Al-Sadi, R., Guo, S., Ye, D. and Ma, T.Y., 2013. TNF- α modulation of intestinal epithelial
1520 tight junction barrier is regulated by ERK1/2 activation of Elk-1. *The American journal of*
1521 *pathology*, 183(6), pp.1871-1884.
- 1522 173. Al-Sadi, R., Ye, D., Boivin, M., Guo, S., Hashimi, M., Ereifej, L. and Ma, T.Y., 2014.
1523 Interleukin-6 modulation of intestinal epithelial tight junction permeability is mediated by
1524 JNK pathway activation of claudin-2 gene. *PloS one*, 9(3), p.e85345.
- 1525 174. Fortes, M.B., Di, U.F., Dolci, A., Junglee, N.A., Crockford, M.J., West, L., Hillier-Smith, R.,
1526 Macdonald, J.H. and Walsh, N.P., 2013. Muscle-damaging exercise increases heat strain
1527 during subsequent exercise heat stress. *Medicine and science in sports and exercise*, 45(10),
1528 pp.1915-1924.
- 1529 175. Dolci, A., Fortes, M.B., Walker, F.S., Haq, A., Riddle, T. and Walsh, N.P., 2015. Repeated
1530 muscle damage blunts the increase in heat strain during subsequent exercise heat
1531 stress. *European journal of applied physiology*, 115(7), pp.1577-1588.
- 1532 176. Cavaillon, J.M. and Annane, D., 2006. Invited review: Compartmentalization of the
1533 inflammatory response in sepsis and SIRS. *Journal of endotoxin research*, 12(3), pp.151-170.
- 1534 177. Ghanim, H., Sia, C.L., Upadhyay, M., Korzeniewski, K., Viswanathan, P., Abuaysheh, S.,
1535 Mohanty, P. and Dandona, P., 2010. Orange juice neutralizes the proinflammatory effect of a
1536 high-fat, high-carbohydrate meal and prevents endotoxin increase and Toll-like receptor
1537 expression. *The American journal of clinical nutrition*, 91(4), pp.940-949.
- 1538 178. Deopurkar, R., Ghanim, H., Friedman, J., Abuaysheh, S., Sia, C.L., Mohanty, P.,
1539 Viswanathan, P., Chaudhuri, A. and Dandona, P., 2010. Differential effects of cream, glucose,
1540 and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and
1541 suppressor of cytokine signaling-3. *Diabetes care*, 33(5), pp.991-997.
- 1542 179. Ghanim, H., Abuaysheh, S., Sia, C.L., Korzeniewski, K., Chaudhuri, A., Fernandez-Real,
1543 J.M. and Dandona, P., 2009. Increase in plasma endotoxin concentrations and the expression
1544 of Toll-like receptors and suppressor of cytokine signaling-3 in mononuclear cells after a
1545 high-fat, high-carbohydrate meal: implications for insulin resistance. *Diabetes care*, 32(12),
1546 pp.2281-2287.
- 1547 180. Edinburgh, R.M., Hengist, A., Smith, H.A., Travers, R.L., Koumanov, F., Betts, J.A.,
1548 Thompson, D., Walhin, J.P., Wallis, G.A., Hamilton, D.L. and Stevenson, E.J., 2018.
1549 Preexercise breakfast ingestion versus extended overnight fasting increases postprandial
1550 glucose flux after exercise in healthy men. *American Journal of Physiology-Endocrinology and*
1551 *Metabolism*, 315(5), pp.E1062-E1074.
- 1552 181. Salvador, A.F., McKenna, C.F., Alamilla, R.A., Cloud, R.M., Keeble, A.R., Miltko, A.,
1553 Scaroni, S.E., Beals, J.W., Ulanov, A.V., Dilger, R.N. and Bauer, L.L., 2019. Potato ingestion is

- 1554 as effective as carbohydrate gels to support prolonged cycling performance. *Journal of*
1555 *Applied Physiology*.
- 1556 182. Deniz, T., Agalar, C., Ozdogan, M., Comu, F., Emirdogan, M., Taskin, S., Saygun, O. and
1557 Agalar, F., 2007. Oral carbohydrate solution ameliorates endotoxemia-induced splanchnic
1558 ischemia. *Digestive diseases and sciences*, 52(1), pp.287-291.
- 1559 183. Ramadass, B., Dokladny, K., Moseley, P.L., Patel, Y.R. and Lin, H.C., 2010. Sucrose co-
1560 administration reduces the toxic effect of lectin on gut permeability and intestinal bacterial
1561 colonization. *Digestive diseases and sciences*, 55(10), pp.2778-2784.
- 1562 184. David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E.,
1563 Ling, A.V., Devlin, A.S., Varma, Y., Fischbach, M.A. and Biddinger, S.B., 2014. Diet rapidly and
1564 reproducibly alters the human gut microbiome. *Nature*, 505(7484), p.559.
- 1565 185. Gentilcore, D., Nair, N.S., Vanis, L., Rayner, C.K., Meyer, J.H., Hausken, T., Horowitz, M.
1566 and Jones, K.L., 2009. Comparative effects of oral and intraduodenal glucose on blood
1567 pressure, heart rate, and splanchnic blood flow in healthy older subjects. *American Journal*
1568 *of Physiology-Regulatory, Integrative and Comparative Physiology*, 297(3), pp.R716-R722.
- 1569 186. Lerner, A. and Matthias, T., 2015. Changes in intestinal tight junction permeability
1570 associated with industrial food additives explain the rising incidence of autoimmune
1571 disease. *Autoimmunity reviews*, 14(6), pp.479-489.
- 1572 187. Erridge, C., Attina, T., Spickett, C.M. and Webb, D.J., 2007. A high-fat meal induces low-
1573 grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *The*
1574 *American journal of clinical nutrition*, 86(5), pp.1286-1292.
- 1575 188. Pöschmüller, M., Schwingshackl, L., Colombani, P.C. and Hoffmann, G., 2016. A
1576 systematic review and meta-analysis of carbohydrate benefits associated with randomized
1577 controlled competition-based performance trials. *Journal of the international society of*
1578 *sports nutrition*, 13(1), p.27.
- 1579 189. McCartney, D., Desbrow, B. and Irwin, C., 2018. Post-exercise ingestion of
1580 carbohydrate, protein and water: a systematic review and meta-analysis for effects on
1581 subsequent athletic performance. *Sports Medicine*, 48(2), pp.379-408.
- 1582 190. Bermon, S., Castell, L.M., Calder, P.C., Bishop, N.C., Blomstrand, E., Mooren, F.C.,
1583 Krüger, K., Kavazis, A.N., Quindry, J.C., Senchina, D.S. and Nieman, D.C., 2017. Consensus
1584 Statement Immunonutrition and Exercise. *Exercise immunology review*, 23, pp.8-50.
- 1585 191. Costa, R.J., Miall, A., Khoo, A., Rauch, C., Snipe, R., Camões-Costa, V. and Gibson, P.,
1586 2017. Gut-training: the impact of two weeks repetitive gut-challenge during exercise on
1587 gastrointestinal status, glucose availability, fuel kinetics, and running performance. *Applied*
1588 *Physiology, Nutrition, and Metabolism*, 42(5), pp.547-557.
- 1589 192. Rehrer, N.J., Goes, E., DuGardeyn, C., Reynaert, H. and DeMeirleir, K., 2005. Effect of
1590 carbohydrate on portal vein blood flow during exercise. *International journal of sports*
1591 *medicine*, 26(03), pp.171-176.

