

## **Do sex-differences in physiology confer a female advantage in ultra-endurance sport?**

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**Funding Disclosures/conflicts of interest:** The authors declare no conflicts of interest and do not have any financial disclosures.

1 **ABSTRACT**

2 Ultra-endurance has been defined as any exercise bout that exceeds 6 h. A number of  
3 exceptional, record-breaking performances by female athletes in ultra-endurance sport has  
4 roused speculation that they might be predisposed to success in such events. Indeed, while  
5 the male-to-female performance gap in traditional endurance sport (e.g., marathon) remains  
6 at ~10%, the disparity in ultra-endurance competition has been reported as low as 4% despite  
7 the markedly lower number of female participants. Moreover, females generally outperform  
8 males in extreme-endurance swimming. The issue is complex, however, with many sports-  
9 specific considerations and caveats. This review summarizes the sex-based differences in  
10 physiological functions and draws attention to those which likely determine success in extreme  
11 exercise endeavors. The aim is to provide a balanced discussion of the female versus male  
12 predisposition to ultra-endurance sport. Herein, we discuss sex-based differences in muscle  
13 morphology and fatigability, respiratory-neuromechanical function, substrate utilization,  
14 oxygen utilization, gastrointestinal structure and function, and hormonal control. The literature  
15 indicates that while females exhibit numerous phenotypes that would be expected to confer  
16 an advantage in ultra-endurance competition (e.g., greater fatigue-resistance, greater  
17 substrate efficiency, and lower energetic requirements), they also exhibit several  
18 characteristics that unequivocally impinge on performance (e.g., lower O<sub>2</sub>-carrying capacity,  
19 increased prevalence of GI distress, and sex-hormone effects on cellular function/ injury risk).  
20 Crucially, the advantageous traits may only manifest as ergogenic in the extreme endurance  
21 events which, paradoxically, are the races that females less often contest. The title question  
22 should be revisited in the coming years when/if the number of female participants increases.

23

24 **KEY POINTS**

- 25 • Females exhibit numerous physiological characteristics that would be expected to confer  
26 an advantage in ultra-endurance competition. However, these traits may only manifest in  
27 the extreme distance events that females less often contest
- 28 • Several aspects of female physiology unequivocally inhibit performance making it unlikely  
29 that the fastest females will surpass the fastest males in this sport
- 30 • More direct physiological comparisons between male and female ultra-endurance  
31 athletes are needed, particularly when/if female participation numbers increase

## 32 1.0 INTRODUCTION

33 A 1992 correspondence published in the journal *Nature* posed the question ‘*Will women soon*  
34 *outrun men?*’ The analysis of distance-running records throughout the 1900s revealed an  
35 essentially linear chronological increase in mean running velocity ( $\bar{v}$ -slope), which was  
36 considerably steeper in the women’s marathon relative to the men’s (~37.8 vs. 9.2 m[insert  
37 raised dot]min<sup>-1</sup>[insert raised dot]decade<sup>-1</sup>) [1]. From this historical trend, Whipp and Ward  
38 calculated that the intersection for the men’s and women’s marathon would occur in the late  
39 1990s [1]. Although linear models have accurately described performance trends in ultra-  
40 distance swimming [2], their utility predicting the “gender” gap in other sports has been  
41 criticized on the basis that athletic adaptation and performance rarely, if ever, follow a linear  
42 progression [3]. In 1989, using a non-linear (hyperbolic) model, Peronnet *et al.* calculated a  
43 ~10% disparity between male and female running performances, owing primarily to greater  
44 maximal aerobic capacities ( $\dot{V}O_2\text{max}$ ) in the former. The model also predicted that males  
45 would retain a biological distance-running advantage well into the future [4]. In point of fact, a  
46 contemporary analysis of ~92,000 marathon finishes revealed a ~10% discrepancy between  
47 non-elite male and female finish times (males = 4 h 28 min ± 53 min; females = 4 h 54 min ±  
48 52 min; [5]). Thus, if females are to further diminish the endurance performance gap, it is most  
49 likely in those contests which depend less on maximal aerobic capacities.

50 Participation in ultra-endurance sport (which has been defined as an exercise bout that  
51 exceeds 6 h; [6]) has steadily increased over the last 30 years [7,8]. Success in these events  
52 is determined by a complex interplay among various factors, including: oxidative capacity, the  
53 energy cost of locomotion, substrate efficiency, fatigue-resistance and musculoskeletal  
54 conditioning, race nutrition, gastrointestinal (GI) function, age/experience, pain management,  
55 decision-making, and motivation and psychological disposition [9–15]. Furthermore, extreme  
56 endurance exercise evokes considerable perturbations in respiratory, neuromuscular,  
57 cardiovascular, digestive, and immune functions [12,13,16,17]. Accordingly, the most  
58 successful competitors are those who not only exhibit the most diverse range of ergogenic  
59 attributes, but who also best endure the high training volumes and extreme physiological strain  
60 of participation.

61 Males and females compete side-by-side in ultra-endurance sport. Males are generally  
62 faster than females over any given distance [2,18,19], but the data may be confounded by the  
63 considerably lower number of female participants, particularly in the very long-distance races.  
64 For instance, while modern marathons comprise fairly equal numbers of males and females  
65 (54% and 46%, respectively; [20]), only 20% of ultra-marathon finishes since the 1970s have  
66 been accomplished by females [7,18]. In ultra-distance cycling (Race Across America;  
67 RAAM), females comprised only ~11% of finishers between 1982 - 2011 [19]. Notwithstanding,  
68 some have calculated the performance gap to be as low as 4% in ultra-marathon [21], 6% in

69 ultra-distance open-water swimming [2], and negligible in cycling events of >200 miles [22]. In  
70 rare instances (yet, more often in ultra-endurance events than in shorter races) females may  
71 surpass their male counterparts [23]. Pertinently, the performance disparity between males  
72 and females is generally smallest in those events of greatest duration [19,21,24], and in those  
73 races with the highest number of female contestants [18,25]. At present, it is unclear what  
74 physical/physiological attributes underpin female ultra-endurance performance, and whether  
75 females might surpass males in this sport should their participation numbers equalize.

76 In recent years, these unknowns have been deliberated *ad nauseam* in the mainstream  
77 media [26–32], but while each publication has argued that females may outperform males in  
78 ultra-endurance sport, most have only speculated on the mechanisms, or provided cursory  
79 overviews of the empirical/published data. Thus, to address the title question, this paper will  
80 review the sex-mediated differences in human physiological function, and draw attention to  
81 those attributes which facilitate or impinge on female success in extreme duration exercise.  
82 The aim is to provide a balanced discussion of the female versus male physiological  
83 propensity for ultra-endurance sport.

84

## 85 **1.1 Performance Trends**

86 It has been argued that the disproportionate improvement in women's endurance performance  
87 in recent decades is attributable largely to sociocultural reform [33]. Women were prohibited  
88 from competing at the first modern Olympic Games in 1896, whereas women comprised ~36%  
89 of athletes at the Olympic Games a century later [34]. Thus, while it is unequivocal that  
90 success in ultra-endurance competition has a strong biological component, the performance  
91 trends may partially reflect factors such as greater participation and training opportunities. The  
92 published competition data are complex and difficult to interpret owing to the variety of sports  
93 examined, the considerable range in distances/durations, age-group categories, and varying  
94 participation numbers. Nevertheless, to contextualize the forthcoming discussions on  
95 physiological differences, what follows is a summary of the trends in male versus female ultra-  
96 endurance performance.

97 When viewed in its entirety, the data show that males generally outperform females in  
98 most sports, irrespective of distance, although the range in the performance disparity is large  
99 (0 – 17%) and there are several notable exceptions. In an analysis of world-record running  
100 performances ranging from 100 m to 200 km, males were on average 12.4% faster than  
101 females [35]. Moreover, in 24-h ultra-marathon, a gap of ~17% was reported between the  
102 annual fastest male and female finishers, ~11% for the annual 10 fastest, and ~14% for the  
103 annual 100 fastest [24]. These data are likely confounded by the lower numbers of female  
104 contestants. Studies that account for the participation disparity show a slightly diminished  
105 performance gap. For example, in a multiple linear regression analysis of >93,000 ultra-

106 marathon finishes between 1975 and 2013 (across the range of distances), the sex difference  
107 in performance was generally <10%, and the discrepancy in finish time was lowest in events  
108 where females participated in greater numbers [18].

109 The data also indicate that the magnitude of the male-to-female performance  
110 discrepancy is influenced by sport, distance, and age category. For instance, females have  
111 reduced the performance gap to less than 10% in ultra-endurance (Ironman) triathlon, and to  
112 just ~7% in the marathon stage of the event [36]. In terms of race distance, the sex difference  
113 in running speed for the fastest ever women and men was higher in 50 km (~15%) relative to  
114 100 km (5.0%) [37]. Moreover, in a study of ~13,000 cycling races, males were generally faster  
115 than females in events of 100 and 200 miles, but no difference was found in the 400- and 500-  
116 mile races [22]. Others make similar observations of a diminished performance disparity over  
117 longer distances in endurance running [38]. From 1977 to 2012, the sex-difference in 24-hour  
118 ultra-marathon was as low as  $4.6 \pm 0.5\%$  for all women and men [24], with other reports of a  
119 similar difference (~4% over 100 miles) in footraces up to 2017 [21]. Interestingly, although  
120 the difference in running speed between the fastest males and females over 100 miles has  
121 been reported as ~17% [39], the decrease in the sex difference observed for 50 and 100-mile  
122 footraces suggests that females are reducing the performance gap [39]. With respect to age  
123 categories, the difference in average cycling speed between men and women, across all race  
124 distances, decreased with increasing age [22], and a recent ultra-marathon analysis similarly  
125 showed that sex differences in performance were attenuated with increasing distance and age  
126 [21].

127 To account for absolute differences in athlete ability, several studies have compared  
128 ultra-marathon performances between males and females whose race times had been  
129 matched over a given distance. One study concluded that equivalent performances were  
130 retained in longer races, and two studies showed the opposite. Specifically, Hoffman  
131 examined race results over three distances (50, 80, and 161-km) between 1990 and 2007,  
132 finding that females and males who were time-matched for 50-km performed similarly in  
133 running races of 80- and 161-km [40]. By contrast, a study by Bam *et al.* [23] compared the  
134 fastest male and female running speeds over distances ranging from 5 – 90 km, and showed  
135 that men were quicker over 5 – 42.2 km but not over 90 km (mean velocity = 2.8 vs. 2.9  
136 m[insert raised dot]s<sup>-1</sup>). Additionally, females with marathon times equivalent to males have  
137 been shown to produce significantly quicker times in a 90-km ultra-marathon [41]. The notion  
138 that female endurance runners may be closing the gap to males in longer distance/duration  
139 races is supported by a recent unpublished analysis of trends in ultra-marathon running over  
140 the last 23 y, which showed that females were 0.6% faster than males in races >195 miles  
141 [42].

142 Finally, performances in ultra-distance swimming appear paradoxical to the trend,  
143 showing a general female dominance. Indeed, while in 10-km open-water swimming the  
144 annual fastest males were ~6% quicker than the fastest females [2], the top 20 females in  
145 extreme-endurance competition (46 km) were ~12 – 14% faster than their male counterparts  
146 [43]. This observation does not appear anomalous. A recent review assessing male and  
147 female performances in several extreme-endurance, open-water swimming events, showed  
148 that females were on average 0.06 km·h<sup>-1</sup> faster than males [44]. Female dominance in ultra-  
149 distance swimming, and the possible explanations, are discussed later.

150 When taken collectively, the data suggest that males generally outperform females in  
151 most ultra-endurance events and over most distances, with the exception of extreme-distance  
152 swimming. However, when scrutinizing the performance trends, the disparity is generally  
153 smallest in very long-distance races, and when there is a relatively greater number of female  
154 participants.

155

## 156 **2.0 PHYSIOLOGICAL CONSIDERATIONS**

157 The following discussion summarizes the sex-based differences in physiological functions,  
158 specifically those which are mostly relevant to ultra-endurance performance. Much of the  
159 literature has erroneously employed the terms “sex” and “gender” interchangeably. For clarity,  
160 a brief description of these terms, and how they will be used henceforth, is warranted.  
161 According to the National Institute of Health (NIH) [45] and the Canadian Institute of Health  
162 Research (CIHR) [46], “sex” is a biological constituent which comprises the genetic  
163 complement of chromosomes, including cellular and molecular differences [47]. By contrast,  
164 “gender” has been described as a social (rather than a biological) construct which varies with  
165 the roles, norms and values of a given society or era [48]. It has been suggested that because  
166 sex is reflected physiologically, the terms “male” and “female” should be employed when  
167 describing the sex of human subjects or when referring to other sex-related  
168 biological/physiological factors [49]. Accordingly, the term “sex-based differences” and the  
169 nouns “male” and “female” will be employed throughout this manuscript, except when referring  
170 to pre-defined race categories (e.g., the women’s marathon).

171

### 172 **2.1 Muscle Morphology and Fatigability**

173 Fatigue can be defined as a disabling symptom in which physical and cognitive function is  
174 limited by interactions between *perceived* fatigability and *performance* fatigability [50]. The  
175 latter of these, also known as neuromuscular fatigue (NMF), results from diminished voluntary  
176 activation (central component) and/or contractile function (peripheral component) [51]. We  
177 presently focus on the sex-differences in acute NMF, and how it might mediate performance  
178 in ultra-endurance competition. In controlled studies, females generally exhibit greater fatigue

179 resistance than males [52,53]. Furthermore, in a detailed review of sex differences in  
180 fatigability, Hunter *et al.* made two specific observations: (i) females typically outperform males  
181 during exercise performed at submaximal intensities; and (ii) the magnitude of the difference  
182 is attenuated as contraction intensity increases [52].

183 As aforementioned, the sex-based differences in fatigue have been assessed in ultra-  
184 marathons of up to 90 km, showing equivocal results [23,40,41]. However, a more  
185 comprehensive exploration requires the objective assessment of fatigue using electrical  
186 and/or magnetic nerve stimulation to artificially stimulate the locomotor muscles. Several  
187 studies have made such assessments following 24-h treadmill running [54], field-based ultra-  
188 marathon [55], and ultra-distance road cycling [56]. Nevertheless, a paucity of data in females  
189 - owing to the low number of female ultra-endurance athletes - makes a direct male/female  
190 comparison problematic. To the best of our knowledge, only one study has examined sex  
191 differences in NMF following a bout of ultra-endurance exercise. Temesi *et al.* used  
192 superimposed transcranial magnetic stimulation and peripheral nerve stimulation to assess  
193 contractile fatigue in males and females matched by relative performance level [57]. After a  
194 110-km ultra-marathon with a large cumulative ascent (Ultra-Trail du Mont-Blanc®, Alps) the  
195 authors showed that: (i) males exhibited greater peripheral fatigue in the plantar flexors; (ii)  
196 the magnitude of central fatigue in the plantar flexors and knee extensors was similar between  
197 sexes; and (iii) there were no between-sex differences in changes in corticospinal excitability  
198 or inhibition. Thus, while there were no overt differences in central fatigue between males and  
199 females, the latter exhibited less peripheral fatigue following the race. There are several  
200 mechanisms that may underpin the potential disparity in male/female muscle fatigability,  
201 including sex-differences in muscle fiber type, muscle mass, and neuromuscular control [52]  
202 (see Fig. 1).

203 **2.1.1 Muscle fiber type.** Human skeletal muscle fibers are classified as oxidative type-  
204 I (slow-twitch), oxidative type-II and glycolytic type-II (fast-twitch) [58]. Type-I fibers are more  
205 fatigue-resistant, partially owing to a greater myoglobin/mitochondrial content [59]. In an  
206 analysis of mRNA in male and female lower-limbs, type-I fibers accounted for 44% of the total  
207 biopsy area in females but only 36% in males [60]. Moreover, of the four myosin-heavy chains  
208 (MyHC) which dominate gene expression in adult mammalian skeletal muscle, females  
209 express ~35% more type-I MYH mRNA (those that are smaller and of a more oxidative  
210 phenotype) when compared to males who express more type-II MYH mRNA (those that are  
211 larger and richer in glycolytic enzymes) [61]. The greater proportion of type-I fibers in females  
212 is associated with greater vasodilatory capacity [62] and capillarization [63]. Pertinent to the  
213 present discussion, individual fibers are 'typed' by a particular isoform which determines  
214 characteristics like contractile velocity and enzymatic makeup [59] (Table 1). Thus, the greater  
215 relative distribution of slow-twitch fibers in females may partially explain their greater

216 contractile fatigue-resistance compared to males; although speculative, this offers a  
217 compelling argument for a sex-based physiological predisposition for ultra-endurance  
218 performance.

219

220 ***\*Insert Table 1\****

221

222 **2.1.2 Muscle mass and strength.** As is the case for age-related discrepancies in  
223 muscle fatigue, muscle mass and strength may partially explain the sex-related differences.  
224 Over 3,000 genes are differentially expressed in male versus female skeletal muscles (e.g.  
225 *GRB10* and *ACVR2B*) [61] and largely mediate sexual dimorphism in muscularity and  
226 strength, in addition to interactions among sex-specific hormones (see *2.4 Endocrine*  
227 *Function*). It is the greater fiber diameter in males, rather than fiber number, that results in  
228 muscle mass differences [64]. Pertinently, stronger muscles exert higher intramuscular  
229 pressures onto the feed arteries, thereby restricting blood flow and rendering them more  
230 fatigable during submaximal isometric exercise [52,65]. Subsequently, the attributes that  
231 confer males an advantage in strength- and power-based sports, may be a potential  
232 disadvantage in events of extreme endurance in which peripheral NMF is an important  
233 determinant.

234 **2.1.3 Central command.** The greater relative fatigability observed in males has been  
235 associated with greater central deficits in motor output [66,67], although it should be noted  
236 that these findings were made largely during maximal efforts and may not extend to  
237 submaximal tasks or sustained dynamic contractions. One explanation for the smaller deficits  
238 in female central motor output is a lesser accumulation of anaerobic metabolites during  
239 sustained, submaximal exercise (owing to more oxidative fibers), resulting in attenuated type-  
240 III and IV muscle afferent feedback; i.e., less inhibitory inputs to the motoneuronal pool.  
241 Although this may evoke less subsequent impairment of voluntary activation, this is considered  
242 an unlikely mechanism to explain central fatigue in ultra-marathon [68]. Given that ultra-  
243 marathons, particularly those contested on trail or mountainous terrain, encompass long  
244 downhill sections and exacerbated eccentric contractions in lower-limb extensors, it is worth  
245 examining sex differences in maximal force reduction after repeated lengthening contractions.  
246 The literature on this topic is somewhat equivocal: animal studies suggest that females are  
247 more resistant to muscle damage, while human studies suggest that females exhibit greater  
248 force decline when compared to males following eccentric contractions [52]. Thus, no firm  
249 conclusions can be made at this stage.

250 When interpreting the data on NMF, an important consideration is that the magnitude  
251 and prevalence of fatigue is task-dependent; i.e., different neuromuscular sites will be stressed  
252 when the requirements of the task are altered, and the stress on these sites can differ for



253 males and females [52]. As such, while females may exhibit less muscle fatigue than males  
254 during maximal voluntary (isometric) contractions [69], such localized responses may be of  
255 little relevance to dynamic, whole-body activities [70] including ultra-endurance exercise. The  
256 greater muscle mass involved in such activities evokes greater demands on cardiorespiratory  
257 and central nervous systems (e.g., greater afferent feedback and central drive), resulting in  
258 lower end-exercise impairments in contractile function [71] and, more generally, different NMF  
259 etiology compared to isolated exercises. In studies evaluating fatigue responses during  
260 dynamic, submaximal exercise, sex differences in fatigability are less consistent [72–74].

261 Accordingly, while females exhibit various characteristics that associate with better  
262 fatigue resistance, supported by data from nerve stimulation studies [57], more research is  
263 needed to compare the phenomenon directly between males and females during and following  
264 ultra-endurance exercise. It is also likely that psychological/sociological factors (e.g.,  
265 competitiveness and risk-taking) may be masking a true understanding of the sex-based  
266 differences in performance and fatigability.

267 **2.1.4 Respiratory muscle fatigue.** Extending the fatigue data from the locomotor  
268 muscles, numerous studies support the notion of better fatigue resistance in the female  
269 respiratory muscles. The primary muscles of inspiration and expiration are the diaphragm and  
270 major abdominals, respectively, which have concurrent roles in ventilating the lungs and  
271 postural control. Respiratory muscle fatigue is a phenomenon whereby muscles attached to  
272 the thoracic cage exhibit a reduced force-generating capacity relative to baseline, usually  
273 following exhaustive exercise [75–78]. In male versus female comparisons, resistive breathing  
274 evoked a slower rate of inspiratory muscle fatigue in the latter, a finding that was independent  
275 of muscle strength [79], although both groups exhibited a similar relative decline in maximal  
276 inspiratory pressure (15%). In another study using cervical magnetic stimulation to artificially  
277 activate the diaphragm before and after constant work-rate cycling, diaphragm fatigue  
278 occurred in 11 out of 19 males (58%) and 8 out of 19 females (42%) [80]; however, contractile  
279 function diminished to a greater extent in the males (31 vs. 21%). Collectively, these data point  
280 to a female diaphragm that may be more fatigue-resistant, and this phenomenon might be  
281 partially attributed to a greater reliance on accessory inspiratory muscles for ventilation during  
282 dynamic exercise [81]. During high-intensity exercise, respiratory muscle fatigue may  
283 compromise ventilatory capacity and endurance, exacerbate dyspnea (sensations of  
284 breathlessness), and compromise limb-locomotor blood flow through “respiratory steal” [75].  
285 However, its effects on ultra-endurance performance have not been adequately studied. Due  
286 to the expiratory muscles’ important role in postural control [82], it has been speculated that  
287 fatigue of the abdominals during ultra-marathon could place the runner at an increased risk of  
288 injury due to a relative inability to sustain the rigors of competition, particularly on challenging

289 terrain [16]. A fatigue resistance in the respiratory muscles may, therefore, be advantageous  
290 to ultra-marathon performance.

291         These observations should be balanced against the fact that, when compared to  
292 males, females exhibit a greater resistive work of breathing at a given level ventilation during  
293 exercise, attributed to innate sex-based differences in lung size and the diameter of conducting  
294 airways [83]. As a result, females are more likely to exhibit expiratory flow limitation and  
295 exercise-induced arterial hypoxaemia [84]. The respiratory muscles of females also utilize a  
296 greater relative percentage of  $\dot{V}O_2$  during exercise [85] which may, at least in part, diminish  
297 oxygen economy (see 2.3 *Oxygen Utilization*).

298         **2.1.5 Pacing strategies.** A relative fatigue-resistance in female muscles has been  
299 postulated to influence pacing strategies during racing. A comprehensive analysis of marathon  
300 finish times in the United States revealed that females were 1.46-times more likely to maintain  
301 their running pace (defined as a decrease in velocity of <10%) and 0.36-times as likely to  
302 exhibit marked slowing (defined as a decrease of >30%) compared to males [5]; the mean  
303 change in pace was 15.6% and 11.7% for male and females, respectively ( $p<0.001$ ). Similar  
304 observations – of more ‘even’ pacing strategies in female marathon runners - have been  
305 reported elsewhere [86,87]. To our knowledge, only one study has assessed sex-differences  
306 in pacing during ultra-endurance sport. In a 100-km ultra-marathon, Renfree *et al.* [88]  
307 assessed the difference between male and female velocities at 10-km splits, finding that  
308 females exhibited a slower relative starting speed but a higher finishing speed than males.  
309 These findings suggest that females may pace better than their male counterparts during both  
310 marathon and ultra-marathon running, certainly in the non-elite category.

311         The mechanisms underpinning the differences in pacing may extend beyond  
312 differences in fatigue resistance. Males have been observed to slow significantly more than  
313 females in short-distance running races (5 km), even when accounting for differences in  
314 absolute finish times [89]. Although peripheral neuromuscular fatigue may still manifest over  
315 such short distances, other aspects of localized fatigue such as glycogen depletion and  
316 dehydration can be discounted in the population at large. The authors supposed, therefore,  
317 that sex-differences in pacing may reflect disparities in decision making, such as over-  
318 confidence, risk perception, or willingness to tolerate discomfort [89]. Compared to females,  
319 males consistently overestimate their abilities in endurance sport, congruent with a greater  
320 degree of slowing in the latter stages of racing [90]. Individuals with a greater proclivity for risk  
321 appear to slow more considerably in distance running, even in regression models which  
322 account for other psychological constructs, training, and experience [91]. Testosterone  
323 concentrations have been associated with risk-taking behavior [92], and we speculate this as  
324 an additional explanation. Accordingly, the sex differences in pacing may be attributable to

325 differences in physiology, decision making, or both [5], but likely play a crucial role in ultra-  
326 endurance performance.

327

328 ***\*Insert Fig. 1\****

329

330 **2.2 Substrate Utilization.** Carbohydrate and fat provide the majority of energy to fuel muscle  
331 metabolism during prolonged, submaximal exercise. Ultra-endurance exercise depends  
332 heavily on oxidative metabolism for the efficient use of glucose and lipids, and there is a  
333 substantial increase in the use of free fatty acids (FFA) with increasing race distance [93]. Fat  
334 is also more energy dense than carbohydrate (containing 9 versus 4 kcal[insert raised  
335 dot]g<sup>-1</sup>), and improved substrate efficiency towards better lipid use exerts a glycogen-sparing  
336 effect to prevent early-onset fatigue [94]. Thus, the ability to better mobilize and oxidize lipids  
337 during ultra-endurance exercise would be considered advantageous and should be a focus of  
338 the periodized ultra-endurance training program [12].

339 During exercise, muscle contractions signal the translocation of clusters of  
340 differentiation-36 (CD36)/fatty acid binding protein to plasma and mitochondrial membranes,  
341 thereby facilitating FFA transport and metabolism [95]. The overexpression of CD36 is  
342 associated with a fourfold greater fatty acid oxidation by contracting muscle in mice [96]. In  
343 humans, females exhibit greater mRNA expression of genes associated with fatty acid  
344 metabolism, including *CD36* [97,98]. Females are generally known to exhibit larger estrogen-  
345 mediated reserves of intramyocellular lipids (IMCL) to support fuel demands for endurance  
346 exercise, as well as a greater percentage of IMCL in contact with mitochondria following a  
347 bout of endurance exercise when compared to males (indicative of greater capacity) [99].  
348 These genotypes may be primarily responsible for the sex-based differences in lipid oxidation  
349 rates.

350 A whole-room calorimeter study over a 24-h period showed that, irrespective of  
351 physical activity levels, females exhibited 24 - 56% greater fat oxidation normalized to fat-free  
352 mass (FFM) when compared to males, and that the former had an enzymatic profile which  
353 favored cellular  $\beta$ -oxidation [100]. Such differences are also apparent during submaximal  
354 exercise. When exercising at a constant work-rate of  $\sim 65\% \dot{V}O_2\text{max}$ , Tarnopolsky *et al.* [101]  
355 showed that males utilized 25% more muscle glycogen and exhibited significantly higher  
356 respiratory exchange ratios than females, even when accounting for differences in diet,  
357 training status, and hormonal status relating to female menstrual phase. Others have made  
358 similar observations throughout the range of submaximal exercise intensities up to  $85\%$   
359  $\dot{V}O_2\text{max}$  [102], and that the exercise intensity eliciting the highest rate of fat oxidation occurs  
360 at a higher percentage of  $\dot{V}O_2\text{max}$  in females relative to males (58 versus  $50\% \dot{V}O_2\text{max}$ ) [102].

361 As a result, at any submaximal relative exercise intensity, the female fat oxidation curve is  
362 rightward- and upward of the male curve [103]. This is a similar pattern one would expect to  
363 see in a more highly-endurance-trained individual. Females may also exhibit greater metabolic  
364 flexibility [104]. These collective differences may confer a metabolic advantage for females  
365 during exercise of extreme duration.

366 There are important caveats to the interpretation of these data. Firstly, the metabolic  
367 advantage of greater lipid oxidation in females may be partially negated by the obligatory  
368 feeding that occurs during ultra-endurance races. In ultra-marathon, for example, runners may  
369 need to consume between 200 – 400 kcal[insert raised dot]h<sup>-1</sup> from various food sources [12].  
370 Relatively greater proportions of carbohydrate are recommended for ultra-distance triathlon  
371 [105] which, in turn, may decrease the expression of genes involved in lipid metabolism for at  
372 least 4 h [106]. Males oxidize more fat than females post-exercise when fasted, but the  
373 difference is nullified when food is consumed to facilitate recovery [107]. Secondly, when  
374 expressed in absolute terms, males generally exhibit greater lipid oxidation rates owing to  
375 greater active muscle mass, lower fat mass, and greater overall energy expenditure during  
376 exercise; thus, the female metabolic advantage may be limited to weight-dependent sports  
377 (e.g., running, cycling, triathlon, etc.) in which lipid oxidation relative to FFM is pertinent.  
378 Finally, the magnitude of the sexual dimorphism in lipid oxidation is small, and any potential  
379 benefit should be framed in the context of ultra-endurance performance. For instance, while a  
380 greater reliance on lipid metabolism by females may spare muscle glycogen during prolonged  
381 exercise (e.g., marathon), this may not confer a considerable advantage during ultra-  
382 endurance exercise which is characterized by lower relative work rates and slower rates of  
383 glycogen depletion. Accordingly, we propose that the better substrate efficiency in females  
384 may instead confer an advantage by attenuating caloric requirements (which may be  
385 considerable during a 24 – 48 h event), and by reducing the need to consume exogenous  
386 carbohydrate which has been shown to be a primary nutrition-related cause of GI distress (see  
387 *2.5 Gastrointestinal Distress*).

388

## 389 **2.3 Oxygen Utilization.**

390 *2.3.1 Maximal oxygen uptake ( $\dot{V}O_2max$ ).* Maximal oxygen uptake sets the upper-limit  
391 for aerobic metabolism and predicts most of the variance in middle-to-long distance endurance  
392 events including running [108] and cycling [109]. A study in female marathon runners found  
393 that  $\dot{V}O_2max$  was the strongest predictor of performance ( $r = -0.74$ ,  $p < 0.01$ ) explaining 56%  
394 of the variance in finish time [110]. The superior performances of males compared to females  
395 in standard endurance events may be largely explained by their higher  $\dot{V}O_2max$  values, in  
396 both trained [111] and untrained states [112].

397 It is generally accepted that a lower  $\dot{V}O_2\text{max}$  in females is the result of sex-differences  
398 in fat mass, and hemoglobin and hematocrit levels [113,114]. When  $\dot{V}O_2\text{max}$  in males and  
399 females was adjusted to FFM, some showed the sex differences to disappear [115] while  
400 others found that males retained higher values [116]. Equalizing hemoglobin concentrations  
401 between sexes via blood withdrawal also failed to completely equalize absolute  $\dot{V}O_2\text{max}$  [115],  
402 thus suggesting that the sex-differences in aerobic capacity are likely attributable to a  
403 combination of the aforementioned factors. The sex-mediated disparity in oxygen utilization  
404 may also be determined at a cellular level (see 2.1.1 *Muscle fiber type*). For example, the rate  
405 of oxidative phosphorylation is influenced by mitochondrial density, and while respiration in  
406 isolated mitochondria is higher in female muscles compared to male [117], the latter tend to  
407 have a higher expression of genes encoding mitochondrial proteins [61]. Importantly,  
408 mitochondrial function, as well as membrane microviscosity, may depend to a large extent on  
409 estrogen concentrations, with lowered levels associated with diminished mitochondrial  
410 function [118] (See 2.4 *Endocrine Function*).

411 Pertinent to the present discussion is that although  $\dot{V}O_2\text{max}$  is important in ultra-  
412 marathon - correlating positively with the distance run in a timed laboratory simulation [9] - its  
413 predictive power on performance diminishes with increasing race distance [119]. Indeed, when  
414 females outperformed males in 90-km ultra-marathon, their performances were not attributed  
415 to greater maximal aerobic capacity or running economy, but rather a greater fraction of  
416  $\dot{V}O_2\text{max}$  sustained during racing [41]. In cycling, the peak power-to-weight ratio did not  
417 correlate with bike finish time in an ultra-endurance triathlon [120] and, in Ironman triathlon  
418 more broadly, factors such as hydration and energy homeostasis are considered the most  
419 prominent predictors of performance [121]. Consequently, while maximal aerobic capacities  
420 and work rates are generally lower in females, this may not represent the distinct disadvantage  
421 in ultra-endurance competition that it does in the 'standard' endurance events like marathon  
422 and Olympic-distance triathlon.

423 2.3.2 *Oxygen economy and energy efficiency*. Aside from  $\dot{V}O_2\text{max}$ , several other  
424 factors underpin middle-to-long distance endurance performance including velocity at  $\dot{V}O_2\text{max}$   
425 ( $v\dot{V}O_2\text{max}$ ), lactate threshold, and oxygen economy/work efficiency [108,122–124]. Although  
426 the greater relative adiposity in females would be expected to diminish their oxygen economy  
427 and work efficiency in weight-dependent sports, the data pertaining to sex-differences in these  
428 characteristics are inconsistent. Some suggest that females tend to have poorer oxygen  
429 economy at a given submaximal work rate [125,126] despite generally exhibiting a lower body  
430 mass. By contrast, at various relative intensities of lactate threshold, Fletcher *et al.* found no  
431 sex-mediated differences in running economy [127], and there are several reports of lower  
432 (better) values for running economy in trained adult females versus trained adult males  
433 [128,129]. In terms of gross energy efficiency - defined as the ratio of work accomplished to

434 total energy expended – Yasuda *et al.* observed no sex-differences during cycling or arm-  
435 cranking across a range of submaximal relative exercise intensities, even in males and  
436 females who were matched for  $\dot{V}O_2$  at the gas exchange threshold [130]. Similar observations  
437 of no sex-differences in energy efficiency have been made in cross-country skiing [131,132]  
438 and in distance running when comparing elite male and female athletes [133,134].

439 Notwithstanding, the importance of oxygen economy/work efficiency in ultra-  
440 endurance footraces has been contested. In a race with considerable cumulative ascent (that  
441 prolonged exercise time), performance was not correlated with the energy cost of running, nor  
442 with any post-race changes in running economy [135]. It has also been suggested that ultra-  
443 marathon runners make tactical decisions (e.g., developing lower-body musculature, changing  
444 stride frequencies, using robust footwear, using poles, etc.) that sacrifice running economy in  
445 favor of mitigating the musculoskeletal damage and fatigue that more prominently impinge on  
446 performance [10]. These strategies may be crucial for very long races, especially those  
447 contested on mountainous and/or technical terrain that are associated with the greatest  
448 muscle damage and peripheral fatigue.

449 Consequently, in weight-bearing endurance events of ‘standard’ distance, the  
450 male/female performance disparity may in large part be associated with differences in maximal  
451 aerobic capacities and work rates. However, these attributes may be less important in ultra-  
452 endurance sport, with performance therein underpinned by a complex interplay among  
453 physiological, neuromuscular, biomechanical, and psychological factors. Fatigue-resistance,  
454 substrate efficiency, mitigating muscle damage, and avoiding GI distress may be just as  
455 relevant as aerobic capacities in the ultra-endurance model [10] (Fig. 2). Although speculative,  
456 it may be that in this context female athletes exhibit a more complete complement of ergogenic  
457 attributes.