- 1592 193. Snipe, R.M., Khoo, A., Kitic, C.M., Gibson, P.R. and Costa, R.J., 2017. Carbohydrate and
1593 protein intake during exertional heat stress ameliorates intestinal epithelial injury and small
1594 intestine permeability. *Applied physiology, nutrition, and metabolism*, 42(12), pp.1283-1292.
- 1595 194. Sessions, J., Bourbeau, K., Rosinski, M., Szczygiel, T., Nelson, R., Sharma, N. and Zuhl,
1596 M., 2016. Carbohydrate gel ingestion during running in the heat on markers of
1597 gastrointestinal distress. *European journal of sport science*, 16(8), pp.1064-1072.
- 1598 195. Moncada-Jiménez, J., Plaisance, E.P., Mestek, M.L., Ratcliff, L., Araya-Ramírez, F., Taylor,
1599 J.K., Grandjean, P.W. and AragónVargas, L.F., 2009. Duathlon performance unaltered by
1600 short-term changes in dietary fat and carbohydrates. *International journal of sport nutrition
1601 and exercise metabolism*, 19(1), pp.47-60.
- 1602 196. Kim, M.H. and Kim, H., 2017. The roles of glutamine in the intestine and its implication
1603 in intestinal diseases. *International journal of molecular sciences*, 18(5), p.1051.
- 1604 197. Zhou, Y.P., Jiang, Z.M., Sun, Y.H., Wang, X.R., Ma, E.L. and Wilmore, D., 2003. The effect
1605 of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe
1606 burns: a randomized, double-blind, controlled clinical trial. *Journal of Parenteral and Enteral
1607 Nutrition*, 27(4), pp.241-245.
- 1608 198. Peng, X., Yan, H., You, Z., Wang, P. and Wang, S., 2004. Effects of enteral
1609 supplementation with glutamine granules on intestinal mucosal barrier function in severe
1610 burned patients. *Burns*, 30(2), pp.135-139.
- 1611 199. Zhou, Q., Verne, M.L., Fields, J.Z., Lefante, J.J., Basra, S., Salameh, H. and Verne, G.N.,
1612 2019. Randomised placebo-controlled trial of dietary glutamine supplements for
1613 postinfectious irritable bowel syndrome. *Gut*, 68(6), pp.996-1002.
- 1614 200. Shu, X.L., Yu, T.T., Kang, K. and Zhao, J., 2016. Effects of glutamine on markers of
1615 intestinal inflammatory response and mucosal permeability in abdominal surgery patients: A
1616 meta-analysis. *Experimental and therapeutic medicine*, 12(6), pp.3499-3506.
- 1617 201. Akobeng, A.K., Miller, V., Stanton, J., Elbadri, A.M. and Thomas, A.G., 2000. Double-
1618 blind randomized controlled trial of glutamine-enriched polymeric diet in the treatment of
1619 active Crohn's disease. *Journal of pediatric gastroenterology and nutrition*, 30(1), pp.78-84.
- 1620 202. Benjamin, J., Makharia, G., Ahuja, V., Rajan, K.A., Kalaivani, M., Gupta, S.D. and Joshi,
1621 Y.K., 2012. Glutamine and whey protein improve intestinal permeability and morphology in
1622 patients with Crohn's disease: a randomized controlled trial. *Digestive diseases and
1623 sciences*, 57(4), pp.1000-1012.
- 1624 203. Rhoads, J.M., Argenzio, R.A., Chen, W.U.N.I.A.N., Rippe, R.A., Westwick, J.K., Cox, A.D.,
1625 Berschneider, H.M. and Brenner, D.A., 1997. L-glutamine stimulates intestinal cell
1626 proliferation and activates mitogen-activated protein kinases. *American Journal of
1627 Physiology-Gastrointestinal and Liver Physiology*, 272(5), pp.G943-G953.
- 1628 204. Singleton, K.D. and Wischmeyer, P.E., 2006. Oral glutamine enhances heat shock
1629 protein expression and improves survival following hyperthermia. *Shock*, 25(3), pp.295-299.

- 1630 205. Xue, H., Sufit, A.J. and Wischmeyer, P.E., 2011. Glutamine therapy improves outcome of
1631 in vitro and in vivo experimental colitis models. *Journal of Parenteral and Enteral*
1632 *Nutrition*, 35(2), pp.188-197.
- 1633 206. Dai, Z.L., Li, X.L., Xi, P.B., Zhang, J., Wu, G. and Zhu, W.Y., 2013. L-Glutamine regulates
1634 amino acid utilization by intestinal bacteria. *Amino Acids*, 45(3), pp.501-512.
- 1635 207. Harward, T.R., Coe, D., Souba, W.W., Klingman, N. and Seeger, J.M., 1994. Glutamine
1636 preserves gut glutathione levels during intestinal ischemia/reperfusion. *Journal of Surgical*
1637 *Research*, 56(4), pp.351-355.
- 1638 208. Li, N., Lewis, P., Samuelson, D., Liboni, K. and Neu, J., 2004. Glutamine regulates Caco-2
1639 cell tight junction proteins. *American Journal of Physiology-Gastrointestinal and Liver*
1640 *Physiology*, 287(3), pp.G726-G733.
- 1641 209. Beutheu, S., Ghouzali, I., Galas, L., Déchelotte, P. and Coëffier, M., 2013. Glutamine and
1642 arginine improve permeability and tight junction protein expression in methotrexate-treated
1643 Caco-2 cells. *Clinical nutrition*, 32(5), pp.863-869.
- 1644 210. Ahmadi, A.R., Rayyani, E., Bahreini, M. and Mansoori, A., 2019. The effect of glutamine
1645 supplementation on athletic performance, body composition, and immune function: A
1646 systematic review and a meta-analysis of clinical trials. *Clinical Nutrition*, 38(3), pp.1076-
1647 1091.
- 1648 211. Zuhl, M.N., Lanphere, K.R., Kravitz, L., Mermier, C.M., Schneider, S., Dokladny, K. and
1649 Moseley, P.L., 2013. Effects of oral glutamine supplementation on exercise-induced
1650 gastrointestinal permeability and tight junction protein expression. *Journal of applied*
1651 *physiology*, 116(2), pp.183-191.
- 1652 212. Pugh, J.N., Sage, S., Hutson, M., Doran, D.A., Fleming, S.C., Highton, J., Morton, J.P. and
1653 Close, G.L., 2017. Glutamine supplementation reduces markers of intestinal permeability
1654 during running in the heat in a dose-dependent manner. *European journal of applied*
1655 *physiology*, 117(12), pp.2569-2577.
- 1656 213. Osborne, J.O., Stewart, I.B., Beagley, K.W., Borg, D.N. and Minett, G.M., 2019. Acute
1657 glutamine supplementation does not improve 20-km self-paced cycling performance in the
1658 heat. *European Journal of Applied Physiology*, 119(11-12), pp.2567-2578.
- 1659 214. Gleeson, M., 2008. Dosing and efficacy of glutamine supplementation in human
1660 exercise and sport training. *The Journal of nutrition*, 138(10), pp.2045S-2049S.
- 1661 215. Rathe, M., Müller, K., Sangild, P.T. and Husby, S., 2014. Clinical applications of bovine
1662 colostrum therapy: a systematic review. *Nutrition reviews*, 72(4), pp.237-254.
- 1663 216. Uruakpa, F.O., Ismond, M.A.H. and Akobundu, E.N.T., 2002. Colostrum and its benefits:
1664 a review. *Nutrition research*, 22(6), pp.755-767.
- 1665 217. Prosser, C., Stelwagen, K., Cummins, R., Guerin, P., Gill, N. and Milne, C., 2004.
1666 Reduction in heat-induced gastrointestinal hyperpermeability in rats by bovine colostrum
1667 and goat milk powders. *Journal of applied physiology*, 96(2), pp.650-654.