458 Finally, given that females generally outperform males in swimming events of extreme  
459 duration, the various factors that underpin ultra-distance swimming performance warrant  
460 independent consideration. It is unlikely that female success in this sport is due to a superior  
461 maximal oxygen uptake. Indeed, male open-water swimmers have been shown to exhibit  
462 considerably higher  $\dot{V}O_{2max}$  values than females (5.51 vs. 5.06 L.min<sup>-1</sup>, respectively) [136].  
463 Moreover, despite the lactate thresholds occurring at speeds equivalent to 89 and 95%  
464  $\dot{V}O_{2max}$  for males and females, respectively, the absolute  $\dot{V}O_2$  at lactate threshold was still  
465 higher in males (4.90 vs. 4.81 L.min<sup>-1</sup>). Thus, female dominance in this sport is likely due to  
466 factors other than oxygen utilization, and may instead relate to differences in the energy cost  
467 of swimming, second to lower hydrodynamic resistance [137]. Indeed, although increases in  
468 body mass have been shown to diminish oxygen economy during running [138], a higher fat  
469 mass may be ergogenic in swimming. Fat has a lower density than muscle, and the greater  
470 relative female adiposity - as well as important differences in adipose tissue distribution - likely

471 increases buoyancy and reduces drag [139]. The generally smaller body size of females  
472 confers a further decrease in hydrodynamic drag, as do shorter lower limbs that result in a  
473 more horizontal and streamlined position in the water [140,141]. Others speculate that female  
474 success in ultra-distance swimming may also be associated with better pacing strategies [44].  
475 Evidently, the extent to which a biological trait (e.g., lower body fat) can be considered  
476 ergogenic, is determined by the specific demands and characteristics of the event in question.

477

478 ***\*Insert Fig. 2\****

479

480 **2.4 Endocrine Function.** Estrogens, progestogens, and androgens regulate human  
481 reproductive function, but also act on non-reproductive tissues (e.g., muscle and bone) in  
482 numerous ways that affect both health and exercise performance, and which are specific to  
483 the respective male and female physiological environments [142]. However, the data are  
484 extremely complex and often equivocal; as such, what follows is an abridged summary of the  
485 intricate and interrelated functions of the sex hormones, and the extent to which they might  
486 impact on the organism's capacity for ultra-endurance exercise.

487 Testosterone is the primary male sex hormone which facilitates increases in muscle  
488 strength and power [143] and decreases in body fat in a dose- and concentration-dependent  
489 fashion [144]. It also appears to act on substrates in the brain to increase aggression and  
490 competitiveness [145]. While not studied directly, higher testosterone concentrations may be  
491 ergogenic in ultra-endurance competition: directly, due to its association with hemoglobin  
492 concentrations [144], mitochondrial function [146], and lipid metabolism [147]; and indirectly,  
493 by augmenting muscle protein synthesis and thereby facilitating recovery [148]. Importantly,  
494 males exhibit a 30-fold increase in circulating testosterone from puberty, resulting in levels  
495 that are 15 – 20 times higher in adult males than females [149]. This sexual dimorphism is  
496 thought to largely account for the sex-based differences in athletic performance. Interestingly,  
497 Storer *et al.* failed to observe a dose-dependent relationship between testosterone and muscle  
498 fatigability; as such, the higher testosterone concentrations exhibited by male athletes may  
499 not strictly regulate this aspect of exercise performance [143].

500 In females, estrogen and progesterone exhibit large fluctuations throughout the  
501 monthly menstrual cycle [150] (Fig. 3). Estrogen augments muscle size, strength, and collagen  
502 content, all of which are conducive to sporting performance [151] (for a review of the effects  
503 of female sex hormones on the nervous system and muscle strength, see [152]).  
504 Paradoxically, elevated estrogen concentrations reduce tendon and ligament stiffness [151],  
505 which may impinge on ultra-endurance performance in two ways. First, there is a significant  
506 positive correlation between tendon stiffness and running economy in females [127], such that  
507 an estrogen-mediated decrease in stiffness might also deteriorate running economy. Second,

508 there are cyclical changes in anterior knee laxity throughout the menstrual cycle [153], and  
509 while there is no consensus that female injury rates are necessarily hormone-mediated, it is  
510 possible that fluctuating sex-hormone concentrations may partially explain the higher  
511 prevalence of anterior cruciate ligament (ACL) ruptures in eumenorrheic females compared to  
512 males [154]. Worthy of note, the knee is one of the most frequently injured body parts in ultra-  
513 endurance athletes [155], and the risk may be greater when traversing technical/challenging  
514 terrain that increases impact and shear forces through the lower limbs. A greater propensity  
515 for injury would certainly attenuate the ability to both train and compete.

516 *2.4.1 Estrogen and substrate metabolism.* There are data to suggest that the lower  
517 female dependence on carbohydrate during exercise (and, therefore, their superior relative  
518 rates of lipid oxidation) may be estrogen-mediated. For instance, a study by Hamadeh *et al.*  
519 showed that males who were supplemented with estrogen, exhibited an enhanced lipid  
520 oxidation both at rest and during submaximal exercise [156]. Moreover, postprandial lipid  
521 oxidation is lower in postmenopausal females (i.e., those with diminished estrogen  
522 concentrations) [157], thereby supporting the notion that hypogonadism/estrogen deficiency  
523 negatively impacts on fat oxidation. There are methodological difficulties in quantifying such  
524 effects (e.g., differences in exercise modality, sex-hormone concentrations, and training status  
525 of participants), but the paradoxical effects of estrogen and progesterone on exercise  
526 metabolism further obfuscates the matter: estrogen appears to impede glucose kinetics in  
527 females while progesterone appears to potentiate it [158]. It has also been suggested that  
528 estrogen-progesterone interactions may influence substrate metabolism to a greater extent  
529 than either hormone independently, and that the estrogen-to-progesterone ratio must be  
530 sufficiently elevated to evoke metabolic changes (for review, see [159]).

531 The flux in lipid oxidation with estrogen concentrations may be partly due to changes  
532 in mitochondrial function and membrane microviscosity, both of which associate with the  
533 estrogen steroid hormone 17 $\beta$ -estradiol [118]. As a result, female ultra-endurance  
534 performance would be expected to fluctuate congruent with monthly perturbations in estrogen,  
535 even if only trivially. Some have reported that the sex-based discrepancy in ultra-marathon  
536 performance begins to widen at around 45 y, after which female performances diminish [18];  
537 this coincides with the increased body fat percentage, decreased lipid oxidation, and  
538 decreased mitochondrial function occurring with the menopause and the associated reduction  
539 in estrogen levels. As an aside, a secondary consequence of an estrogen-mediated  
540 mitochondrial dysfunction is an increased hydrogen peroxide production [160], and decreased  
541 levels of antioxidant genes [160,161]. This may be of particular relevance for ultra-endurance  
542 events which exacerbate oxidative stress and reactive oxygen species in a linear fashion with  
543 exercise duration [162], although it is yet to be decisively determined if alternations in redox  
544 homeostasis affect performance in ultra-endurance sport.



545           2.4.2 *Energy availability*. An important consideration for the female ultra-endurance  
546 athlete is the effect of energy availability on sex hormone concentrations, and the combined  
547 manifestations. The foremost nutritional challenge facing ultra-endurance athletes is the ability  
548 to meet their daily caloric demands [12]. Low energy availability – resulting from high training  
549 volumes and/or unintentional or deliberate restriction of dietary energy intake - can affect both  
550 male [163] and female endurance athletes [164]. There is, however, less evidence to support  
551 the magnitude of its effects on male health and performance. The consequences of low energy  
552 availability likely affect females more profoundly and rapidly owing to its synergism with  
553 menstrual dysfunction (i.e., amenorrhea) that, in turn, reduces bone health (as described in  
554 the Female Athlete Triad [165]). Given that estrogen associates positively with bone mineral  
555 density via osteoblast activity [166], females with diminished estrogen levels (e.g.,  
556 amenorrheic athletes) are at an increased risk of stress fracture [167], and this may have  
557 implications for the high-mileage running that characterizes ultra-marathon, ultra-distance  
558 triathlon, and adventure racing. Even eumenorrheic females appear to be more susceptible  
559 than males to adverse changes in bone health following short-term low energy availability  
560 [168]. For a detailed summary of endocrine changes in the hypothalamic pituitary gonadal  
561 axis, using markers of low energy availability in males and females, see Elliott-Sale *et al.* [169].

562           On balance, there is a wealth of literature on the effects of estrogen and progesterone  
563 on female musculoskeletal, metabolic, and cellular function, and all such effects directly or  
564 indirectly influence ultra-endurance performance. However, the data are confounded by large  
565 inter- and intraindividual variability in sex hormone concentrations. From puberty to  
566 menopause, female sex-hormone concentrations are in a constant state of flux: (i) across any  
567 given menstrual cycle; (ii) as a result of perturbations in the menstrual cycle (e.g., anovulation);  
568 (iii) during pregnancy; (iv) due to clinical conditions (e.g., polycystic ovarian syndrome); (v) as  
569 a consequence of low energy availability and subsequent amenorrhea; and (vi) in response to  
570 external supplementation (e.g., hormonal contraceptives which are used by approximately half  
571 of elite female athletes [170]). As such, while ultra-endurance performance may not be  
572 inhibited by the female sex hormones, *per se*, it is the perturbations in estrogen concentrations  
573 manifesting across the lifespan that likely contribute to the male/female performance disparity.  
574 More high-quality, well-controlled studies are needed to explore the effects of  
575 endogenous/exogenous estrogen and progesterone on ultra-endurance performance.

576

577           ***\*Insert Fig. 3\****

578

579           **2.5 Gastrointestinal Distress.** Ultra-endurance exercise is associated with widespread  
580 reporting of gastrointestinal symptoms [171–173]. The most well-documented, performance-  
581 altering GI disturbances are nausea/vomiting [174] and abdominal cramping [175,176],

582 although other symptoms include reflux, bloating, loose stools, and flatulence [177]. GI  
583 distress is often cited as a reason for non-completion and/or attenuated performance,  
584 particularly in single stage running races [178]. The mechanisms that underpin GI distress  
585 during ultra-endurance exercise are complex and multi-faceted, but likely include impairments  
586 to gut perfusion and neuroendocrine alterations [179]. Gastrointestinal symptoms may also be  
587 triggered or exacerbated by aggressive and/or unaccustomed nutritional intake [180].  
588 Certainly, a biological propensity for less frequent/severe GI distress, and/or a greater ability  
589 to tolerate/mitigate the symptoms, would be considered ergogenic in ultra-endurance  
590 competition.

591         2.5.1 *Gut anatomy and physiology.* To contextualize the forthcoming overview of sex  
592 differences in the character and prevalence of GI distress during exercise, a brief discussion  
593 of the general differences in gut structure and function is warranted. On average, the female  
594 stomach is ~10% smaller than the male stomach [181] and may, therefore, be less capable of  
595 gastric accommodation after consuming a given food volume [182]. As a result, females are  
596 likely to exhibit greater postprandial fullness following a standardized feeding [183]. Whole-  
597 gut and colonic transit times are longer in females when compared to males [184,185], and  
598 females exhibit attenuated rates of gastric emptying [186] for both solid foods and fluids [187].  
599 These latter findings may have important implications for fueling during prolonged exercise.  
600 While the precise mechanisms for sex-differences in gastric emptying are unclear, it has been  
601 hypothesized to be related to female sex-hormone effects on the gastrointestinal tract [187],  
602 speculation which has been supported empirically only in rodent models [188]. There are data  
603 on sex-differences in the gut microbiome that is thought to influence gut function and GI  
604 symptoms [189], but most of this research is also from animal models which may not closely  
605 reflect human physiology and behavior. Finally, there may also be sex-differences in gut  
606 barrier function which has been speculated to play a role in the development of endotoxemia  
607 (bacterial translocation into the blood), congruent with systemic inflammation and GI  
608 symptoms [190]. This may be particularly relevant to the present discussion owing to the  
609 positive association of endotoxemia biomarkers with the frequency and/or severity of GI  
610 symptoms (particularly nausea) during ultra-endurance competition [191,192], although this is  
611 not a universal finding [193]. To the authors' knowledge, sex differences in the vulnerability to  
612 GI permeability and endotoxemia has not been systematically studied in ultra-endurance  
613 exercise. However, in studies assessing the phenomenon in various resting conditions - via  
614 the postprandial measurement of urine or blood levels of non-metabolizable sugars - gut  
615 permeability was shown to be higher in males versus females [194–196].

616         2.5.2 *Symptomology.* In population-based research, females report a higher frequency  
617 of GI symptoms [197–199], most commonly nausea, bloating, abdominal pain, and  
618 constipation. While a greater prevalence of bloating and constipation in females may be due

619 to slower whole-gut and colonic transit times [184,185] - thereby contributing to greater  
620 fermentation of dietary fiber and reabsorption of colonic water - the greater frequency of  
621 nausea and abdominal pain may be associated with the onset of monthly menses in  
622 individuals with eumenorrhea [200]. The observations of population-based studies generally  
623 extend to those made during exercise, although the most informative data stem from research  
624 in standard- as opposed to ultra-endurance competition [172,201–203]. For example, in a  
625 1984 survey of >700 marathon runners (85% male), females more commonly reported  
626 symptoms of lower-GI distress (e.g., abdominal cramping, urge to defecate, diarrhea, bloody  
627 defecation) [203]. While interesting, these data may be confounded by external factors (e.g.,  
628 training experience), particularly given that years of training associates negatively with GI  
629 symptoms [201]. A multivariate analysis of >1,200 endurance runners contesting races from  
630 10 - 42 km also observed female sex to independently associate with increased prevalence of  
631 GI complaints [201].

632 Notwithstanding, reports on sex-differences in GI distress during ultra-endurance  
633 exercise are sparse. This can be attributed to lower female participation numbers and/or the  
634 failure of most studies to differentiate GI distress prevalence by sex (e.g., [204,205]). In reports  
635 that do make such distinctions, the data are less equivocal than for marathon. For instance,  
636 there was little difference in the frequency and/or severity of most GI symptoms between  
637 males and females during a 161-km ultra-marathon, with the exception of stomach bloating  
638 which was more common in females [173]. Furthermore, over a similar distance, Stuempfle *et*  
639 *al.* [191] reported no sex-mediated differences in nausea. When interpreting these data it  
640 should be noted that neither study was specifically designed to assess sex-differences in GI  
641 distress. In addition, both had a relatively low number of female participants, congruent with  
642 the trend in ultra-endurance participation numbers. Thus, more research is warranted to  
643 establish if the greater female propensity for GI distress extends to ultra-endurance  
644 competition. Such a predisposition would negatively impact on an athlete's ability to perform:  
645 directly, due to pain and discomfort associated with lower-GI issues; and/or indirectly owing to  
646 the difficulty of adequately fueling and hydrating.

647 *2.5.3 Gut training.* There is a growing interest in the concept of “training the gut” to  
648 enhance the digestion of, and tolerance to, exogenous carbohydrate and fluid intake during  
649 prolonged exercise. Such gut-training strategies are premised on the notion that high intakes  
650 of carbohydrate (at rest or during exercise) will increase the density and activity of intestinal  
651 glucose transports, thereby facilitating greater carbohydrate absorption and oxidation during  
652 exercise [206]. These adaptations would be expected to mitigate the magnitude and  
653 prevalence of GI distress during exercise. Gut training may be particularly relevant for ultra-  
654 endurance competition given the large energetic demands and nutritional intakes associated  
655 with training and racing [12]. Although anecdotal accounts of “speed eaters” show the GI tract

656 to be highly adaptable [207], studies focused on the physiological and ergogenic appraisal of  
657 gut-training strategies are still relatively scarce. One such study on a group of trained cyclists  
658 and triathletes showed that a 28-d period of aggressive in-task fueling facilitated metabolic  
659 adaptations (including increased exogenous carbohydrate oxidation during exercise) [208].  
660 Others report that gut-training evoked reductions in GI symptoms and carbohydrate  
661 malabsorption [209]. Nevertheless, the ergogenic effects of these strategies are mixed. The  
662 two studies that comprised mixed-sex cohorts showed that females were more likely to report  
663 GI symptoms during exercise when challenged with high rates of carbohydrate intake ( $90 \text{ g}\cdot\text{h}^{-1}$   
664  $^1$ ) [209,210]. Furthermore, following two weeks of gut training in a small group (5 male, 5  
665 female), the magnitude of the reduction in GI symptoms associated with in-task fueling was  
666 lower in females relative to males [209]. Clearly, more data from larger samples are needed  
667 in order to make more robust direct comparisons.

668 Females report being less accustomed to feeding during exercise when compared to  
669 males [209]; therefore, it may be that integrating gut-training into periodized race preparation  
670 may still be beneficial for the female athlete, particularly if they intend on aggressively fueling  
671 with carbohydrate when racing. Perhaps the more relevant consideration is whether high rates  
672 of carbohydrate ingestion ( $>60 \text{ g}\cdot\text{h}^{-1}$ ) - after a period of gut training - are likely to enhance ultra-  
673 endurance performance for the female athlete when compared to more modest intakes ( $30 -$   
674  $60 \text{ g}\cdot\text{h}^{-1}$ ) that are less likely to provoke GI symptoms in the first instance. This may be  
675 particularly relevant in light of a recent study showing the feasibility of very high rates of  
676 carbohydrate intake ( $120 \text{ g}\cdot\text{h}^{-1}$ ) in elite ultra-marathon runners who had previously undergone  
677 nutritional and gut-training [211]. Rather predictably, the study comprised an exclusively male  
678 cohort, and so whether such nutritional strategies are viable, or even possible, in female ultra-  
679 marathon runners remains unclear. Given the aforementioned sex-differences in the rates of  
680 gastric emptying and gut transit time, not to mention the existing data in endurance events of  
681 shorter duration, it is likely that females may be somewhat less tolerant to such high rates of  
682 intake. Moreover, the appropriate gut-training strategy is almost certainly to differ between  
683 sexes.