- 1668 218. Playford, R.J., Floyd, D.N., Macdonald, C.E., Calnan, D.P., Adenekan, R.O., Johnson, W.,
1669 Goodlad, R.A. and Marchbank, T., 1999. Bovine colostrum is a health food supplement which
1670 prevents NSAID induced gut damage. *Gut*, *44*(5), pp.653-658.
- 1671 219. Eslamian, G., Ardehali, S.H., Baghestani, A.R. and Shariatpanahi, Z.V., 2019. Effects of
1672 early enteral bovine colostrum supplementation on intestinal permeability in critically ill
1673 patients: A randomized, double-blind, placebo-controlled study. *Nutrition*, *60*, pp.106-111.
- 1674 220. Bodammer, P., Kerkhoff, C., Maletzki, C. and Lamprecht, G., 2013. Bovine colostrum
1675 increases pore-forming claudin-2 protein expression but paradoxically not ion permeability
1676 possibly by a change of the intestinal cytokine milieu. *PLoS one*, *8*(5), p.e64210.
- 1677 221. Khan, Z., Macdonald, C., Wicks, A.C., Holt, M.P., Floyd, D., Ghosh, S., Wright, N.A. and
1678 Playford, R.J., 2002. Use of the 'nutriceutical', bovine colostrum, for the treatment of distal
1679 colitis: results from an initial study. *Alimentary pharmacology & therapeutics*, *16*(11),
1680 pp.1917-1922.
- 1681 222. Antonio, J., Sanders, M.S. and Van Gammeren, D., 2001. The effects of bovine
1682 colostrum supplementation on body composition and exercise performance in active men
1683 and women. *Nutrition*, *17*(3), pp.243-247.
- 1684 223. Jones, A.W., March, D.S., Curtis, F. and Bridle, C., 2016. Bovine colostrum
1685 supplementation and upper respiratory symptoms during exercise training: a systematic
1686 review and meta-analysis of randomised controlled trials. *BMC Sports Science, Medicine and
1687 Rehabilitation*, *8*(1), p.21.
- 1688 224. Shing, C.M., Hunter, D.C. and Stevenson, L.M., 2009. Bovine colostrum supplementation
1689 and exercise performance. *Sports Medicine*, *39*(12), pp.1033-1054.
- 1690 225. March, D.S., Marchbank, T., Playford, R.J., Jones, A.W., Thatcher, R. and Davison, G.,
1691 2017. Intestinal fatty acid-binding protein and gut permeability responses to
1692 exercise. *European journal of applied physiology*, *117*(5), pp.931-941.
- 1693 226. McKenna, Z., Berkemeier, Q., Naylor, A., Kleint, A., Gorini, F., Ng, J., Kim, J.K., Sullivan, S.
1694 and Gillum, T., 2017. Bovine colostrum supplementation does not affect plasma I-FABP
1695 concentrations following exercise in a hot and humid environment. *European journal of
1696 applied physiology*, *117*(12), pp.2561-2567.
- 1697 227. Hałasa, M., Maciejewska, D., Baśkiewicz-Hałasa, M., Machaliński, B., Safranow, K. and
1698 Stachowska, E., 2017. Oral supplementation with bovine colostrum decreases intestinal
1699 permeability and stool concentrations of zonulin in athletes. *Nutrients*, *9*(4), p.370.
- 1700 228. Buckley, J., Butler, R., Southcott, E. and Brinkworth, G., 2009. Bovine colostrum
1701 supplementation during running training increases intestinal permeability. *Nutrients*, *1*(2),
1702 pp.224-234.
- 1703 229. Jasion, V.S. and Burnett, B.P., 2015. Survival and digestibility of orally-administered
1704 immunoglobulin preparations containing IgG through the gastrointestinal tract in
1705 humans. *Nutrition journal*, *14*(1), p.22.

- 1706 230. Davison, G., Jones, A.W., Marchbank, T. and Playford, R.J., 2019. Oral bovine colostrum
1707 supplementation does not increase circulating insulin-like growth factor-1 concentration in
1708 healthy adults: results from short-and long-term administration studies. *European journal of*
1709 *nutrition*, pp.1-7.
- 1710 231. Lundberg, J.O., Carlström, M. and Weitzberg, E., 2018. Metabolic effects of dietary
1711 nitrate in health and disease. *Cell metabolism*, 28(1), pp.9-22.
- 1712 232. Castillo, L., DeRojas, T.C., Chapman, T.E., Vogt, J., Burke, J.F., Tannenbaum, S.R. and
1713 Young, V.R., 1993. Splanchnic metabolism of dietary arginine in relation to nitric oxide
1714 synthesis in normal adult man. *Proceedings of the National Academy of Sciences*, 90(1),
1715 pp.193-197.
- 1716 233. Petersson, J., Phillipson, M., Jansson, E.A., Patzak, A., Lundberg, J.O. and Holm, L., 2007.
1717 Dietary nitrate increases gastric mucosal blood flow and mucosal defense. *American Journal*
1718 *of Physiology-Gastrointestinal and Liver Physiology*, 292(3), pp.G718-G724.
- 1719 234. Tanaka, A., Araki, H., Komoike, Y., Hase, S. and Takeuchi, K., 2001. Inhibition of both
1720 COX-1 and COX-2 is required for development of gastric damage in response to nonsteroidal
1721 antiinflammatory drugs. *Journal of Physiology-Paris*, 95(1-6), pp.21-27.
- 1722 235. Batista, M.A., Nicoli, J.R., dos Santos Martins, F., Nogueira Machado, J.A., Esteves
1723 Arantes, R.M., Pacífico Quirino, I.E., Davisson Correia, M.I.T. and Cardoso, V.N., 2012.
1724 Pretreatment with citrulline improves gut barrier after intestinal obstruction in mice. *Journal*
1725 *of Parenteral and Enteral Nutrition*, 36(1), pp.69-76.
- 1726 236. Sukhotnik, I., Helou, H., Mogilner, J., Lurie, M., Bernsteyn, A., Coran, A.G. and Shiloni, E.,
1727 2005. Oral arginine improves intestinal recovery following ischemia-reperfusion injury in
1728 rat. *Pediatric surgery international*, 21(3), pp.191-196.
- 1729 237. Gou, L., Zhang, L., Yin, C., Jia, G., Yin, X., Zhuang, X., Xu, X. and Liu, Y., 2011. Protective
1730 effect of l-citrulline against acute gastric mucosal lesions induced by ischemia-reperfusion in
1731 rats. *Canadian journal of physiology and pharmacology*, 89(5), pp.317-327.
- 1732 238. Rubanyi, G.M., Ho, E.H., Cantor, E.H., Lumma, W.C. and Botelho, L.H.P., 1991.
1733 Cytoprotective function of nitric oxide: inactivation of superoxide radicals produced by
1734 human leukocytes. *Biochemical and biophysical research communications*, 181(3), pp.1392-
1735 1397.
- 1736 239. Kubes, P., Suzuki, M. and Granger, D.N., 1991. Nitric oxide: an endogenous modulator
1737 of leukocyte adhesion. *Proceedings of the National Academy of Sciences*, 88(11), pp.4651-
1738 4655.
- 1739 240. Beutheu, S., Ouelaa, W., Guérin, C., Belmonte, L., Aziz, M., Tennonne, N., Bôle-Feysot,
1740 C., Galas, L., Déchelotte, P. and Coëffier, M., 2014. Glutamine supplementation, but not
1741 combined glutamine and arginine supplementation, improves gut barrier function during
1742 chemotherapy-induced intestinal mucositis in rats. *Clinical nutrition*, 33(4), pp.694-701.