684 A final consideration is the extent to which sex-differences in substrate efficiency and  
685 body mass impact on race nutrition and the propensity for nutrition-induced GI distress. Owing  
686 to their greater dependence on lipid oxidation during exercise (see 2.2 *Substrate Utilization*),  
687 female endurance athletes may be less susceptible to glycogen degradation [212] and its  
688 debilitating effects. Better substrate efficiency may also explain, at least in part, the lower  
689 carbohydrate and general caloric intakes of females during ultra-endurance competition  
690 [213,214]. Lower caloric intakes in females is also a factor of a smaller average body size,  
691 smaller stomach, and possibly deliberate strategies aimed at mitigating GI symptoms. A lesser  
692 need to consume exogenous carbohydrate to sustain a given work rate may be pertinent given

693 that the primary nutritional cause of GI distress during endurance exercise is the high intake  
694 of carbohydrate, particularly hyperosmolar solutions [171]. The lower average body mass of  
695 the female athlete may also explain their lower sweat rates at both absolute and relative work  
696 rates [215]. This may, in turn, attenuate their fluid requirements during exercise, and decrease  
697 the need to ingest high volumes that provoke GI distress. Therefore, while it may be that  
698 female athletes are more prone to GI distress during exercise, it remains unclear whether this  
699 extends to the durations typical of ultra-endurance and whether this might be partially  
700 mitigated by their reduced caloric, carbohydrate, and fluid requirements. More studies are  
701 needed to further explore this complex issue in the context of ultra-endurance performance.

702

### 703 **3.0 BEYOND PHYSIOLOGY**

704 There are several considerations that should accompany the discussions presented in this  
705 paper. Firstly, this review has not discussed sex differences in all aspects of human  
706 physiology, just those that are prominent predictors of ultra-endurance performance. That  
707 said, in the interest of concision, there were several omissions including sex-differences in  
708 thermoregulation [215], the effects of sleep deprivation [216], and the responses to nutritional  
709 and training regimens [99]. Furthermore, while physiology is certainly a crucial determinant of  
710 performance in ultra-endurance sport, we did not explore sex-differences in psychological  
711 attributes that are arguably the greatest predictors of success in such events. At the least, we  
712 would expect there to be sex-based differences in sporting motivation, competitiveness, and  
713 risk taking [217]; as such, these psychological characteristics and their impact on the  
714 propensity for ultra-endurance performance warrant further consideration.

715         Second, we earlier reviewed the male and female performance trends in a number of  
716 ultra-distance sports, finding that the sex-based disparity was generally smallest in the events  
717 of longest distance/duration and when females were represented more numerous. It has  
718 been postulated that females may have lesser interest in competitive sports, and that the lower  
719 number of athletes may not simply be due to sociocultural factors and fewer opportunities  
720 [217]. Thus, there may exist a degree of selection bias, in that those females competing in the  
721 extreme endurance events may be self-selecting as the fittest, strongest, and most motivated  
722 among their sex. This might, in turn, lead to a skewed interpretation of the performance trends.  
723 Accordingly, direct comparisons remain problematic until participation numbers equalize.

724         Finally, this review discussed numerous physiological attributes that may facilitate or  
725 impede ultra-endurance performance. However, ultra-endurance events are highly variable in  
726 terms of the exercise mode (e.g., running, cycling, swimming, adventure racing, etc.),  
727 distance/duration, cumulative ascent/descent, terrain, and environmental extremes. It stands  
728 to reason, therefore, that the physical/physiological attributes of individuals will be differentially  
729 suited to different events. For instance, those contested on relatively flat, non-technical terrain

730 may favor athletes with larger maximal aerobic capacities and higher ventilatory thresholds,  
731 whereas individuals with smaller frames and greater peripheral conditioning/robustness may  
732 excel on technical terrain with downhill running components. As such, the nuances of each  
733 event should be considered before arbitrarily designating a physical/physiological trait as  
734 advantageous. Certainly, optimal performances will stem from matching individual  
735 physiological profiles with individual race types.

736

#### 737 **4.0 CONCLUSION**

738 When compared to their male counterparts, females exhibit numerous phenotypes that would  
739 be expected to confer an advantage in ultra- and/or extreme-endurance competition. These  
740 include a greater relative distribution of type-I (oxidative) fibers, greater fatigue-resistance  
741 owing to neuromuscular, contractile, and metabolic factors, better substrate efficiency (higher  
742 rates of lipid oxidation), lower energetic requirements, and higher subcutaneous body fat  
743 which is likely beneficial in ultra-distance swimming. The data also suggest that females may  
744 be better at pacing. These factors may explain why the sex-mediated performance disparity  
745 is lowest in ultra-endurance sport than in any other. However, there are two caveats. First,  
746 these collective traits may only manifest as ergogenic in the extreme endurance events which,  
747 paradoxically, are the races that females less-often contest. Second, several important  
748 characteristics of female physiology - including mechanical-ventilatory function, O<sub>2</sub>-carrying  
749 capacity, prevalence of GI distress, and sex-hormone effects on both cellular function and  
750 injury risk – unequivocally impinge on female ultra-endurance performance, making it unlikely  
751 that the fastest females will ever outperform the fastest males (ultra-distance swimming a  
752 notable exception). In light of these caveats and the numerous considerations proposed in our  
753 discussion, we urge a skeptical approach to cursory or simplified answers to this complex  
754 question. We encourage more research into the physiological determinants of ultra-endurance  
755 sport, as well as more direct comparisons of male versus female ultra-endurance physiology,  
756 particularly when/if the number of female participants increases.

757

#### 758 **Acknowledgements**

759 The authors wish to thank Professor Sue Ward (University of Leeds, UK) for her guidance in  
760 developing the manuscript.

761

#### 762 **Declarations**

763 *Funding.* No funding was received in developing this manuscript. Nicholas B. Tiller is  
764 funded by a postdoctoral fellowship from the Tobacco-Related Disease Research Program  
765 (TRDRP; award no. T31FT1692).

766            *Conflicts of interest.* Nicholas B. Tiller, Kirsty J. Elliott-Sale, Beat Knechtle, Patrick B.  
767 Wilson, Justin D. Roberts and Guillaume Y. Millet declare that they have no conflicts of interest  
768 relevant to the content of this review.

769            *Authors' contributions.* NBT, GYM, KJES, and PBW drafted the manuscript; JDR and  
770 BK provided additional comments and contributions; all authors approved the final version

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772 **REFERENCES**

773

- 774 1. Whipp BJ, Ward SA. Will women soon outrun men? *Nature*. Nature Publishing Group;  
775 1992. p. 25.
- 776 2. Zingg MA, Rüst CA, Rosemann T, Lepers R, Knechtle B. Analysis of sex differences in  
777 open-water ultra-distance swimming performances in the FINA World Cup races in 5 km, 10  
778 km and 25 km from 2000 to 2012. *BMC Sports Science, Medicine and Rehabilitation*.  
779 BioMed Central Ltd.; 2014;6:7.
- 780 3. Reinboud W. Linear models can't keep up with sport gender gap [1]. *Nature*. Nature  
781 Publishing Group; 2004. p. 147.
- 782 4. Peronnet F, Thibault G. Mathematical analysis of running performance and world running  
783 records. *Journal of Applied Physiology*. *J Appl Physiol* (1985); 1989;67:453–65.
- 784 5. Deaner RO, Carter RE, Joyner MJ, Hunter SK. Men are more likely than women to slow in  
785 the marathon. *Medicine and Science in Sports and Exercise*. Lippincott Williams and Wilkins;  
786 2014;47:607–16.
- 787 6. Zaryski C, Smith DJ. Training principles and issues for ultra-endurance athletes. *Current*  
788 *Sports Medicine Reports* [Internet]. *Curr Sports Med Rep*; 2005 [cited 2020 Jun 22];4:165–  
789 70. Available from: <https://pubmed.ncbi.nlm.nih.gov/15907270/>
- 790 7. Hoffman MD, Ong JC, Wang G. Historical analysis of participation in 161km  
791 ultramarathons in North America. *International Journal of the History of Sport*. 2010. p.  
792 1877–91.
- 793 8. Scheer V. Participation Trends of Ultra Endurance Events. *Sports Medicine and*  
794 *Arthroscopy Review* [Internet]. Lippincott Williams and Wilkins; 2019 [cited 2020 Jun  
795 17];27:3–7. Available from: <http://journals.lww.com/00132585-201903000-00002>
- 796 9. Millet GY, Banfi JC, Kerherve H, Morin JB, Vincent L, Estrade C, et al. Physiological and  
797 biological factors associated with a 24 h treadmill ultra-marathon performance.  
798 *Scandinavian Journal of Medicine & Science in Sports* [Internet]. John Wiley & Sons, Ltd;  
799 2011 [cited 2020 Mar 3];21:54–61. Available from: <http://doi.wiley.com/10.1111/j.1600-0838.2009.01001.x>
- 801 10. Millet GY, Hoffman MD, Morin JB. Sacrificing economy to improve running performance -  
802 A reality in the ultramarathon? [Internet]. *Journal of Applied Physiology*. American  
803 Physiological Society Bethesda, MD; 2012 [cited 2020 Jun 10]. p. 507–9. Available from:  
804 <https://www.physiology.org/doi/10.1152/jappphysiol.00016.2012>
- 805 11. Hoffman MD, Lee J, Zhao H, Tsodikov A. Pain Perception After Running a 100-Mile  
806 Ultramarathon. *Archives of Physical Medicine and Rehabilitation*. *Arch Phys Med Rehabil*;  
807 2007;88:1042–8.
- 808 12. Tiller NB, Roberts JD, Beasley L, Chapman S, Pinto JM, Smith L, et al. International  
809 Society of Sports Nutrition Position Stand: Nutritional considerations for single-stage ultra-  
810 marathon training and racing. *Journal of the International Society of Sports Nutrition*. *Journal*  
811 *of the International Society of Sports Nutrition*; 2019;16:1–23.
- 812 13. Knechtle B, Nikolaidis PT. Physiology and pathophysiology in ultra-marathon running.  
813 *Frontiers in Physiology*. Frontiers Media S.A.; 2018.



- 814 14. Cona G, Cavazzana A, Paoli A, Marcolin G, Grainer A, Bisiacchi PS. It's a Matter of  
815 Mind! Cognitive Functioning Predicts the Athletic Performance in Ultra-Marathon Runners. di  
816 Pellegrino G, editor. PLOS ONE [Internet]. Public Library of Science; 2015 [cited 2020 Jun  
817 5];10:e0132943. Available from: <https://dx.plos.org/10.1371/journal.pone.0132943>
- 818 15. Thompson M. No Title Physiological and Biomechanical Mechanisms of Distance Specific  
819 Human Running Performance. *Integrative and comparative biology*. 2017;57:293–300.
- 820 16. Tiller NB. Pulmonary and Respiratory Muscle Function in Response to Marathon and  
821 Ultra-Marathon Running: A Review. *Sports Medicine*. Springer International Publishing;  
822 2019. p. 1031–41.
- 823 17. Tiller NB, Stewart GM, Illidi CR, Levine BD. Exercise is medicine? The cardiorespiratory  
824 implications of ultra-marathon. *Current Sports Medicine Reports* [Internet]. Lippincott  
825 Williams and Wilkins; 2020 [cited 2020 Sep 22];19:290–7. Available from:  
826 <https://pubmed.ncbi.nlm.nih.gov/32769665/>
- 827 18. Knechtle B, Valeri F, Nikolaidis PT, Zingg MA, Rosemann T, Rüst CA. Do women reduce  
828 the gap to men in ultra-marathon running? *SpringerPlus*. SpringerOpen; 2016;5.
- 829 19. Knechtle B, Abou Shoak, Knechtle, Rüst, Rosemann T, Lepers R. Participation and  
830 performance trends in ultracycling. *Open Access Journal of Sports Medicine*. Dove Medical  
831 Press Ltd.; 2013;4:41.
- 832 20. Knechtle B, di Gangi S, Rüst CA, Nikolaidis PT. Performance Differences Between the  
833 Sexes in the Boston Marathon From 1972 to 2017. *Journal of strength and conditioning  
834 research*. NLM (Medline); 2020;34:566–76.
- 835 21. Waldvogel KJ, Nikolaidis PT, di Gangi S, Rosemann T, Knechtle B. Women reduce the  
836 performance difference to men with increasing age in ultra-marathon running. *International  
837 Journal of Environmental Research and Public Health*. MDPI AG; 2019;16.
- 838 22. Baumgartner S, Victor Sousa C, Nikolaidis PT, Knechtle B. Can the performance gap  
839 between women and men be reduced in ultra-cycling? *International Journal of  
840 Environmental Research and Public Health*. MDPI AG; 2020;17.
- 841 23. Bam J, Noakes TD, Juritz J, Dennis SC. Could women outrun men in ultramarathon  
842 races? *Medicine and Science in Sports and Exercise*. *Med Sci Sports Exerc*; 1997;29:244–7.
- 843 24. Peter L, Rust CA, Knechtle B, Rosemann T, Lepers R, Peter L, et al. Sex differences in  
844 24-hour ultra-marathon performance - A retrospective data analysis from 1977 to 2012.  
845 *Clinics* [Internet]. Faculdade de Medicina / USP; 2014 [cited 2020 Jun 22];69:38–46.  
846 Available from: [http://www.scielo.br/scielo.php?script=sci\\_arttext&pid=S1807-  
847 59322014000100038&lng=en&nrm=iso&tlng=en](http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-59322014000100038&lng=en&nrm=iso&tlng=en)
- 848 25. Senefeld J, Smith C, Hunter SK. Sex differences in participation, performance, and age  
849 of ultramarathon runners. *International Journal of Sports Physiology and Performance*  
850 [Internet]. Human Kinetics Publishers Inc.; 2016 [cited 2020 Jun 22];11:635–42. Available  
851 from: <https://pubmed.ncbi.nlm.nih.gov/26561864/>
- 852 26. Williams S. Are women better ultra-endurance athletes than men? [Internet]. *BBC World  
853 News*. 2019 [cited 2020 Jun 3]. Available from: <https://www.bbc.co.uk/news/world-49284389>
- 854 27. Carter K. 'Women have less ego. Men think: How hard can this be?': the female ultra-  
855 athletes leading the field. [Internet]. *The Guardian*. 2020 [cited 2020 Jun 3]. Available from:

856 [https://www.theguardian.com/lifeandstyle/2020/jan/03/female-ultra-athletes-leading-field-](https://www.theguardian.com/lifeandstyle/2020/jan/03/female-ultra-athletes-leading-field-women-less-ego)  
857 [women-less-ego](https://www.theguardian.com/lifeandstyle/2020/jan/03/female-ultra-athletes-leading-field-women-less-ego)

858 28. Why women are better at ultra running. [Internet]. Women's Running. 2016 [cited 2020  
859 Jun 3]. Available from: [https://www.womensrunning.co.uk/inspiration/why-women-are-better-](https://www.womensrunning.co.uk/inspiration/why-women-are-better-at-ultrarunning/)  
860 [at-ultrarunning/](https://www.womensrunning.co.uk/inspiration/why-women-are-better-at-ultrarunning/)

861 29. Brueck H. Women are faster long-distance runners than men, and it's probably because  
862 they've got more estrogen. [Internet]. Insider. 2020 [cited 2020 Jun 3]. Available from:  
863 <https://www.insider.com/women-are-faster-long-distance-runners-estrogen-2020-1>

864 30. Jhung L. Why women rule. [Internet]. Runner's World. 2010 [cited 2020 Jun 3]. Available  
865 from: <https://www.runnersworld.com/trail-running/a20803612/why-women-rule-ultrarunning/>

866 31. Bloom B. Could women run faster than men? [Internet]. The Telegraph. 2020 [cited 2020  
867 Sep 1]. Available from: [https://www.telegraph.co.uk/athletics/2020/07/29/could-women-run-](https://www.telegraph.co.uk/athletics/2020/07/29/could-women-run-faster-men-science-says-might-possible/)  
868 [faster-men-science-says-might-possible/](https://www.telegraph.co.uk/athletics/2020/07/29/could-women-run-faster-men-science-says-might-possible/)

869 32. Loudin A. More women gain ground in ultramarathons, other long-distance races  
870 [Internet]. The Washington Post. 2020 [cited 2020 Oct 2]. Available from:  
871 [https://www.washingtonpost.com/health/women-long-distance-runners/2020/09/25/bffdda10-](https://www.washingtonpost.com/health/women-long-distance-runners/2020/09/25/bffdda10-1871-11ea-a659-7d69641c6ff7_story.html)  
872 [1871-11ea-a659-7d69641c6ff7\\_story.html](https://www.washingtonpost.com/health/women-long-distance-runners/2020/09/25/bffdda10-1871-11ea-a659-7d69641c6ff7_story.html)

873 33. Chevront SN, Carter R, Deruisseau KC, Moffatt RJ. Running performance differences  
874 between men and women: An update. *Sports Medicine. Sports Med*; 2005. p. 1017–24.

875 34. Kuscsik N. THE HISTORY OF WOMEN'S PARTICIPATION IN THE MARATHON.  
876 *Annals of the New York Academy of Sciences* [Internet]. John Wiley & Sons, Ltd; 1977 [cited  
877 2020 Jun 1];301:862–76. Available from: [http://doi.wiley.com/10.1111/j.1749-](http://doi.wiley.com/10.1111/j.1749-6632.1977.tb38253.x)  
878 [6632.1977.tb38253.x](http://doi.wiley.com/10.1111/j.1749-6632.1977.tb38253.x)

879 35. Coast JR, Blevins JS, Wilson BA. Do gender differences in running performance  
880 disappear with distance? *Canadian Journal of Applied Physiology. Human Kinetics*  
881 *Publishers Inc.*; 2004;29:139–45.

882 36. Lepers R. Sex Difference in Triathlon Performance. *Frontiers in Physiology* [Internet].  
883 *Frontiers Media S.A.*; 2019 [cited 2020 Jun 5];10:973. Available from:  
884 <https://www.frontiersin.org/article/10.3389/fphys.2019.00973/full>

885 37. Zingg MA, Karner-Rezek K, Rosemann T, Knechtle B, Lepers R, Rüst CA. Will women  
886 outrun men in ultra-marathon road races from 50 km to 1,000 km? *SpringerPlus*.  
887 *SpringerOpen*; 2014;3.

888 38. Vickers AJ, Vertosick EA. An empirical study of race times in recreational endurance  
889 runners. *BMC Sports Science, Medicine and Rehabilitation* [Internet]. *BioMed Central Ltd.*;  
890 2016 [cited 2020 Jun 1];8:26. Available from:  
891 <https://bmcsportsscimedrehabil.biomedcentral.com/articles/10.1186/s13102-016-0052-y>

892 39. Knechtle B, Zingg M, Rosemann T, Rüst C. Performance differences between sexes in  
893 50-mile to 3,100-mile ultramarathons. *Open Access Journal of Sports Medicine* [Internet].  
894 *Dove Medical Press Ltd.*; 2015 [cited 2020 Aug 28];6:7. Available from:  
895 [/pmc/articles/PMC4309798/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/27111111/)

896 40. Hoffman MD. Ultramarathon trail running comparison of performance-matched men and  
897 women. *Medicine and Science in Sports and Exercise* [Internet]. *Med Sci Sports Exerc*; 2008  
898 [cited 2020 Aug 4];40:1681–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/18685521/>

- 899 41. Speechly DP, Taylor SR, Rogers GG. Differences in ultra-endurance exercise in  
900 performance-matched male and female runners. *Medicine and Science in Sports and*  
901 *Exercise*. *Med Sci Sports Exerc*; 1996;28:359–65.
- 902 42. Ronto P. The state of ultra running 2020 [Internet]. *RunRepeat*. 2020 [cited 2020 Jun  
903 11]. Available from: <https://runrepeat.com/state-of-ultra-running>
- 904 43. Knechtle B, Rosemann T, Lepers R, Rüst CA. Women outperform men in ultradistance  
905 swimming: The Manhattan Island Marathon Swim from 1983 to 2013. *International Journal of*  
906 *Sports Physiology and Performance* [Internet]. Human Kinetics Publishers Inc.; 2014 [cited  
907 2020 Aug 31];9:913–24. Available from: <https://pubmed.ncbi.nlm.nih.gov/24584647/>
- 908 44. Knechtle B, Dalamitros AA, Barbosa TM, Sousa CV, Rosemann T, Nikolaidis PT. Sex  
909 differences in swimming disciplines—can women outperform men in swimming?  
910 *International Journal of Environmental Research and Public Health* [Internet]. MDPI AG;  
911 2020 [cited 2020 Aug 31];17. Available from: <https://pubmed.ncbi.nlm.nih.gov/32456109/>
- 912 45. Sex & Gender | Office of Research on Women’s Health [Internet]. [cited 2020 Jun 22].  
913 Available from: <https://orwh.od.nih.gov/sex-gender>
- 914 46. IGH Learning - CIHR [Internet]. [cited 2020 Jun 22]. Available from: [https://cihr-](https://cihr-irsc.gc.ca/e/49347.html)  
915 [irsc.gc.ca/e/49347.html](https://cihr-irsc.gc.ca/e/49347.html)
- 916 47. Heidari S, Babor TF, de Castro P, Tort S, Curno M. Sex and Gender Equity in Research:  
917 rationale for the SAGER guidelines and recommended use. *Research Integrity and Peer*  
918 *Review* [Internet]. Springer Nature; 2016 [cited 2020 Jun 22];1:2. Available from:  
919 <http://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6>
- 920 48. Phillips SP. Defining and measuring gender: A social determinant of health whose time  
921 has come [Internet]. *International Journal for Equity in Health*. BioMed Central; 2005 [cited  
922 2020 Jun 23]. p. 11. Available from:  
923 <http://equityhealthj.biomedcentral.com/articles/10.1186/1475-9276-4-11>
- 924 49. Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research?  
925 [Internet]. *JAMA - Journal of the American Medical Association*. American Medical  
926 Association; 2016 [cited 2020 Jun 22]. p. 1863–4. Available from:  
927 <https://jamanetwork.com/journals/jama/fullarticle/2577142>
- 928 50. Enoka RM, Duchateau J. Translating fatigue to human performance. *Medicine and*  
929 *Science in Sports and Exercise* [Internet]. Lippincott Williams and Wilkins; 2016 [cited 2020  
930 Aug 4];48:2228–38. Available from: </pmc/articles/PMC5035715/?report=abstract>
- 931 51. Millet GY. Can neuromuscular fatigue explain running strategies and performance in  
932 ultra-marathons?: The flush model [Internet]. *Sports Medicine*. Springer; 2011 [cited 2020  
933 Aug 4]. p. 489–506. Available from: [https://link.springer.com/article/10.2165/11588760-](https://link.springer.com/article/10.2165/11588760-000000000-00000)  
934 [000000000-00000](https://link.springer.com/article/10.2165/11588760-000000000-00000)
- 935 52. Hunter SK. Sex differences in human fatigability: Mechanisms and insight to  
936 physiological responses. *Acta Physiologica*. Blackwell Publishing Ltd; 2014;210:768–89.
- 937 53. Hicks AL, Kent-Braun J, Ditor DS. Sex differences in human skeletal muscle fatigue.  
938 *Exercise and Sport Sciences Reviews* [Internet]. Lippincott Williams and Wilkins; 2001 [cited  
939 2020 Jun 23];29:109–12. Available from: <https://pubmed.ncbi.nlm.nih.gov/11474957/>
- 940 54. Martin V, Kerhervé H, Messonnier LA, Banfi JC, Geysant A, Bonnefoy R, et al. Central  
941 and peripheral contributions to neuromuscular fatigue induced by a 24-h treadmill run.

- 942 Journal of Applied Physiology [Internet]. *J Appl Physiol* (1985); 2010 [cited 2020 Aug  
943 4];108:1224–33. Available from: <https://pubmed.ncbi.nlm.nih.gov/20167672/>
- 944 55. Millet GY, Tomazin K, Verges S, Vincent C, Bonnefoy R, Boisson RC, et al.  
945 Neuromuscular consequences of an extreme mountain ultra-marathon. *PLoS ONE* [Internet].  
946 Public Library of Science; 2011 [cited 2020 Aug 4];6:17059. Available from:  
947 [/pmc/articles/PMC3043077/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/20167672/)
- 948 56. Millet GY, Millet GP, Lattier G, Maffiuletti NA, Candau R. Alteration of neuromuscular  
949 function after a prolonged road cycling race. *International Journal of Sports Medicine*  
950 [Internet]. *Int J Sports Med*; 2003 [cited 2020 Aug 4];24:190–4. Available from:  
951 <https://pubmed.ncbi.nlm.nih.gov/12740737/>
- 952 57. TEMESI J, ARNAL PJ, RUPP T, FÉASSON L, CARTIER R, GERGELÉ L, et al. Are  
953 Females More Resistant to Extreme Neuromuscular Fatigue? *Medicine & Science in Sports*  
954 *& Exercise* [Internet]. Lippincott Williams and Wilkins; 2015 [cited 2020 Jun 10];47:1372–82.  
955 Available from: <http://journals.lww.com/00005768-201507000-00007>
- 956 58. Brooke MH, Kaiser KK. Muscle Fiber Types: How Many and What Kind? *Archives of*  
957 *Neurology* [Internet]. *Arch Neurol*; 1970 [cited 2020 Jun 22];23:369–79. Available from:  
958 <https://pubmed.ncbi.nlm.nih.gov/4248905/>
- 959 59. Zierath JR, Hawley JA. Skeletal Muscle Fiber Type: Influence on Contractile and  
960 Metabolic Properties. *PLoS Biology* [Internet]. Public Library of Science; 2004 [cited 2020  
961 Jun 2];2:e348. Available from: <https://dx.plos.org/10.1371/journal.pbio.0020348>
- 962 60. Staron RS, Hagerman FC, Hikida RS, Murray TF, Hostler DP, Crill MT, et al. Fiber type  
963 composition of the vastus lateralis muscle of young men and women. *Journal of*  
964 *Histochemistry and Cytochemistry* [Internet]. Histochemical Society Inc.; 2000 [cited 2020  
965 Jun 23];48:623–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/10769046/>
- 966 61. Welle S, Tawil R, Thornton CA. Sex-related differences in gene expression in human  
967 skeletal muscle. *PLoS ONE*. *PLoS One*; 2008;3.
- 968 62. Parker BA, Smithmyer SL, Pelberg JA, Mishkin AD, Herr MD, Proctor DN. Sex  
969 differences in leg vasodilation during graded knee extensor exercise in young adults. *Journal*  
970 *of Applied Physiology* [Internet]. *J Appl Physiol* (1985); 2007 [cited 2020 Aug 4];103:1583–  
971 91. Available from: <https://pubmed.ncbi.nlm.nih.gov/17717115/>
- 972 63. Roepstorff C, Thiele M, Hillig T, Pilegaard H, Richter EA, Wojtaszewski JFP, et al. Higher  
973 skeletal muscle  $\alpha$ 2AMPK activation and lower energy charge and fat oxidation in men than  
974 in women during submaximal exercise. *Journal of Physiology* [Internet]. *J Physiol*; 2006  
975 [cited 2020 Aug 4];574:125–38. Available from: <https://pubmed.ncbi.nlm.nih.gov/16600998/>
- 976 64. Miller AEJ, MacDougall JD, Tarnopolsky MA, Sale DG. Gender differences in strength  
977 and muscle fiber characteristics. *European Journal of Applied Physiology and Occupational*  
978 *Physiology* [Internet]. Springer-Verlag; 1993 [cited 2020 Aug 4];66:254–62. Available from:  
979 <https://link.springer.com/article/10.1007/BF00235103>
- 980 65. Barnes WS. The relationship between maximum isometric strength and intramuscular  
981 circulatory occlusion. *Ergonomics* [Internet]. *Ergonomics*; 1980 [cited 2020 Aug 28];23:351–  
982 7. Available from: <https://pubmed.ncbi.nlm.nih.gov/7202390/>
- 983 66. Martin PG, Rattey J. Central fatigue explains sex differences in muscle fatigue and  
984 contralateral cross-over effects of maximal contractions. *Pflugers Archiv European Journal of*

- 985 Physiology [Internet]. Springer; 2007 [cited 2020 Aug 4];454:957–69. Available from:  
986 <https://link.springer.com/article/10.1007/s00424-007-0243-1>
- 987 67. Russ DW, Kent-Braun JA. Sex differences in human skeletal muscle fatigue are  
988 eliminated under ischemic conditions. *Journal of Applied Physiology* [Internet]. American  
989 Physiological Society; 2003 [cited 2020 Aug 4];94:2414–22. Available from:  
990 <https://pubmed.ncbi.nlm.nih.gov/12562681/>
- 991 68. Millet GY, Martin V, Temesi J. The role of the nervous system in neuromuscular fatigue  
992 induced by ultra-endurance exercise [Internet]. *Applied Physiology, Nutrition and*  
993 *Metabolism*. Canadian Science Publishing; 2018 [cited 2020 Aug 29]. p. 1151–7. Available  
994 from: <https://pubmed.ncbi.nlm.nih.gov/29726694/>
- 995 69. Sato H, Ohashi J. Sex Differences in Static Muscular Endurance. *Journal of Human*  
996 *Ergology*. 1989;18:53.
- 997 70. Brownstein CG, Millet GY, Thomas K. Neuromuscular responses to fatiguing locomotor  
998 exercise. *Acta Physiologica* [Internet]. Blackwell Publishing Ltd; 2020 [cited 2020 Aug 4];  
999 Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/apha.13533>
- 1000 71. Rossman MJ, Venturelli M, Mcdaniel J, Amann M, Richardson RS. Muscle mass and  
1001 peripheral fatigue: A potential role for afferent feedback? *Acta Physiologica* [Internet]. *Acta*  
1002 *Physiol (Oxf)*; 2012 [cited 2020 Aug 4];206:242–50. Available from:  
1003 <https://pubmed.ncbi.nlm.nih.gov/22762286/>
- 1004 72. O’Leary TJ, Saunders SC, McGuire SJ, Iazard RM. Sex differences in neuromuscular  
1005 fatigability in response to load carriage in the field in British Army recruits. *Journal of Science*  
1006 *and Medicine in Sport* [Internet]. Elsevier Ltd; 2018 [cited 2020 Aug 4];21:591–5. Available  
1007 from: <http://www.jsams.org/article/S1440244017316687/fulltext>
- 1008 73. Boccia G, Dardanello D, Tarperi C, Festa L, la Torre A, Pellegrini B, et al. Women show  
1009 similar central and peripheral fatigue to men after half-marathon\*. *European Journal of Sport*  
1010 *Science* [Internet]. Taylor and Francis Ltd.; 2018 [cited 2020 Aug 4];18:695–704. Available  
1011 from: <https://pubmed.ncbi.nlm.nih.gov/29490592/>
- 1012 74. Glace BW, McHugh MP, Gleim GW. Effects of a 2-hour run on metabolic economy and  
1013 lower extremity strength in men and women. *Journal of Orthopaedic and Sports Physical*  
1014 *Therapy* [Internet]. Movement Science Media; 1998 [cited 2020 Aug 4];27:189–96. Available  
1015 from: <https://pubmed.ncbi.nlm.nih.gov/9513864/>
- 1016 75. Romer LM, Polkey MI. Exercise-induced respiratory muscle fatigue: Implications for  
1017 performance. *Journal of Applied Physiology*. 2008. p. 879–88.
- 1018 76. Taylor BJ, How SC, Romer LM. Exercise-induced abdominal muscle fatigue in healthy  
1019 humans. *Journal of Applied Physiology* [Internet]. *J Appl Physiol* (1985); 2006 [cited 2020  
1020 Aug 31];100:1554–62. Available from: <https://pubmed.ncbi.nlm.nih.gov/16424068/>
- 1021 77. Johnson BD, Babcock MA, Suman OE, Dempsey JA. Exercise-induced diaphragmatic  
1022 fatigue in healthy humans. *The Journal of Physiology* [Internet]. John Wiley & Sons, Ltd;  
1023 1993 [cited 2020 Aug 19];460:385–405. Available from:  
1024 <https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/jphysiol.1993.sp019477>
- 1025 78. Tiller NB, Campbell IG, Romer LM. Influence of Upper-Body Exercise on the Fatigability  
1026 of Human Respiratory Muscles. *Medicine and Science in Sports and Exercise*.  
1027 2017;49:1461–72.

- 1028 79. Gonzales JU, Scheuermann BW. Gender differences in the fatigability of the inspiratory  
1029 muscles. *Medicine and Science in Sports and Exercise* [Internet]. Med Sci Sports Exerc;  
1030 2006 [cited 2020 Jun 22];38:472–9. Available from:  
1031 <https://pubmed.ncbi.nlm.nih.gov/16540834/>
- 1032 80. Guenette JA, Romer LM, Querido JS, Chua R, Eves ND, Road JD, et al. SEX  
1033 DIFFERENCES IN EXERCISE-INDUCED DIAPHRAGMATIC FATIGUE IN 2 ENDURANCE-  
1034 TRAINED ATHLETES 3 4. *Articles in PresS J Appl Physiol*. 2010;
- 1035 81. Mitchell RA, Schaeffer MR, Ramsook AH, Wilkie SS, Guenette JA. Sex differences in  
1036 respiratory muscle activation patterns during high-intensity exercise in healthy humans.  
1037 *Respiratory Physiology and Neurobiology* [Internet]. Elsevier B.V.; 2018 [cited 2020 Sep  
1038 18];247:57–60. Available from: <https://pubmed.ncbi.nlm.nih.gov/28890403/>
- 1039 82. Abraham KA, Feingold H, Fuller DD, Jenkins M, Mateika JH, Fregosi RF. Respiratory-  
1040 related activation of human abdominal muscles during exercise. *Journal of Physiology*  
1041 [Internet]. Wiley-Blackwell; 2002 [cited 2020 Jun 22];541:653–63. Available from:  
1042 </pmc/articles/PMC2290343/?report=abstract>
- 1043 83. Dominelli PB, Molgat-Seon Y, Bingham D, Swartz PM, Road JD, Foster GE, et al.  
1044 Dysanapsis and the resistive work of breathing during exercise in healthy men and women.  
1045 *Journal of Applied Physiology* [Internet]. American Physiological Society; 2015 [cited 2020  
1046 Jun 22];119:1105–13. Available from: </pmc/articles/PMC4816413/?report=abstract>
- 1047 84. Sheel AW, Dominelli PB, Molgat-Seon Y. Revisiting dysanapsis: Sex-based differences  
1048 in airways and the mechanics of breathing during exercise. *Experimental Physiology*.  
1049 Blackwell Publishing Ltd; 2016. p. 213–8.
- 1050 85. Dominelli PB, Render JN, Molgat-Seon Y, Foster GE, Romer LM, Sheel AW. Oxygen  
1051 cost of exercise hyperpnoea is greater in women compared with men. *The Journal of*  
1052 *Physiology* [Internet]. Blackwell Publishing Ltd; 2015 [cited 2020 Jun 15];593:1965–79.  
1053 Available from: <http://doi.wiley.com/10.1113/jphysiol.2014.285965>
- 1054 86. Nikolaidis P, Ćuk I, Knechtle B. Pacing of Women and Men in Half-Marathon and  
1055 Marathon Races. *Medicina* [Internet]. MDPI AG; 2019 [cited 2020 Sep 1];55:14. Available  
1056 from: <http://www.mdpi.com/1010-660X/55/1/14>
- 1057 87. March DS, Vanderburgh PM, Titlebaum PJ, Hoops ML. Age, Sex, and Finish Time as  
1058 Determinants of Pacing in the Marathon. *Journal of Strength and Conditioning Research*  
1059 [Internet]. 2011 [cited 2020 Sep 1];25:386–91. Available from:  
1060 <http://journals.lww.com/00124278-201102000-00014>
- 1061 88. Renfree A, Crivoi do Carmo E, Martin L. The influence of performance level, age and  
1062 gender on pacing strategy during a 100-km ultramarathon. *European Journal of Sport*  
1063 *Science*. Taylor and Francis Ltd.; 2016;16:409–15.
- 1064 89. Deaner RO, Lowen A. Males and Females Pace Differently in High School Cross-  
1065 Country Races. *Journal of Strength and Conditioning Research*. NSCA National Strength  
1066 and Conditioning Association; 2016;30:2991–7.
- 1067 90. Hubble C, Zhao J. Gender differences in marathon pacing and performance prediction.  
1068 *Journal of Sports Analytics*. 2016;2:19–36.
- 1069 91. Deaner RO, Addona V, Hanley B. Risk taking runners slow more in the marathon.  
1070 *Frontiers in Psychology*. Frontiers Media S.A.; 2019;10.