- 1743 241. Jones, A.M., Thompson, C., Wylie, L.J. and Vanhatalo, A., 2018. Dietary nitrate and
1744 physical performance. *Annual Review of Nutrition*, 38, pp.303-328.
- 1745 242. Bailey, S.J., Blackwell, J.R., Lord, T., Vanhatalo, A., Winyard, P.G. and Jones, A.M., 2015.
1746 L-citrulline supplementation improves O₂ uptake kinetics and high-intensity exercise
1747 performance in humans. *Journal of Applied Physiology*, 119(4), pp.385-395.
- 1748 243. Costa, K.A., Soares, A.D.N., Wanner, S.P., Santos, R.D.G.C.D., Fernandes, S.O.A., Martins,
1749 F.D.S., Nicoli, J.R., Coimbra, C.C. and Cardoso, V.N., 2013. L-arginine supplementation
1750 prevents increases in intestinal permeability and bacterial translocation in male Swiss mice
1751 subjected to physical exercise under environmental heat stress. *The Journal of*
1752 *nutrition*, 144(2), pp.218-223.
- 1753 244. McMahan, N.F., Leveritt, M.D. and Pavey, T.G., 2017. The effect of dietary nitrate
1754 supplementation on endurance exercise performance in healthy adults: a systematic review
1755 and meta-analysis. *Sports Medicine*, 47(4), pp.735-756.
- 1756 245. Kuennen, M., Jansen, L., Gillum, T., Granados, J., Castillo, W., Nabiyyar, A. and Christmas,
1757 K., 2015. Dietary nitrate reduces the O₂ cost of desert marching but elevates the rise in core
1758 temperature. *European journal of applied physiology*, 115(12), pp.2557-2569.
- 1759 246. McQuillan, J.A., Casadio, J.R., Dulson, D.K., Laursen, P.B. and Kilding, A.E., 2018. The
1760 effect of nitrate supplementation on cycling performance in the heat in well-trained
1761 cyclists. *International journal of sports physiology and performance*, 13(1), pp.50-56.
- 1762 247. Parvez, S., Malik, K.A., Ah Kang, S. and Kim, H.Y., 2006. Probiotics and their fermented
1763 food products are beneficial for health. *Journal of applied microbiology*, 100(6), pp.1171-
1764 1185.
- 1765 248. van Hemert, S., Verwer, J. and Schütz, B., 2013. Clinical studies evaluating effects of
1766 probiotics on parameters of intestinal barrier function. *Advances in Microbiology*, 3(2),
1767 p.212.
- 1768 249. Bron, P.A., Van Baarlen, P. and Kleerebezem, M., 2012. Emerging molecular insights into
1769 the interaction between probiotics and the host intestinal mucosa. *Nature Reviews*
1770 *Microbiology*, 10(1), p.66.
- 1771 250. Resta-Lenert, S. and Barrett, K.E., 2006. Probiotics and commensals reverse TNF- α -and
1772 IFN- γ -induced dysfunction in human intestinal epithelial cells. *Gastroenterology*, 130(3),
1773 pp.731-746.
- 1774 251. Hsieh, C.Y., Osaka, T., Moriyama, E., Date, Y., Kikuchi, J. and Tsuneda, S., 2015.
1775 Strengthening of the intestinal epithelial tight junction by *Bifidobacterium*
1776 *bifidum*. *Physiological reports*, 3(3).
- 1777 252. West, N.P., Pyne, D.B., Peake, J.M. and Cripps, A.W., 2009. Probiotics, immunity and
1778 exercise: a review. *Exerc Immunol Rev*, 15(107), p.e26.
- 1779 253. Pyne, D.B., West, N.P., Cox, A.J. and Cripps, A.W., 2015. Probiotics supplementation for
1780 athletes—clinical and physiological effects. *European journal of sport science*, 15(1), pp.63-72.

- 1781 254. Roberts, J., Suckling, C., Peedle, G., Murphy, J., Dawkins, T. and Roberts, M., 2016. An
1782 exploratory investigation of endotoxin levels in novice long distance triathletes, and the
1783 effects of a multi-strain probiotic/prebiotic, antioxidant intervention. *Nutrients*, 8(11), p.733.
- 1784 255. Carbuhn, A., Reynolds, S., Campbell, C., Bradford, L., Deckert, J., Kreutzer, A. and Fry, A.,
1785 2018. Effects of probiotic (*Bifidobacterium longum* 35624) supplementation on exercise
1786 performance, immune modulation, and cognitive outlook in Division I female
1787 swimmers. *Sports*, 6(4), p.116.
- 1788 256. Axelrod, C.L., Brennan, C.J., Cresci, G., Paul, D., Hull, M., Fealy, C.E. and Kirwan, J.P.,
1789 2019. UCC118 supplementation reduces exercise-induced gastrointestinal permeability and
1790 remodels the gut microbiome in healthy humans. *Physiological reports*, 7(22).
- 1791 257. Karl, J.P., Margolis, L.M., Madslie, E.H., Murphy, N.E., Castellani, J.W., Gundersen, Y.,
1792 Hoke, A.V., Levangie, M.W., Kumar, R., Chakraborty, N. and Gautam, A., 2017. Changes in
1793 intestinal microbiota composition and metabolism coincide with increased intestinal
1794 permeability in young adults under prolonged physiological stress. *American Journal of*
1795 *Physiology-Gastrointestinal and Liver Physiology*, 312(6), pp.G559-G571.
- 1796 258. De Vries, J.H., Hollman, P.C., Meyboom, S., Buysman, M.N., Zock, P.L., van Staveren,
1797 W.A. and Katan, M.B., 1998. Plasma concentrations and urinary excretion of the antioxidant
1798 flavonols quercetin and kaempferol as biomarkers for dietary intake. *The American journal*
1799 *of clinical nutrition*, 68(1), pp.60-65.
- 1800 259. Sukhotnik, I., Moati, D., Shaoul, R., Loberman, B., Pollak, Y. and Schwartz, B., 2018.
1801 Quercetin prevents small intestinal damage and enhances intestinal recovery during
1802 methotrexate-induced intestinal mucositis of rats. *Food & nutrition research*, 62.
- 1803 260. Amasheh, M., Schlichter, S., Amasheh, S., Mankertz, J., Zeitz, M., Fromm, M. and
1804 Schulzke, J.D., 2008. Quercetin enhances epithelial barrier function and increases claudin-4
1805 expression in Caco-2 cells. *The Journal of nutrition*, 138(6), pp.1067-1073.
- 1806 261. Suzuki, T. and Hara, H., 2009. Quercetin enhances intestinal barrier function through
1807 the assembly of zonula occludens-2, occludin, and claudin-1 and the expression of claudin-4
1808 in Caco-2 cells. *The Journal of nutrition*, 139(5), pp.965-974.
- 1809 262. Dokladny, K., Ye, D., Kennedy, J.C., Moseley, P.L. and Ma, T.Y., 2008. Cellular and
1810 molecular mechanisms of heat stress-induced up-regulation of occludin protein expression:
1811 regulatory role of heat shock factor-1. *The American journal of pathology*, 172(3), pp.659-
1812 670.
- 1813 263. Freedman, J.E., Parker Iii, C., Li, L., Perlman, J.A., Frei, B., Ivanov, V., Deak, L.R., Iafrazi,
1814 M.D. and Folts, J.D., 2001. Select flavonoids and whole juice from purple grapes inhibit
1815 platelet function and enhance nitric oxide release. *Circulation*, 103(23), pp.2792-2798.
- 1816 264. Oteiza, P.I., Fraga, C.G., Mills, D.A. and Taft, D.H., 2018. Flavonoids and the
1817 gastrointestinal tract: Local and systemic effects. *Molecular aspects of medicine*, 61, pp.41-
1818 49.

- 1819 265. Valenzano, M.C., DiGuilio, K., Mercado, J., Teter, M., To, J., Ferraro, B., Mixson, B.,
1820 Manley, I., Baker, V., Moore, B.A. and Wertheimer, J., 2015. Remodeling of tight junctions
1821 and enhancement of barrier integrity of the CACO-2 intestinal epithelial cell layer by
1822 micronutrients. *PloS one*, 10(7), p.e0133926.
- 1823 266. Hosokawa, N., Hirayoshi, K., Kudo, H., Takechi, H., Aoike, A., Kawai, K. and Nagata, K.,
1824 1992. Inhibition of the activation of heat shock factor in vivo and in vitro by
1825 flavonoids. *Molecular and Cellular Biology*, 12(8), pp.3490-3498.
- 1826 267. Dokladny, K., Wharton, W., Lobb, R., Ma, T.Y. and Moseley, P.L., 2006. Induction of
1827 physiological thermotolerance in MDCK monolayers: contribution of heat shock protein
1828 70. *Cell stress & chaperones*, 11(3), p.268.
- 1829 268. Sergent, T., Piront, N., Meurice, J., Toussaint, O. and Schneider, Y.J., 2010. Anti-
1830 inflammatory effects of dietary phenolic compounds in an in vitro model of inflamed human
1831 intestinal epithelium. *Chemico-Biological Interactions*, 188(3), pp.659-667.
- 1832 269. Knapik, J.J., Austin, K.G., Farina, E.K. and Lieberman, H.R., 2018. Dietary supplement use
1833 in a large, representative sample of the US armed forces. *Journal of the Academy of Nutrition
1834 and Dietetics*, 118(8), pp.1370-1388.
- 1835 270. Myburgh, K.H., 2014. Polyphenol supplementation: benefits for exercise performance
1836 or oxidative stress?. *Sports Medicine*, 44(1), pp.57-70.
- 1837 271. Nieman, D.C. and Mitmesser, S.H., 2017. Potential impact of nutrition on immune
1838 system recovery from heavy exertion: a metabolomics perspective. *Nutrients*, 9(5), p.513.
- 1839 272. Somerville, V., Bringans, C. and Braakhuis, A., 2017. Polyphenols and performance: A
1840 systematic review and meta-analysis. *Sports Medicine*, 47(8), pp.1589-1599.
- 1841 273. Szymanski, M.C., Gillum, T.L., Gould, L.M., Morin, D.S. and Kuennen, M.R., 2017. Short-
1842 term dietary curcumin supplementation reduces gastrointestinal barrier damage and
1843 physiological strain responses during exertional heat stress. *Journal of Applied
1844 Physiology*, 124(2), pp.330-340.
- 1845 274. Takei, M., 2012. Development of polaprezinc research. *Yakugaku zasshi: Journal of the
1846 Pharmaceutical Society of Japan*, 132(3), pp.271-277.
- 1847 275. Matsukura, T. and Tanaka, H., 2000. Applicability of Zinc Complex of L-Carnosine for
1848 Medical Use. *Biochemistry*, 65(7), pp.817-823.
- 1849 276. Mahmood, A., Fitzgerald, A.J., Marchbank, T., Ntatsaki, E., Murray, D., Ghosh, S. and
1850 Playford, R.J., 2007. Zinc carnosine, a health food supplement that stabilises small bowel
1851 integrity and stimulates gut repair processes. *Gut*, 56(2), pp.168-175.
- 1852 277. Roohani, N., Hurrell, R., Kelishadi, R. and Schulin, R., 2013. Zinc and its importance for
1853 human health: An integrative review. *Journal of Research in Medical Sciences*, 18(2), p.144.
- 1854 278. Sale, C., Artioli, G.G., Gualano, B., Saunders, B., Hobson, R.M. and Harris, R.C., 2013.
1855 Carnosine: from exercise performance to health. *Amino acids*, 44(6), pp.1477-1491.