- 1071 92. Goudriaan AE, Lapauw B, Ruige J, Feyen E, Kaufman J-M, Brand M, et al. The influence  
1072 of high-normal testosterone levels on risk-taking in healthy males in a 1-week letrozole  
1073 administration study. *Psychoneuroendocrinology* [Internet]. 2010 [cited 2020 Jun  
1074 9];35:1416–21. Available from:  
1075 <https://linkinghub.elsevier.com/retrieve/pii/S0306453010000958>
- 1076 93. Waśkiewicz Z, Kápcińska B, Sadowska-Krępa E, Czuba M, Kempa K, Kimsa E, et al.  
1077 Acute metabolic responses to a 24-h ultra-marathon race in male amateur runners.  
1078 *European Journal of Applied Physiology*. *Eur J Appl Physiol*; 2012. p. 1679–88.
- 1079 94. Bergström J, Hultman E. Muscle glycogen synthesis after exercise: An enhancing factor  
1080 localized to the muscle cells in man [22]. *Nature*. *Nature*; 1966. p. 309–10.
- 1081 95. Monaco C, Whitfield J, Jain SS, Spriet LL, Bonen A, Holloway GP. Activation of AMPK $\alpha$ 2  
1082 Is Not Required for Mitochondrial FAT/CD36 Accumulation during Exercise. Moro C, editor.  
1083 *PLOS ONE* [Internet]. Public Library of Science; 2015 [cited 2020 Jun 10];10:e0126122.  
1084 Available from: <https://dx.plos.org/10.1371/journal.pone.0126122>
- 1085 96. Ibrahimi A, Bonen A, Blinn WD, Hajri T, Li X, Zhong K, et al. Muscle-specific  
1086 overexpression of FAT/CD36 enhances fatty acid oxidation by contracting muscle, reduces  
1087 plasma triglycerides and fatty acids, and increases plasma glucose and insulin. *Journal of*  
1088 *Biological Chemistry*. *J Biol Chem*; 1999;274:26761–6.
- 1089 97. Kiens B, Roepstorff C, Glatz JFC, Bonen A, Schjerling P, Knudsen J, et al. Lipid-binding  
1090 proteins and lipoprotein lipase activity in human skeletal muscle: Influence of physical  
1091 activity and gender. *Journal of Applied Physiology*. *J Appl Physiol* (1985); 2004;97:1209–18.
- 1092 98. Miotto PM, McGlory C, Holloway TM, Phillips SM, Holloway GP. Sex differences in  
1093 mitochondrial respiratory function in human skeletal muscle. *American Journal of*  
1094 *Physiology-Regulatory, Integrative and Comparative Physiology* [Internet]. American  
1095 *Physiological Society*; 2018 [cited 2020 May 30];314:R909–15. Available from:  
1096 <https://www.physiology.org/doi/10.1152/ajpregu.00025.2018>
- 1097 99. Devries MC. Sex-based differences in endurance exercise muscle metabolism: Impact  
1098 on exercise and nutritional strategies to optimize health and performance in women.  
1099 *Experimental Physiology*. Blackwell Publishing Ltd; 2016;101:243–9.
- 1100 100. Melanson EL, Sharp TA, Seagle HM, Horton TJ, Donahoo WT, Grunwald GK, et al.  
1101 Effect of exercise intensity on 24-h energy expenditure and nutrient oxidation. *Journal of*  
1102 *applied physiology* (Bethesda, Md : 1985) [Internet]. American Physiological Society; 2002  
1103 [cited 2020 Jun 17];92:1045–52. Available from:  
1104 <http://www.ncbi.nlm.nih.gov/pubmed/11842038>
- 1105 101. Tarnopolsky LJ, MacDougall JD, Atkinson SA, Tarnopolsky MA, Sutton JR. Gender  
1106 differences in substrate for endurance exercise. *Journal of Applied Physiology* [Internet]. *J*  
1107 *Appl Physiol* (1985); 1990 [cited 2020 Jun 22];68:302–8. Available from:  
1108 <https://pubmed.ncbi.nlm.nih.gov/2179207/>
- 1109 102. Chenevière X, Borrani F, Sangsue D, Gojanovic B, Malatesta D. Gender differences in  
1110 whole-body fat oxidation kinetics during exercise. *Applied Physiology, Nutrition and*  
1111 *Metabolism*. *Appl Physiol Nutr Metab*; 2011;36:88–95.
- 1112 103. Venables MC, Achten J, Jeukendrup AE. Determinants of fat oxidation during exercise  
1113 in healthy men and women: A cross-sectional study. *Journal of Applied Physiology*.  
1114 *American Physiological Society*; 2005;98:160–7.

- 1115 104. Lundsgaard A, Kiens B. Gender differences in skeletal muscle substrate metabolism -  
1116 molecular mechanisms and insulin sensitivity. *Frontiers in Endocrinology*. 2014;5.
- 1117 105. Jeukendrup AE, Jentjens RPLG, Moseley L. Nutritional Considerations in Triathlon.  
1118 *Sports Med*. 2005.
- 1119 106. Civitarese AE, Hesselink MKC, Russell AP, Ravussin E, Schrauwen P. Glucose  
1120 ingestion during exercise blunts exercise-induced gene expression of skeletal muscle fat  
1121 oxidative genes. *American Journal of Physiology-Endocrinology and Metabolism* [Internet].  
1122 American Physiological Society; 2005 [cited 2020 Jun 11];289:E1023–9. Available from:  
1123 <https://www.physiology.org/doi/10.1152/ajpendo.00193.2005>
- 1124 107. Henderson GC. Sexual dimorphism in the effects of exercise on metabolism of lipids to  
1125 support resting metabolism. *Frontiers in Endocrinology*. Frontiers Media S.A.; 2014.
- 1126 108. Coyle EF. Physiological regulation of marathon performance. *Sports Medicine*. Adis  
1127 International Ltd; 2007. p. 306–11.
- 1128 109. Tanaka H, Bassett DR, Swensen TC, Sampedro RM. Aerobic and anaerobic power  
1129 characteristics of competitive cyclists in the United States cycling federation. *International*  
1130 *Journal of Sports Medicine* [Internet]. *Int J Sports Med*; 1993 [cited 2020 Jun 22];14:334–8.  
1131 Available from: <https://pubmed.ncbi.nlm.nih.gov/8407064/>
- 1132 110. Emerick P, Teed K, Rusk G, Fernhall B. Predictors of marathon performance in female  
1133 runners. *Sports Medicine, Training and Rehabilitation*. Taylor & Francis Group ; 1997;8:23–  
1134 36.
- 1135 111. Maughan RJ, Leiper JB. Aerobic capacity and fractional utilisation of aerobic capacity in  
1136 elite and non-elite male and female marathon runners. *European Journal of Applied*  
1137 *Physiology and Occupational Physiology*. Springer; 1983;52:80–7.
- 1138 112. Loe H, Rognmo Ø, Saltin B, Wisløff U. Aerobic Capacity Reference Data in 3816  
1139 Healthy Men and Women 20-90 Years. 2013 [cited 2020 Jun 10]; Available from:  
1140 [www.ntnu.edu/hunt](http://www.ntnu.edu/hunt)
- 1141 113. Calbet JAL, Joyner MJ. Disparity in regional and systemic circulatory capacities: Do  
1142 they affect the regulation of the circulation? [Internet]. *Acta Physiologica*. Blackwell  
1143 Publishing Ltd; 2010 [cited 2020 Aug 14]. p. 393–406. Available from:  
1144 [/pmc/articles/PMC3011865/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/20111865/)
- 1145 114. Astrand P. Human Physical Fitness With Special Reference to Sex and Age From the  
1146 Department of Physiology. *Physiological Reviews*. 1956;36:307–35.
- 1147 115. Cureton KJ, Bishop P, Cureton K, Bishop P, Hutchinson P, Newland H, et al. Sex  
1148 difference in maximal oxygen uptake Effect of equating haemoglobin concentration.  
1149 *European Journal of Applied Physiology-and Occupational Physiology O Spmger-Vedag*  
1150 [Internet]. 1986 [cited 2020 Sep 1];54:656–60. Available from:  
1151 <https://www.researchgate.net/publication/19212802>
- 1152 116. Barun Sharma H, Kailashiya J. Gender Difference in Aerobic Capacity and the  
1153 Contribution by Body Composition and Haemoglobin Concentration: A Study in Young Indian  
1154 National Hockey Players. *Journal of Clinical and Diagnostic Research*. 2016;10:CC09-CC13.
- 1155 117. Cardinale DA, Larsen FJ, Schiffer TA, Morales-Alamo D, Ekblom B, Calbet JAL, et al.  
1156 Superior intrinsic mitochondrial respiration in women than in men. *Frontiers in Physiology*.  
1157 Frontiers Media S.A.; 2018;9.



- 1158 118. Torres MJ, Kew KA, Ryan TE, Pennington ER, Lin C te, Buddo KA, et al. 17 $\beta$ -Estradiol  
1159 Directly Lowers Mitochondrial Membrane Microviscosity and Improves Bioenergetic Function  
1160 in Skeletal Muscle. *Cell Metabolism*. Cell Press; 2018;27:167-179.e7.
- 1161 119. Davies CTM, Thompson MW. Aerobic performance of female marathon and male  
1162 ultramarathon athletes. *European Journal of Applied Physiology and Occupational*  
1163 *Physiology*. Springer-Verlag; 1979;41:233–45.
- 1164 120. Whyte G, Lumley S, George K, Gates P, Sharma S, Prasad K, et al. Physiological  
1165 profile and predictors of cycling performance in ultra-endurance triathletes. *Journal of Sports*  
1166 *Medicine and Physical Fitness*. 2000;40:103–9.
- 1167 121. Laursen PB, Rhodes EC. Factors affecting performance in an ultraendurance triathlon.  
1168 *Sports Medicine*. Adis International Ltd; 2001. p. 195–209.
- 1169 122. Ingham SA, Whyte GP, Pedlar C, Bailey DM, Dunman N, Nevill AM. Determinants of  
1170 800-m and 1500-m running performance using allometric models. *Medicine and Science in*  
1171 *Sports and Exercise*. *Med Sci Sports Exerc*; 2008;40:345–50.
- 1172 123. Joyner MJ. Modeling: Optimal marathon performance on the basis of physiological  
1173 factors. *Journal of Applied Physiology*. *J Appl Physiol* (1985); 1991;70:683–7.
- 1174 124. Joyner MJ. Physiological limits to endurance exercise performance: influence of sex  
1175 [Internet]. *Journal of Physiology*. Blackwell Publishing Ltd; 2017 [cited 2020 Sep 21]. p.  
1176 2949–54. Available from: [/pmc/articles/PMC5407964/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/3407964/)
- 1177 125. Helgerud J, Ingjer F, Strømme SB. Sex differences in performance-matched marathon  
1178 runners. *European Journal of Applied Physiology and Occupational Physiology*. Springer-  
1179 Verlag; 1990;61:433–9.
- 1180 126. Daniels J, Daniels N. Running Economy of Elite Male and Elite Female Runners.  
1181 *Medicine & Science in Sports & Exercise*. 1992;24:483–9.
- 1182 127. Fletcher JR, Pfister TR, Macintosh BR. Energy cost of running and achilles tendon  
1183 stiffness in man and woman trained runners. *Physiological Reports* [Internet]. American  
1184 Physiological Society; 2013 [cited 2020 Aug 31];1. Available from:  
1185 <https://pubmed.ncbi.nlm.nih.gov/24744857/>
- 1186 128. Bourdin M, Pastene J, Germain M, Lacour JR. Influence of training, sex, age and body  
1187 mass on the energy cost of running. *European Journal of Applied Physiology and*  
1188 *Occupational Physiology* [Internet]. Springer-Verlag; 1993 [cited 2020 Aug 31];66:439–44.  
1189 Available from: <https://pubmed.ncbi.nlm.nih.gov/8330613/>
- 1190 129. Bielik V. Gender differences of running kinematics and economy in trained distance  
1191 runners. *Gazzetta Medica Italiana Archivio per le Scienze Mediche*. Edizioni Minerva  
1192 Medica; 2019;178:403–10.
- 1193 130. Yasuda N, Gaskill SE, Ruby BC. No gender-specific differences in mechanical  
1194 efficiency during arm or leg exercise relative to ventilatory threshold. *Scandinavian Journal*  
1195 *of Medicine and Science in Sports* [Internet]. *Scand J Med Sci Sports*; 2008 [cited 2020 Sep  
1196 21];18:205–12. Available from: <https://pubmed.ncbi.nlm.nih.gov/17490463/>
- 1197 131. Ainegren M, Carlsson P, Tinnsten M, Laaksonen MS. Skiing economy and efficiency in  
1198 recreational and elite cross-country skiers. *Journal of Strength and Conditioning Research*  
1199 [Internet]. *J Strength Cond Res*; 2013 [cited 2020 Sep 21];27:1239–52. Available from:  
1200 <https://pubmed.ncbi.nlm.nih.gov/22344058/>

- 1201 132. Hegge AM, Bucher E, Ettema G, Faude O, Holmberg HC, Sandbakk Ø. Gender  
1202 differences in power production, energetic capacity and efficiency of elite cross-country  
1203 skiers during whole-body, upper-body, and arm poling. *European Journal of Applied*  
1204 *Physiology* [Internet]. Springer Verlag; 2016 [cited 2020 Sep 21];116:291–300. Available  
1205 from: <https://pubmed.ncbi.nlm.nih.gov/26476546/>
- 1206 133. Billat V, Lepretre PM, Heugas AM, Laurence MH, Salim D, Koralsztein JP. Training and  
1207 bioenergetic characteristics in elite male and female Kenyan runners. *Medicine and Science*  
1208 *in Sports and Exercise* [Internet]. *Med Sci Sports Exerc*; 2003 [cited 2020 Sep 21];35:297–  
1209 304. Available from: <https://pubmed.ncbi.nlm.nih.gov/12569219/>
- 1210 134. Lacour JR, Bourdin M. Factors affecting the energy cost of level running at submaximal  
1211 speed [Internet]. *European Journal of Applied Physiology*. Springer Verlag; 2015 [cited 2020  
1212 Sep 21]. p. 651–73. Available from: <https://pubmed.ncbi.nlm.nih.gov/25681108/>
- 1213 135. Balducci P, Cléménçon M, Trama R, Blache Y, Hautier C. Performance Factors in a  
1214 Mountain Ultramarathon. *International Journal of Sports Medicine* [Internet]. Georg Thieme  
1215 Verlag; 2017 [cited 2020 Jun 10];38:819–26. Available from: [http://www.thieme-](http://www.thieme-connect.de/DOI/DOI?10.1055/s-0043-112342)  
1216 [connect.de/DOI/DOI?10.1055/s-0043-112342](http://www.thieme-connect.de/DOI/DOI?10.1055/s-0043-112342)
- 1217 136. VanHeest JL, Mahoney CE, Herr L. Characteristics of elite open-water swimmers.  
1218 *Journal of Strength and Conditioning Research* [Internet]. *J Strength Cond Res*; 2004 [cited  
1219 2020 Aug 31];18:302–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/15142018/>
- 1220 137. Toussaint HM, de Groot G, Savelberg HHCM, Vervoorn K, Hollander AP, van Ingen  
1221 Schenau GJ. Active drag related to velocity in male and female swimmers. *Journal of*  
1222 *Biomechanics* [Internet]. *J Biomech*; 1988 [cited 2020 Sep 21];21:435–8. Available from:  
1223 <https://pubmed.ncbi.nlm.nih.gov/3417695/>
- 1224 138. Cureton K, Sparling P, Evans B, Johnson S, Kong U, Purvis J. Effect of experimental  
1225 alterations in excess weight on aerobic capacity and distance running performance.  
1226 *Medicine and Science in Sports*. 1978;10:194–9.
- 1227 139. Sandbakk Ø, Solli GS, Holmberg HC. Sex differences in world-record performance: The  
1228 influence of sport discipline and competition duration [Internet]. *International Journal of*  
1229 *Sports Physiology and Performance*. Human Kinetics Publishers Inc.; 2018 [cited 2020 Aug  
1230 31]. p. 2–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/28488921/>
- 1231 140. Pendergast DR, di Prampero PE, Craig AB, Wilson DR, Rennie DW. Quantitative  
1232 analysis of the front crawl in men and women. *Journal of Applied Physiology Respiratory*  
1233 *Environmental and Exercise Physiology* [Internet]. *J Appl Physiol Respir Environ Exerc*  
1234 *Physiol*; 1977 [cited 2020 Sep 21];43:475–9. Available from:  
1235 <https://pubmed.ncbi.nlm.nih.gov/914719/>
- 1236 141. Lavoie JM, Montpetit RR. Applied Physiology of Swimming [Internet]. *Sports Medicine:*  
1237 *An International Journal of Applied Medicine and Science in Sport and Exercise*. *Sports*  
1238 *Med*; 1986 [cited 2020 Sep 21]. p. 165–89. Available from:  
1239 <https://pubmed.ncbi.nlm.nih.gov/3520747/>
- 1240 142. Wierman ME. Sex steroid effects at target tissues: mechanisms of action. *Advances in*  
1241 *Physiology Education* [Internet]. American Physiological Society; 2007 [cited 2020 Jun  
1242 18];31:26–33. Available from: <https://www.physiology.org/doi/10.1152/advan.00086.2006>
- 1243 143. Storer TW, Magliano L, Woodhouse L, Lee ML, Dzekov C, Dzekov J, et al.  
1244 Testosterone dose-dependently increases maximal voluntary strength and leg power, but