- 1856 279. Watari, I., Oka, S., Tanaka, S., Aoyama, T., Imagawa, H., Shishido, T., Yoshida, S. and
1857 Chayama, K., 2013. Effectiveness of polaprezinc for low-dose aspirin-induced small-bowel
1858 mucosal injuries as evaluated by capsule endoscopy: a pilot randomized controlled
1859 study. *BMC gastroenterology*, 13(1), p.108.
- 1860 280. Omatsu, T., Naito, Y., Handa, O., Mizushima, K., Hayashi, N., Qin, Y., Harusato, A.,
1861 Hirata, I., Kishimoto, E., Okada, H. and Uchiyama, K., 2010. Reactive oxygen species-
1862 quenching and anti-apoptotic effect of polaprezinc on indomethacin-induced small intestinal
1863 epithelial cell injury. *Journal of gastroenterology*, 45(7), pp.692-702.
- 1864 281. Fujii, Y., Matura, T., Kai, M., Kawasaki, H. and Yamada, K., 2000. Protection by
1865 polaprezinc, an anti-ulcer drug, against indomethacin-induced apoptosis in rat gastric
1866 mucosal cells. *The Japanese Journal of Pharmacology*, 84(1), pp.63-70.
- 1867 282. Choi, H.S., Lim, J.Y., Chun, H.J., Lee, M., Kim, E.S., Keum, B., Seo, Y.S., Jeon, Y.T., Um,
1868 S.H., Lee, H.S. and Kim, C.D., 2013. The effect of polaprezinc on gastric mucosal protection in
1869 rats with ethanol-induced gastric mucosal damage: comparison study with rebamipide. *Life*
1870 *sciences*, 93(2-3), pp.69-77.
- 1871 283. Saunders, B., Elliott-Sale, K., Artioli, G.G., Swinton, P.A., Dolan, E., Roschel, H., Sale, C.
1872 and Gualano, B., 2017. β -alanine supplementation to improve exercise capacity and
1873 performance: a systematic review and meta-analysis. *Br J Sports Med*, 51(8), pp.658-669.
- 1874 284. Sakae, K. and Yanagisawa, H., 2014. Oral treatment of pressure ulcers with polaprezinc
1875 (zinc L-carnosine complex): 8-week open-label trial. *Biological trace element*
1876 *research*, 158(3), pp.280-288.
- 1877 285. Barbalho, S.M., Goulart, A.R., Quesada, K. and Bechara, M.D., 2016. Inflammatory
1878 bowel disease: can omega-3 fatty acids really help?. *Annals of gastroenterology*, 29(1),
1879 pp.37-43.
- 1880 286. Ashton, T., Young, I.S., Davison, G.W., Rowlands, C.C., McEneny, J., Van Blerk, C., Jones,
1881 E., Peters, J.R. and Jackson, S.K., 2003. Exercise-induced endotoxemia: the effect of ascorbic
1882 acid supplementation. *Free Radical Biology and Medicine*, 35(3), pp.284-291.
- 1883 287. Buchman, A.L., Killip, D., Ou, C.N., Rognerud, C.L., Pownall, H., Dennis, K. and Dunn, J.K.,
1884 1999. Short-term vitamin E supplementation before marathon running: a placebo-controlled
1885 trial. *Nutrition*, 15(4), pp.278-283.
- 1886 288. Raftery, T., Martineau, A.R., Greiller, C.L., Ghosh, S., McNamara, D., Bennett, K.,
1887 Meddings, J. and O'Sullivan, M., 2015. Effects of vitamin D supplementation on intestinal
1888 permeability, cathelicidin and disease markers in Crohn's disease: Results from a randomised
1889 double-blind placebo-controlled study. *United European Gastroenterology Journal*, 3(3),
1890 pp.294-302.
- 1891 289. Carlson, J. and Slavin, J., 2016. Health benefits of fibre, prebiotics and probiotics: A
1892 review of intestinal health and related health claims. *Quality Assurance and Safety of Crops*
1893 *& Foods*, 8(4), pp.539-554.

- 1894 290. Buchman, A.L., O'Brien, W., Ou, C.N., Rognerud, C., Alvarez, M., Dennis, K. and Ahn, C.,
1895 1999. The effect of arginine or glycine supplementation on gastrointestinal function, muscle
1896 injury, serum amino acid concentrations and performance during a marathon
1897 run. *International journal of sports medicine*, 20(05), pp.315-321.
- 1898 291. Snipe, R.M. and Costa, R.J., 2018. Does biological sex impact intestinal epithelial injury,
1899 small intestine permeability, gastrointestinal symptoms and systemic cytokine profile in
1900 response to exertional-heat stress?. *Journal of sports sciences*, 36(24), pp.2827-2835.
- 1901 292. Lambert, G.P., Murray, R., Eddy, D., Scott, W., Laird, R. and Gisolfi, C.V., 1999.
1902 INTESTINAL PERMEABILITY FOLLOWING THE 1998 IRONMAN TRIATHLON. *Medicine &*
1903 *Science in Sports & Exercise*, 31(5), p.S318.
- 1904 293. JanssenDuijghuijsen, L., Van Norren, K., Grefte, S., Koppelman, S., Lenaerts, K., Keijer, J.,
1905 Witkamp, R. and Wichers, H., 2017. Endurance exercise increases intestinal uptake of the
1906 peanut allergen Ara h 6 after peanut consumption in humans. *Nutrients*, 9(1), p.84.
- 1907 294. Nava, R.C., Zuhl, M.N., Moriarty, T.A., Amorim, F.T., Bourbeau, K.C., Welch, A.M.,
1908 McCormick, J.J., King, K.E. and Mermier, C.M., 2019. The effect of acute glutamine
1909 supplementation on markers of inflammation and fatigue during consecutive days of
1910 simulated wildland firefighting. *Journal of occupational and environmental medicine*, 61(2),
1911 pp.e33-e42.
- 1912 295. Lis, D., Stellingwerff, T., Kitic, C.K., Ahuja, K.D. and Fell, J., 2015. No effects of a short-
1913 term gluten-free diet on performance in nonceliac athletes. *Medicine and science in sports*
1914 *and exercise*, 47(12), pp.2563-2570.
- 1915 296. Kashima, H., Harada, N., Miyamoto, K., Fujimoto, M., Fujita, C., Endo, M.Y., Kobayashi,
1916 T., Miura, A. and Fukuba, Y., 2017. Timing of postexercise carbohydrate-protein
1917 supplementation: roles of gastrointestinal blood flow and mucosal cell damage on gastric
1918 emptying in humans. *Journal of Applied Physiology*, 123(3), pp.606-613.
- 1919 297. Antunes, B.M., Campos, E.Z., dos Santos, R.V.T., Rosa-Neto, J.C., Franchini, E., Bishop,
1920 N.C. and Lira, F.S., 2019. Anti-inflammatory response to acute exercise is related with
1921 intensity and physical fitness. *Journal of cellular biochemistry*, 120(4), pp.5333-5342.
- 1922 298. Guy, J.H., Edwards, A.M., Miller, C.M., Deakin, G.B. and Pyne, D.B., 2017. Short-term
1923 reliability of inflammatory mediators and response to exercise in the heat. *Journal of sports*
1924 *sciences*, 35(16), pp.1622-1628.
- 1925 299. Guy, J.H., Pyne, D.B., Deakin, G.B., Miller, C.M. and Edwards, A.M., 2016. Acclimation
1926 training improves endurance cycling performance in the heat without inducing
1927 endotoxemia. *Frontiers in physiology*, 7, p.318.
- 1928 300. Machado, P., Caris, A., Santos, S., Silva, E., Oyama, L., Tufik, S. and Santos, R., 2017.
1929 Moderate exercise increases endotoxin concentration in hypoxia but not in normoxia: A
1930 controlled clinical trial. *Medicine*, 96(4), p.e5504.

1931 301. Stuempfle, K.J., Valentino, T., Hew-Butler, T., Hecht, F.M. and Hoffman, M.D., 2016.
1932 Nausea is associated with endotoxemia during a 161-km ultramarathon. *Journal of sports*
1933 *sciences*, 34(17), pp.1662-1668.

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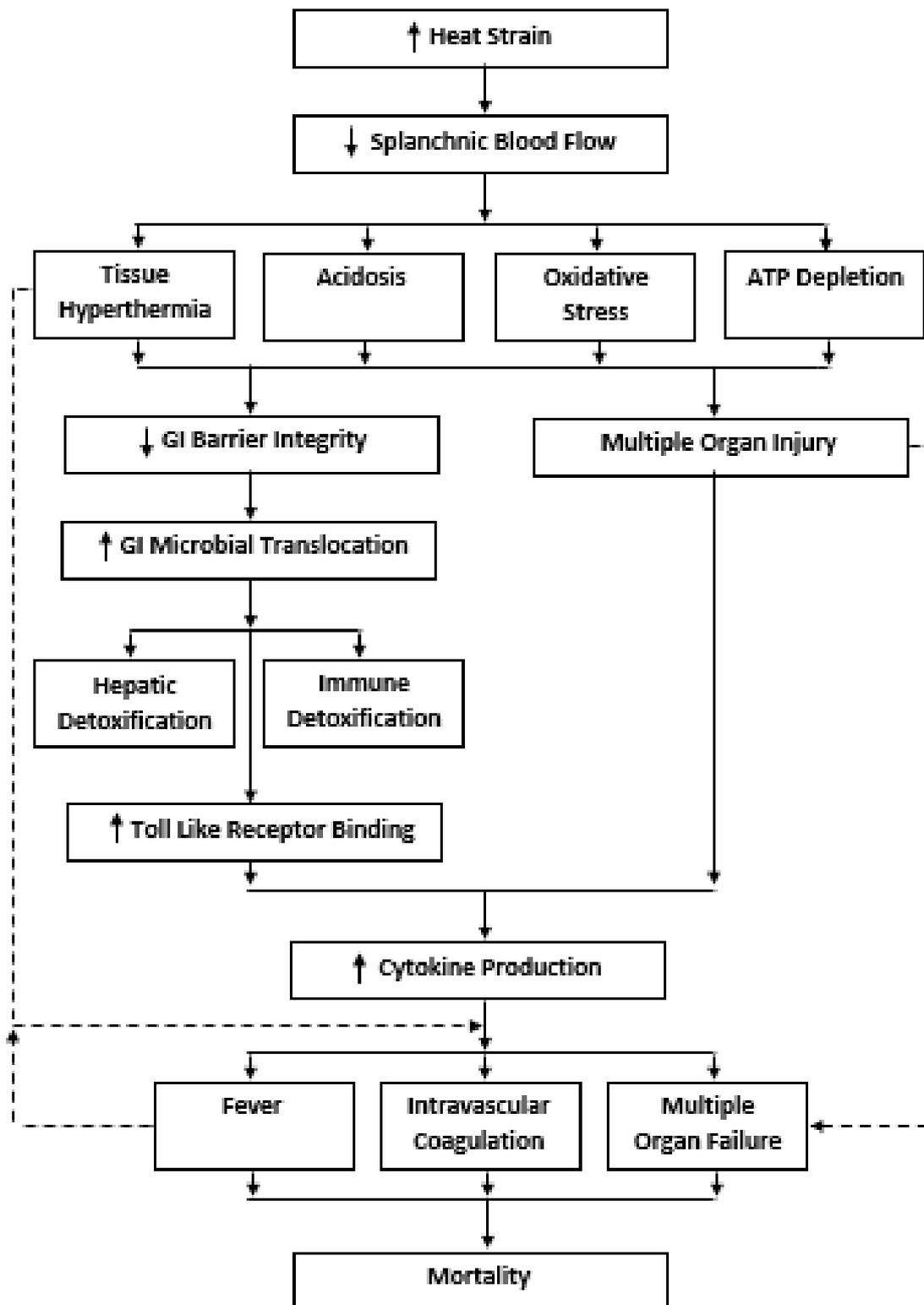
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1955 **Figure 1.** The gastrointestinal paradigm of exertional heat stroke

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

Technique	Sample	Method	Site	Limitations
Active Techniques				
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.
Passive Techniques				
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), α -Glutathione s-Transferase (α -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.

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

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

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

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

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

1962 LT = Low-trained (35-49 ml·kg·min⁻¹ VO_{2max}); MT = Moderate-trained (50-59 ml·kg·min⁻¹
1963 VO_{2max}); HT = High-trained (60+ ml·kg·min⁻¹ VO_{2max}). 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 _{Core} (°C)	Mean HR (bpm)	FABP2 (Δ pre-to- post exercise)
Janssen-Duijghuijsen et al. [109]	11 male (HT)	90 minutes cycling at 50% watt _{max} (fed) in T _{amb} not reported following a “sleep-low” glycogen depletion regime	N/A	N/A	~90 pg·ml ⁻¹ (~65%) ^c
Kartaram et al. (Part A) [129]	15 male (MT)	60 minutes cycling at 50% watt _{max} (fed) in T _{amb} not reported	N/A	N/A	~50 pg·ml ⁻¹ (~10%) ^{ns}
Lee and Thake (Part A) [128]	7 male (MT)	60 minutes cycling at 50% VO _{2max} (fed) in T _{amb} 18°C (35% RH) on day one of temperate acclimation	37.9	133	28 pg·ml ⁻¹ (8%) ^{ns,c}
Trommelen et al. [130]	10 male (HT)	180 minutes cycling at 50% watt _{max} (fasted) in T _{amb} 18-22°C (55-65% RH)	N/A	N/A	N/A pg·ml ⁻¹ (20%) ^{ns,c}
Edinburgh et al. (Part A) [180]	12 male (MT)	60 minutes cycling at 50% VO _{2max} (fed) in T _{amb} 18°C (35% RH)	N/A	N/A	70 pg·ml ⁻¹ (34%) ^s
Edinburgh et al. (Part B) [180]	12 male (MT)	60 minutes cycling at 50% VO _{2max} (fasted) in T _{amb} 18°C (35% RH)	N/A	N/A	88 pg·ml ⁻¹ (20%) ^s
Osborne et al. (Part A) [133]	8 male (MT-HT)	30 minutes cycling at 50/70% Watt _{max} , then 30 minutes at 50% watt _{max} (fasted) in T _{amb} 20°C (55% RH)	38.5	139	138 pg·ml ⁻¹ (29%) ^{ns}
Salvador et al. 2019 [181]	12 male (MT-HT)	120 minutes cycling at 60% VO _{2max} (fed) then 30-40 minutes (20 km) time trial in T _{amb} not reported	37.9	~168	N/A pg·ml ⁻¹ (~50%) ^{s,c}
van Wijck et al. [127]	10 male (MT)	60 minutes cycling at 70% watt _{max} (fasted) in T _{amb} not reported	N/A	N/A	153 pg·ml ⁻¹ (72%) ^s
Nava et al. [294]	7 male and 4 female (LT-MT)	56 minutes mixed intensity (~55% VO _{2max}) discontinuous firefighting exercises (fed) in T _{amb} 38°C (35% RH) on day one of two	38.7	~161	~160 pg·ml ⁻¹ (23%) ^{ns,c}
Van Wijck et al. [124]	9 male (MT)	60 minutes cycling at 70% watt _{max} (fasted) in T _{amb} not reported	N/A	N/A	179 pg·ml ⁻¹ (61%) ^s
Lee et al. (Part C) [128]	7 male (MT)	60 minutes cycling at 50% VO _{2max} (fed) in T _{amb} 18°C (35% RH) and FiO ₂ = 0.14 on day one of hypoxic acclimation	38.2	149	193 pg·ml ⁻¹ (43%) ^{s,c}
Lis et al. [295]	13 male and female (MT)	45 minutes cycling at 70% watt _{max} and 15 min cycling time trial (fed) in 20°C (40% RH)	N/A	168	210 pg·ml ⁻¹ (223%) ^{s,c}
Pugh et al. [148]	10 male (MT)	60 minutes at 70% VO _{2max} running (fasted) in T _{amb} 30°C (4-45% RH)	38.5	82.5% of HR max	250 pg·ml ⁻¹ (71%) ^{s,c}
Snipe et al. (Part A) [115, 125]	6 male and 4 female (MT)	120 minutes running at 60% VO _{2max} (fed) in T _{amb} 22°C (44% RH)	38.5	~150	274 pg·ml ⁻¹ (127%) ^s
Sheahen et al. (Part A) [136]	12 male (MT)	45 minutes running at 70% VO _{2max} (fasted) in T _{amb} 20°C (40% RH)	38.2	165	281 pg·ml ⁻¹ (49%) ^s