- 1245 does not affect fatigability or specific tension. *Journal of Clinical Endocrinology and*  
1246 *Metabolism*. *J Clin Endocrinol Metab*; 2003;88:1478–85.
- 1247 144. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, et al.  
1248 Testosterone dose-response relationships in healthy young men. *American Journal of*  
1249 *Physiology - Endocrinology and Metabolism*. American Physiological Society; 2001;281.
- 1250 145. Gleason ED, Fuxjager MJ, Oyegbile TO, Marler CA. Testosterone release and social  
1251 context: When it occurs and why. *Frontiers in Neuroendocrinology*. *Front Neuroendocrinol*;  
1252 2009;30:460–9.
- 1253 146. Rovira-Llopis S, Bañuls C, de Marañon AM, Diaz-Morales N, Jover A, Garzon S, et al.  
1254 Low testosterone levels are related to oxidative stress, mitochondrial dysfunction and altered  
1255 subclinical atherosclerotic markers in type 2 diabetic male patients. *Free Radical Biology and*  
1256 *Medicine*. Elsevier Inc.; 2017;108:155–62.
- 1257 147. Petersson SJ, Christensen LL, Kristensen JM, Kruse R, Andersen M, Højlund K. Effect  
1258 of testosterone on markers of mitochondrial oxidative phosphorylation and lipid metabolism  
1259 in muscle of aging men with subnormal bioavailable testosterone. *European Journal of*  
1260 *Endocrinology* [Internet]. 2014 [cited 2020 Jun 22];171:77–88. Available from: [www.eje-](http://www.eje-online.org)  
1261 [online.org](http://www.eje-online.org)
- 1262 148. Griggs RC, Kingston W, Jozefowicz RF, Herr BE, Forbes G, Halliday D, et al. Effect of  
1263 testosterone on muscle mass and muscle protein synthesis. *J. Appl. Physiol*. 1989.
- 1264 149. Handelsman DJ, Hirschberg AL, Bermon S. Circulating testosterone as the hormonal  
1265 basis of sex differences in athletic performance. *Endocrine Reviews*. Oxford University  
1266 Press; 2018. p. 803–29.
- 1267 150. McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, et al. The  
1268 Effects of Menstrual Cycle Phase on Exercise Performance in Eumenorrhic Women: A  
1269 Systematic Review and Meta-Analysis [Internet]. *Sports Medicine*. Springer; 2020 [cited  
1270 2020 Aug 17]. p. 1–15. Available from: <https://doi.org/10.1007/s40279-020-01319-3>
- 1271 151. Chidi-Ogbolu N, Baar K. Effect of estrogen on musculoskeletal performance and injury  
1272 risk. *Frontiers in Physiology*. Frontiers Media S.A.; 2019. p. 1834.
- 1273 152. Tenan MS. Sex hormone effects on the nervous system and their impact on muscle  
1274 strength and motor performance in women. *Sex Hormones, Exercise and Women: Scientific*  
1275 *and Clinical Aspects* [Internet]. Springer International Publishing; 2016 [cited 2020 Jul 28]. p.  
1276 59–70. Available from: [https://link.springer.com/chapter/10.1007/978-3-319-44558-8\\_4](https://link.springer.com/chapter/10.1007/978-3-319-44558-8_4)
- 1277 153. Shultz SJ, Schmitz RJ, Beynnon BD. Variations in varus/valgus and internal/external  
1278 rotational knee laxity and stiffness across the menstrual cycle. *Journal of Orthopaedic*  
1279 *Research*. NIH Public Access; 2011;29:318–25.
- 1280 154. The female ACL: Why is it more prone to injury? *Journal of Orthopaedics* [Internet].  
1281 Reed Elsevier India Pvt. Ltd.; 2016 [cited 2020 Aug 31];13:A1–4. Available from:  
1282 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4805849/>
- 1283 155. Almekinders LC, Engle CR. Common and uncommon injuries in ultra-endurance sports.  
1284 *Sports Medicine and Arthroscopy Review*. Lippincott Williams and Wilkins; 2019. p. 25–30.
- 1285 156. Hamadeh MJ, Devries MC, Tarnopolsky MA. Estrogen Supplementation Reduces  
1286 Whole Body Leucine and Carbohydrate Oxidation and Increases Lipid Oxidation in Men  
1287 during Endurance Exercise. *The Journal of Clinical Endocrinology & Metabolism* [Internet].

- 1288 Oxford Academic; 2005 [cited 2020 Jun 17];90:3592–9. Available from:  
1289 <https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2004-1743>
- 1290 157. Santosa S, Jensen MD. Adipocyte fatty acid storage factors enhance subcutaneous fat  
1291 storage in postmenopausal women. *Diabetes*. *Diabetes*; 2013;62:775–82.
- 1292 158. D'Eon TM, Sharoff C, Chipkin SR, Grow D, Ruby BC, Braun B. Regulation of exercise  
1293 carbohydrate metabolism by estrogen and progesterone in women. *American Journal of*  
1294 *Physiology - Endocrinology and Metabolism* [Internet]. American Physiological Society; 2002  
1295 [cited 2020 Jul 28];283:1046–55. Available from: <http://www.ajpendo.orgE1046>
- 1296 159. Isacco L, Boisseau N. Sex hormones and substrate metabolism during endurance  
1297 exercise. *Sex Hormones, Exercise and Women: Scientific and Clinical Aspects* [Internet].  
1298 Springer International Publishing; 2016 [cited 2020 Jul 28]. p. 35–58. Available from:  
1299 [https://link.springer.com/chapter/10.1007/978-3-319-44558-8\\_3](https://link.springer.com/chapter/10.1007/978-3-319-44558-8_3)
- 1300 160. Valencia AP, Schappal AE, Matthew Morris E, Thyfault JP, Lowe DA, Spangenburg EE.  
1301 The presence of the ovary prevents hepatic mitochondrial oxidative stress in young and  
1302 aged female mice through glutathione peroxidase 1. *Experimental Gerontology*. Elsevier  
1303 Inc.; 2016;73:14–22.
- 1304 161. Baltgalvis KA, Greising SM, Warren GL, Lowe DA. Estrogen regulates estrogen  
1305 receptors and antioxidant gene expression in mouse skeletal muscle. *PLoS ONE*. *PLoS*  
1306 *One*; 2010;5.
- 1307 162. Vezzoli A, Dellanoce C, Mrakic-Sposta S, Montorsi M, Moretti S, Tonini A, et al.  
1308 Oxidative Stress Assessment in Response to Ultraendurance Exercise: Thiols Redox Status  
1309 and ROS Production according to Duration of a Competitive Race. *Oxidative Medicine and*  
1310 *Cellular Longevity*. Hindawi Limited; 2016;2016.
- 1311 163. Heikura IA, Uusitalo ALT, Stellingwerff T, Bergland D, Mero AA, Burke LM. Low energy  
1312 availability is difficult to assess but outcomes have large impact on bone injury rates in elite  
1313 distance athletes. *International Journal of Sport Nutrition and Exercise Metabolism* [Internet].  
1314 Human Kinetics Publishers Inc.; 2018 [cited 2020 Jul 28];28:403–11. Available from:  
1315 <https://pubmed.ncbi.nlm.nih.gov/29252050/>
- 1316 164. Miller S, Kukuljan S, Turner A, van der Pligt P, Ducher G. Energy Deficiency, Menstrual  
1317 Disturbances, and Low Bone Mass: What Do Exercising Australian Women Know About the  
1318 Female Athlete Triad? *International Journal of Sport Nutrition and Exercise Metabolism*.  
1319 2012;22:131–8.
- 1320 165. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP. The  
1321 female athlete triad. *Medicine and Science in Sports and Exercise* [Internet]. *Med Sci Sports*  
1322 *Exerc*; 2007 [cited 2020 Jul 28];39:1867–82. Available from:  
1323 <https://pubmed.ncbi.nlm.nih.gov/17909417/>
- 1324 166. Riggs BL. The mechanisms of estrogen regulation of bone resorption. *Journal of*  
1325 *Clinical Investigation*. The American Society for Clinical Investigation; 2000. p. 1203–4.
- 1326 167. Chen YT, Tenforde AS, Fredericson M. Update on stress fractures in female athletes:  
1327 Epidemiology, treatment, and prevention. *Current Reviews in Musculoskeletal Medicine*.  
1328 Springer; 2013;6:173–81.
- 1329 168. Papageorgiou M, Elliott-Sale KJ, Parsons A, Tang JCY, Greeves JP, Fraser WD, et al.  
1330 Effects of reduced energy availability on bone metabolism in women and men. *Bone*

- 1331 [Internet]. Elsevier Inc.; 2017 [cited 2020 Jul 28];105:191–9. Available from:  
1332 <https://pubmed.ncbi.nlm.nih.gov/28847532/>
- 1333 169. Elliott-Sale KJ, Tenforde AS, Parziale AL, Holtzman B, Ackerman KE. Endocrine effects  
1334 of relative energy deficiency in sport. *International Journal of Sport Nutrition and Exercise*  
1335 *Metabolism* [Internet]. Human Kinetics Publishers Inc.; 2018 [cited 2020 Jul 28];28:335–49.  
1336 Available from: <https://pubmed.ncbi.nlm.nih.gov/30008240/>
- 1337 170. Martin D, Sale C, Cooper SB, Elliott-Sale KJ. Period prevalence and perceived side  
1338 effects of hormonal contraceptive use and the menstrual cycle in elite athletes. *International*  
1339 *Journal of Sports Physiology and Performance* [Internet]. Human Kinetics Publishers Inc.;  
1340 2018 [cited 2020 Jul 28];13:926–32. Available from:  
1341 <https://pubmed.ncbi.nlm.nih.gov/29283683/>
- 1342 171. de Oliveira EP, Burini RC, Jeukendrup A. Gastrointestinal complaints during exercise:  
1343 Prevalence, etiology, and nutritional recommendations. *Sports Medicine*. Springer  
1344 International Publishing; 2014;44:79.
- 1345 172. Riddoch C, Trinick T. Gastrointestinal disturbances in marathon runners. *British journal*  
1346 *of sports medicine*. BMJ Publishing Group; 1988;22:71–4.
- 1347 173. Stuempfle KJ, Hoffman MD. Gastrointestinal distress is common during a 161-km  
1348 ultramarathon. *Journal of Sports Sciences*. Routledge; 2015;33:1814–21.
- 1349 174. Wilson PB. ‘I think I’m gonna hurl’: A Narrative Review of the Causes of Nausea and  
1350 Vomiting in Sport. *Sports* [Internet]. MDPI AG; 2019 [cited 2020 Sep 15];7:162. Available  
1351 from: <https://pubmed.ncbi.nlm.nih.gov/31277403/>
- 1352 175. Rowlands DS, Swift M, Ros M, Green JG. Composite versus single transportable  
1353 carbohydrate solution enhances race and laboratory cycling performance. *Applied*  
1354 *Physiology, Nutrition and Metabolism* [Internet]. *Appl Physiol Nutr Metab*; 2012 [cited 2020  
1355 Sep 15];37:425–36. Available from: <https://pubmed.ncbi.nlm.nih.gov/22468766/>
- 1356 176. O’Brien WJ, Stannard SR, Clarke JA, Rowlands DS. Fructose-maltodextrin ratio  
1357 governs exogenous and other cho oxidation and performance. *Medicine and Science in*  
1358 *Sports and Exercise* [Internet]. *Med Sci Sports Exerc*; 2013 [cited 2020 Sep 15];45:1814–24.  
1359 Available from: <https://pubmed.ncbi.nlm.nih.gov/23949097/>
- 1360 177. Costa RJS, Hoffman MD, Stellingwerff T. Considerations for ultra-endurance activities:  
1361 part 1- nutrition [Internet]. *Research in Sports Medicine*. Taylor and Francis Inc.; 2019 [cited  
1362 2020 Sep 15]. p. 166–81. Available from: <https://pubmed.ncbi.nlm.nih.gov/30056753/>
- 1363 178. Hoffman MD, Fogard K. Factors related to successful completion of a 161-km  
1364 ultramarathon. *International Journal of Sports Physiology and Performance* [Internet].  
1365 Human Kinetics Publishers Inc.; 2011 [cited 2020 Sep 15];6:25–37. Available from:  
1366 <https://pubmed.ncbi.nlm.nih.gov/21487147/>
- 1367 179. Costa RJS, Snipe RMJ, Kitic CM, Gibson PR. Systematic review: exercise-induced  
1368 gastrointestinal syndrome—implications for health and intestinal disease [Internet].  
1369 *Alimentary Pharmacology and Therapeutics*. Blackwell Publishing Ltd; 2017 [cited 2020 Sep  
1370 15]. p. 246–65. Available from: <https://pubmed.ncbi.nlm.nih.gov/28589631/>
- 1371 180. Wilson PB. Does carbohydrate intake during endurance running improve performance?  
1372 A critical review [Internet]. *Journal of Strength and Conditioning Research*. NSCA National  
1373 Strength and Conditioning Association; 2016 [cited 2020 Sep 15]. p. 3539–59. Available  
1374 from: <https://pubmed.ncbi.nlm.nih.gov/27045602/>

- 1375 181. Cox AJ. Variations in Size of the Human Stomach. *California and western medicine*  
1376 [Internet]. BMJ Publishing Group; 1945 [cited 2020 Sep 15];63:267–8. Available from:  
1377 <http://www.ncbi.nlm.nih.gov/pubmed/18747178>
- 1378 182. Bouras EP, Delgado-Aros S, Camilleri M, Castillo EJ, Burton DD, Thomforde GM, et al.  
1379 SPECT imaging of the stomach: Comparison with barostat, and effects of sex, age, body  
1380 mass index, and fundoplication. *Gut* [Internet]. BMJ Publishing Group; 2002 [cited 2020 Sep  
1381 15];51:781–6. Available from: [/pmc/articles/PMC1773479/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/1173479/)
- 1382 183. Monrroy H, Borghi G, Pribic T, Galan C, Nieto A, Amigo N, et al. Biological response to  
1383 meal ingestion: Gender differences. *Nutrients* [Internet]. MDPI AG; 2019 [cited 2020 Sep  
1384 15];11. Available from: [/pmc/articles/PMC6471145/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/36471145/)
- 1385 184. Probert CJS, Emmett PM, Heaton KW. Intestinal transit time in the population  
1386 calculated from self made observations of defecation. *Journal of Epidemiology and*  
1387 *Community Health* [Internet]. BMJ Publishing Group; 1993 [cited 2020 Sep 15];47:331–3.  
1388 Available from: [/pmc/articles/PMC1059804/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/1059804/)
- 1389 185. Rao SSC, Kuo B, McCallum RW, Chey WD, DiBaise JK, Hasler WL, et al. Investigation  
1390 of Colonic and Whole-Gut Transit With Wireless Motility Capsule and Radiopaque Markers  
1391 in Constipation. *Clinical Gastroenterology and Hepatology* [Internet]. Clin Gastroenterol  
1392 Hepatol; 2009 [cited 2020 Sep 15];7:537–44. Available from:  
1393 <https://pubmed.ncbi.nlm.nih.gov/19418602/>
- 1394 186. Mori H, Suzuki H, Matsuzaki J, Taniguchi K, Shimizu T, Yamane T, et al. Gender  
1395 Difference of Gastric Emptying in Healthy Volunteers and Patients with Functional  
1396 Dyspepsia. *Digestion* [Internet]. S. Karger AG; 2017 [cited 2020 Sep 15];95:72–8. Available  
1397 from: <https://pubmed.ncbi.nlm.nih.gov/28052285/>
- 1398 187. Datz F, Christian P, Moore J. Gender-related differences in gastric emptying. *Journal of*  
1399 *Nuclear Medicine*. 1987;28:1204–7.
- 1400 188. Gangula PRR, Sekhar KR, Mukhopadhyay S. Gender bias in gastroparesis: Is nitric  
1401 oxide the answer? [Internet]. *Digestive Diseases and Sciences*. NIH Public Access; 2011  
1402 [cited 2020 Sep 16]. p. 2520–7. Available from: [/pmc/articles/PMC3170494/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/3170494/)
- 1403 189. Kim YS, Unno T, Kim BY, Park MS. Sex differences in gut microbiota [Internet]. *World*  
1404 *Journal of Men's Health*. Korean Society for Sexual Medicine and Andrology; 2020 [cited  
1405 2020 Sep 15]. p. 48–60. Available from: [/pmc/articles/PMC6920072/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/36920072/)
- 1406 190. Pires W, Veneroso CE, Wanner SP, Pacheco DAS, Vaz GC, Amorim FT, et al.  
1407 Association Between Exercise-Induced Hyperthermia and Intestinal Permeability: A  
1408 Systematic Review [Internet]. *Sports Medicine*. Springer International Publishing; 2017 [cited  
1409 2020 Sep 21]. p. 1389–403. Available from: [https://link.springer.com/article/10.1007/s40279-](https://link.springer.com/article/10.1007/s40279-016-0654-2)  
1410 [016-0654-2](https://link.springer.com/article/10.1007/s40279-016-0654-2)
- 1411 191. Stuempfle KJ, Valentino T, Hew-Butler T, Hecht FM, Hoffman MD. Nausea is  
1412 associated with endotoxemia during a 161-km ultramarathon. *Journal of Sports Sciences*  
1413 [Internet]. Routledge; 2016 [cited 2020 Sep 15];34:1662–8. Available from:  
1414 <https://www.tandfonline.com/doi/full/10.1080/02640414.2015.1130238>
- 1415 192. Brock-Utne J, Gaffin S, Wells M, Gathiram P, Sohar E, James M, et al. Endotoxaemia  
1416 in exhausted runners after a long-distance race. *South African Medical Journal*.  
1417 1988;73:533–6.