Lee et al. (Part B) [128]	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%) ^{s,c}
Morrison et al. (Part B) [152]	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%) ^{s,c}
Barberio et al. [72]	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%) ^{s,c}
Hill et al. [134]	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%) ^{ns,c}
van Wijck et al. [86]	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%) ^s
Kashima et al. [296]	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%) ^s
Pugh et al. [88]	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%) ^s
March et al. [225]	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%) ^{s,c}
Janssen-Duijghuijsen et al. [293]	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%) ^{s,c}
Sheahen et al. (Part B) [136]	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%) ^s
Costa et al. [135]	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%) ^{ns,c}
Osborne et al. [213]	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%) ^{s,c}
Kartaram et al. (Part B) [129]	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%) ^s
Kartaram et al. (Part C) [129]	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%) ^s
McKenna et al. [226]	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%) ^{s,c}
Karhu et al. [132]	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%) ^s
Snipe and Costa [137]	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%) ^{s,c}
Snipe et al. (Part B) [125]	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%)

Hill et al. [134]	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%) ^{ns,c}
Osborne et al. (Part B) [133]	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%) ^s
Szymanski et al. [273]	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%) ^{s,c}
Morrison et al. (Part A) [152]	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%) ^{s,c}
Snipe et al. [193]	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%) ^{s,c}
Snipe et al. (Part B) [115]	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%) ^s
Pugh et al. [148]	10 male and 2 female (MT)	42.4 km track marathon (247 ± 47 minutes; fed) in T_{amb} 16-17°C (N/A RH)	N/A	~160	1246 $pg \cdot ml^{-1}$ (371%) ^{s,c}
March et al. [105]	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%) ^{s,c}
Snipe and Costa [291]	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%) ^s
Snipe et al. [291]	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%) ^s
Jonvik et al. [131]	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%) ^s
Gaskell et al. [147]	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%) ^{s,c}

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

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1991

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

Reference	Subjects	Exercise Protocol	Peak T _{core} (°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	¹⁴¹	-3 pg·ml ⁻¹ (-3%) ^{ns}
Yeh et al. (Part B) [138]	15 male and 1 female (LT)	60 minutes running at 70% VO _{2max} (fed) in T _{amb} 22°C (66% RH)	38.4	~145	-1.1 pg·ml ⁻¹ (-10%) ^{ns}
Zuhl et al. [116]	2 male and 5 female (LT/MT)	60 minutes running at 70% VO _{2max} (fasted) in T _{amb} 30°C (12-20% RH)	39.5	N/A	-0.2 pg·ml ⁻¹ (-7%) ^{ns, c}
Osborne et al. (Part A) [133]	8 Male (MT-HT)	30 minutes cycling at 50/70% Watt _{max} , then 30 minutes at 50% watt _{max} (fasted) in T _{amb} 20°C (55% RH)	38.5	165	0.1 pg·ml ⁻¹ (1%) ^{ns, #}
Osborne et al. (Part B) [133]	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	182	0.2 pg·ml ⁻¹ (1%) ^{s, #}
Karhu et al. [132]	17 males (MT-HT)	90 minutes running at 80% of best 10 km race time (fed) in T _{amb} not reported	N/A	N/A	0.3 pg·ml ⁻¹ (~ 1%) ^{ns, c}
Kuennen et al. [143]	8 male (MT)	100 minutes walking (6.3 km·h ⁻¹) at 50% VO _{2max} (fasted) in T _{amb} 46.5°C (20% RH)	39.3	N/A	~0.5 pg·ml ⁻¹ (10%) ^{ns, c}
Ng et al. [73]	30 males (HT)	Half-marathon (fed) in T _{amb} 27°C (84% RH)	40.7	172	0.6 pg·ml ⁻¹ (32%) ^s
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 _{amb} 9-32°C	N/A	N/A	1.7 pg·ml ⁻¹ (666%) ^s
Guy et al. [298]	20 male (LT-MT)	10 minutes cycling at 50%, 60%, and 70% watt _{max} , then 5 km (fasted) in T _{amb} 35°C (70% RH)	38.9	160	2 pg·ml ⁻¹ (9%) ^{ns}
Selkirk et al. (Part B) [126]	12 male (HT)	To fatigue (~122 minutes) uphill walk at 4.5 km·h ⁻¹ (fasted) in T _{amb} 40°C (30% RH)	39.7	156	~3 pg·ml ⁻¹ (200%) ^s
Shing et al. [146]	10 male (HT)	~33 minutes running to fatigue at 80% VE (fed) in T _{amb} 35°C (40% RH)	39.4	172	4 pg·ml ⁻¹ (15%) ^s
Snipe et al. (Part A) [115, 125]	6 male and 4 female (MT)	120 minutes running at 60% VO _{2max} (fed) in T _{amb} 22°C (44% RH)	38.5	~150	4.1 pg·ml ⁻¹ (5%) ^{ns}
Yeh et al. (Part B) [138]	15 male and 1 female (LT)	60 minutes running at 70% VO _{2max} (fed) in T _{amb} 33°C (50% RH)	39.3	~145	5 pg·ml ⁻¹ (54%) ^s
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	¹⁶²	5 pg·ml ⁻¹ (7%) ^{ns}

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

Moncada-Jiminez et al. [195]	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 ~0.59 µg·ml ⁻¹ (22%) ^{s, c}
Selkirk et al. (Part B) [146]	12 male (LT-MT)	To fatigue (~106 minutes) uphill walk at 4.5 km·h ⁻¹ (fasted) in T _{amb} 40°C (30% RH)	39.7	156	LBP ~1.5 µg·ml ⁻¹ (15%) ^s
Jonvik et al. [131]	16 male (HT)	60 minutes cycling at 70% watt _{max} (fasted) in T _{amb} not reported	N/A	N/A	LBP 1.6 µg·ml ⁻¹ (13%) ^s
Costa et al. [135]	11 male (MT-HT)	120 minutes running at 70% VO _{2max} (fed) in T _{amb} 25°C (35% RH)	N/A	148	sCD14-ST 0.05 µg·ml ⁻¹ (N/A%) ^{ns, c}
Gaskell et al. [147]	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	sCD14-ST 0.1 µg·ml ⁻¹ (N/A%) ^{s, c}
Stuempfle et al. [301]	15 male and 5 female (MT)	161-km ultramarathon (26.8 ± 2.4 hours; fed) in T _{amb} 0-30°C (N/A RH)	38.3	N/A	sCD14-ST 0.6 µg·ml ⁻¹ (63%) ^s
Pugh et al. [148]	10 male and 2 female (MT)	42.4 km track marathon (4.1 ± 0.8 hours; fed) in T _{amb} 16-17°C (N/A RH)	N/A	~160	sCD14-ST 5.4 µg·ml ⁻¹ (164%) ^{s, c}

1992 LT = Low-trained (35-49 ml·kg·min⁻¹ VO_{2max}); MT = Moderate-trained (50-59 ml·kg·min⁻¹
1993 VO_{2max}); HT = High-trained (60+ ml·kg·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 EU·ml⁻¹ to pg·ml⁻¹ through standard conversions (1 EU·ml⁻¹ = 100 pg·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

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

2010