- 1418 193. Jeukendrup A, Vet-Joop K, Sturk A, Stegen J, Senden J, Saris W, et al. Relationship  
1419 between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-  
1420 phase reaction during and after a long-distance triathlon in highly trained men. *Clinical*  
1421 *Science* (London, England). 2000;98:47–55.
- 1422 194. Edogawa S, Peters SA, Jenkins GD, Gurunathan S v., Sundt WJ, Johnson S, et al. Sex  
1423 differences in NSAID-induced perturbation of human intestinal barrier function and  
1424 microbiota. *The FASEB Journal* [Internet]. FASEB; 2018 [cited 2020 Sep 21];32:6615–25.  
1425 Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1096/fj.201800560R>
- 1426 195. Mujagic Z, Ludidi S, Keszthelyi D, Hesselink MAM, Kruijmel JW, Lenaerts K, et al. Small  
1427 intestinal permeability is increased in diarrhoea predominant IBS, while alterations in  
1428 gastroduodenal permeability in all IBS subtypes are largely attributable to confounders.  
1429 *Alimentary Pharmacology and Therapeutics* [Internet]. Blackwell Publishing Ltd; 2014 [cited  
1430 2020 Sep 21];40:288–97. Available from: <https://pubmed.ncbi.nlm.nih.gov/24943095/>
- 1431 196. Suenart, Bulteel, den Hond, Hiele, Peeters, Monsuur, et al. The effects of smoking  
1432 and indomethacin on small intestinal permeability. *Alimentary Pharmacology and*  
1433 *Therapeutics* [Internet]. John Wiley & Sons, Ltd; 2000 [cited 2020 Sep 21];14:819–22.  
1434 Available from: <http://doi.wiley.com/10.1046/j.1365-2036.2000.00754.x>
- 1435 197. Haug TT, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal  
1436 symptoms in the general population? *Scandinavian Journal of Gastroenterology* [Internet].  
1437 Taylor & Francis; 2002 [cited 2020 Sep 15];37:294–8. Available from:  
1438 <https://www.tandfonline.com/doi/abs/10.1080/003655202317284192>
- 1439 198. Bytzer P, Howell S, Leemon M, Young LJ, Jones MP, Talley NJ. Low socioeconomic  
1440 class is a risk factor for upper and lower gastrointestinal symptoms: A population based  
1441 study in 15 000 Australian adults. *Gut* [Internet]. Gut; 2001 [cited 2020 Sep 15];49:66–72.  
1442 Available from: <https://pubmed.ncbi.nlm.nih.gov/11413112/>
- 1443 199. Tibblin G, Bengtsson C, Furunes B, Lapidus L. Symptoms by age and sex: The  
1444 population studies of men and women in gothenburg, Sweden. *Scandinavian Journal of*  
1445 *Primary Health Care* [Internet]. Informa Healthcare; 1990 [cited 2020 Sep 15];8:9–17.  
1446 Available from: <https://www.tandfonline.com/doi/abs/10.3109/02813439008994923>
- 1447 200. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the  
1448 menstrual cycle? *BJOG: An International Journal of Obstetrics and Gynaecology* [Internet].  
1449 John Wiley & Sons, Ltd; 1998 [cited 2020 Sep 15];105:1322–5. Available from:  
1450 <http://doi.wiley.com/10.1111/j.1471-0528.1998.tb10014.x>
- 1451 201. ter Steege RWF, van der Palen J, Kolkman JJ. Prevalence of gastrointestinal  
1452 complaints in runners competing in a long-distance run: An internet-based observational  
1453 study in 1281 subjects. *Scandinavian Journal of Gastroenterology* [Internet]. *Scand J*  
1454 *Gastroenterol*; 2008 [cited 2020 Sep 15];43:1477–82. Available from:  
1455 <https://pubmed.ncbi.nlm.nih.gov/18777440/>
- 1456 202. Rehrer NJ, Janssen GME, Brouns F, Saris WHM. Fluid intake and gastrointestinal  
1457 problems in runners competing in a 25-km race and a marathon. *International Journal of*  
1458 *Sports Medicine* [Internet]. *Int J Sports Med*; 1989 [cited 2020 Sep 15];10. Available from:  
1459 <https://pubmed.ncbi.nlm.nih.gov/2744925/>
- 1460 203. Keefe EB, Lowe DK, Goss JR, Wayne R. Gastrointestinal symptoms of marathon  
1461 runners. *Western Journal of Medicine* [Internet]. BMJ Publishing Group; 1984 [cited 2020  
1462 Sep 15];141:481–4. Available from: [/pmc/articles/PMC1021858/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/2744925/)

- 1463 204. Wilson PB, Rhodes GS, Ingraham SJ. Saccharide Composition of Carbohydrates  
1464 Consumed during an Ultra-endurance Triathlon. *Journal of the American College of Nutrition*  
1465 [Internet]. Routledge; 2015 [cited 2020 Sep 15];34:497–506. Available from:  
1466 <https://pubmed.ncbi.nlm.nih.gov/25941980/>
- 1467 205. Costa RJ, Swancott AJ, Gill S, Hankey J, Scheer V, Murray A, et al. Compromised  
1468 energy and macronutrient intake of ultra-endurance runners during a multi-stage ultra-  
1469 marathon conducted in a hot ambient environment. *International Journal of Sports Science*  
1470 [Internet]. Scientific & Academic Publishing Co.; 2013 [cited 2020 Sep 15];3:51–62. Available  
1471 from: <https://www.researchgate.net/publication/256846395>
- 1472 206. Jeukendrup AE. Training the Gut for Athletes [Internet]. *Sports Medicine*. Springer  
1473 International Publishing; 2017 [cited 2020 Sep 15]. p. 101–10. Available from:  
1474 <https://pubmed.ncbi.nlm.nih.gov/28332114/>
- 1475 207. Levine MS, Spencer G, Alavi A, Metz DC. Competitive Speed Eating: Truth and  
1476 Consequences. *American Journal of Roentgenology* [Internet]. American Roentgen Ray  
1477 Society; 2007 [cited 2020 Sep 15];189:681–6. Available from:  
1478 <http://www.ajronline.org/doi/10.2214/AJR.07.2342>
- 1479 208. Cox GR, Clark SA, Cox AJ, Halson SL, Hargreaves M, Hawley JA, et al. Daily training  
1480 with high carbohydrate availability increases exogenous carbohydrate oxidation during  
1481 endurance cycling. *Journal of Applied Physiology* [Internet]. American Physiological Society;  
1482 2010 [cited 2020 Sep 15];109:126–34. Available from:  
1483 <https://pubmed.ncbi.nlm.nih.gov/20466803/>
- 1484 209. Miall A, Khoo A, Rauch C, Snipe RMJ, Camões-Costa VL, Gibson PR, et al. Two  
1485 weeks of repetitive gut-challenge reduce exercise-associated gastrointestinal symptoms and  
1486 malabsorption. *Scandinavian Journal of Medicine and Science in Sports* [Internet]. Blackwell  
1487 Munksgaard; 2018 [cited 2020 Sep 15];28:630–40. Available from:  
1488 <https://pubmed.ncbi.nlm.nih.gov/28508559/>
- 1489 210. Costa RJS, Miall A, Khoo A, Rauch C, Snipe R, Camões-Costa V, et al. Gut-training:  
1490 the impact of two weeks repetitive gut-challenge during exercise on gastrointestinal status,  
1491 glucose availability, fuel kinetics, and running performance. *Applied physiology, nutrition,*  
1492 *and metabolism = Physiologie appliquee, nutrition et metabolisme* [Internet]. *Appl Physiol*  
1493 *Nutr Metab*; 2017 [cited 2020 Sep 15];42:547–57. Available from:  
1494 <https://pubmed.ncbi.nlm.nih.gov/28177715/>
- 1495 211. Viribay A, Arribalzaga S, Mielgo-Ayuso J, Castañeda-Babarro A, Seco-Calvo J,  
1496 Urdampilleta A. Effects of 120 g/h of carbohydrates intake during a mountain marathon on  
1497 exercise-induced muscle damage in elite runners. *Nutrients* [Internet]. MDPI AG; 2020 [cited  
1498 2020 Sep 15];12. Available from: <https://pubmed.ncbi.nlm.nih.gov/32403259/>
- 1499 212. Impey S, Jevons E, Mees G, Cocks M, Strauss J, Chester N, et al. Glycogen Utilization  
1500 during Running: Intensity, Sex, and Muscle-specific Responses. *Medicine and Science in*  
1501 *Sports and Exercise*. 2020;Online ahe.
- 1502 213. Costa RJS, Gill SK, Hankey J, Wright A, Marczak S. Perturbed energy balance and  
1503 hydration status in ultra-endurance runners during a 24 h ultra-marathon. *British Journal of*  
1504 *Nutrition* [Internet]. Cambridge University Press; 2014 [cited 2020 Sep 15];112:428–37.  
1505 Available from: <https://pubmed.ncbi.nlm.nih.gov/24818799/>
- 1506 214. Wardenaar FC, Dijkhuizen R, Ceelen IJM, Jonk E, de Vries JHM, Witkamp RF, et al.  
1507 Nutrient intake by ultramarathon runners: Can they meet recommendations? *International*



- 1508 Journal of Sport Nutrition and Exercise Metabolism [Internet]. Human Kinetics Publishers  
1509 Inc.; 2015 [cited 2020 Sep 15];25:375–86. Available from:  
1510 <https://pubmed.ncbi.nlm.nih.gov/25811196/>
- 1511 215. Gagnon D, Kenny GP. Does sex have an independent effect on thermoeffector  
1512 responses during exercise in the heat? [Internet]. Journal of Physiology. Wiley-Blackwell;  
1513 2012 [cited 2020 Sep 15]. p. 5963–73. Available from:  
1514 </pmc/articles/PMC3530110/?report=abstract>
- 1515 216. Hajali V, Andersen ML, Negah SS, Sheibani V. Sex differences in sleep and sleep loss-  
1516 induced cognitive deficits: The influence of gonadal hormones. Hormones and Behavior.  
1517 Academic Press Inc.; 2019. p. 50–61.
- 1518 217. Deaner RO, Balish SM, Lombardo MP. Sex Differences in Sports Interest and  
1519 Motivation: An Evolutionary Perspective. 2015 [cited 2020 Jun 23]; Available from:  
1520 <http://dx.doi.org/10.1037/ebs0000049>
- 1521
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1523 **TABLES AND FIGURES**

1524

1525 **Table 1.** Comparison of contractile and metabolic properties of the various skeletal muscle  
1526 fiber types. All values are expressed as a fold-change relative to ST oxidative fibers [59]. ST  
1527 = slow-twitch; FT = fast-twitch.

1528

1529 **Fig. 1.** Proposed physiological mechanisms underpinning the sex difference in muscle fatigue,  
1530 these include differences in: 1) motor neuron activation; 2) contractile function of the activated  
1531 fibers; and 3) the magnitude of metabolites accumulating that interfere with contractile  
1532 function. Mechanisms are stipulated with large arrows. Black boxes indicate processes within  
1533 the muscle, white boxes are processes in the nervous system, and the grey are hormonal/  
1534 sympathetic actions. Negative signs indicate physiological variables/processes that are  
1535 exhibited less by females; positive signs indicate physiological variables/processes that are  
1536 exhibited more by females Reproduced from Hunter [52], with permission.

1537

1538 **Fig. 2.** Determinants of performance in ultra-endurance events, and the compromise between  
1539 energy cost and lower-limb tissue damage (dashed lines). The principal determinants are in  
1540 bold. Reproduced from Millet et al [10], with permission. GI = gastrointestinal; NM =  
1541 neuromuscular;  $\dot{V}O_2\text{max}$  = maximal oxygen uptake.

1542

1543 **Fig. 3.** Schematic showing the hormonal fluctuations across an idealized 28-d menstrual cycle,  
1544 with ovulation occurring at day 14 [150].

1545

1546 Table 1.

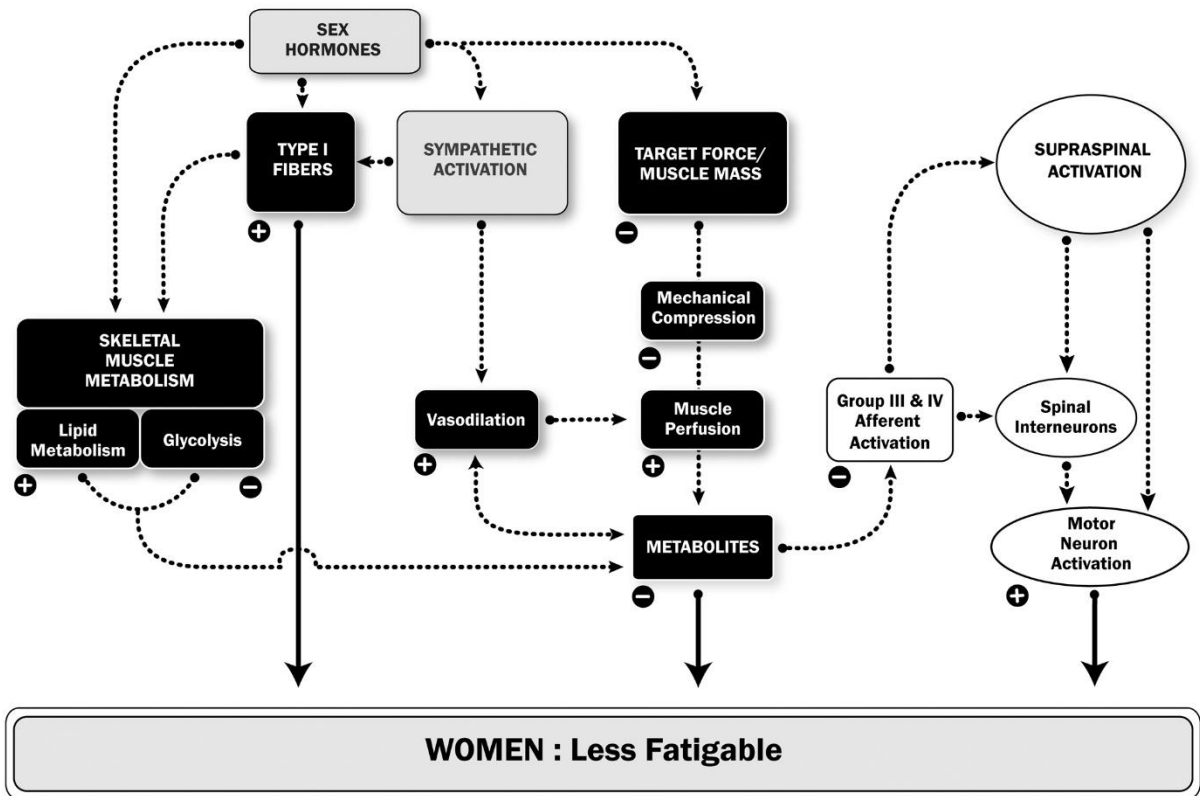
1547

<b>Characteristic</b>	<b>ST Oxidative</b>	<b>FTa Oxidative</b>	<b>FTb Glycolytic</b>
<b>Contractile</b>			
Time to peak tension	1.0	0.4	0.4
Ca <sup>2+</sup> myosin ATPase	1.0	3.0	3.0
Mg <sup>2+</sup> actomyosin ATPase	1.0	2.8	2.8
<b>Enzymatic</b>			
	1.0		
Creatine phosphokinase	1.0	1.3	1.3
Phosphofructokinase	1.0	1.5	2.1
Glycogen phosphorylase	1.0	2.1	3.1
Citrate synthase	1.0	0.8	0.6
<b>Morphological</b>			
Capillary density	1.0	0.8	0.6
Mitochondrial density	1.0	0.7	0.4
<b>Metabolic</b>			
Oxidative potential	1.0	0.7	0.2
Glycolytic potential	1.0	1.5	2.0
Phosphocreatine	1.0	1.2	1.2
Glycogen	1.0	1.3	1.5
Triacylglycerol	1.0	0.4	0.2

1548

1549

1550 Figure 1.

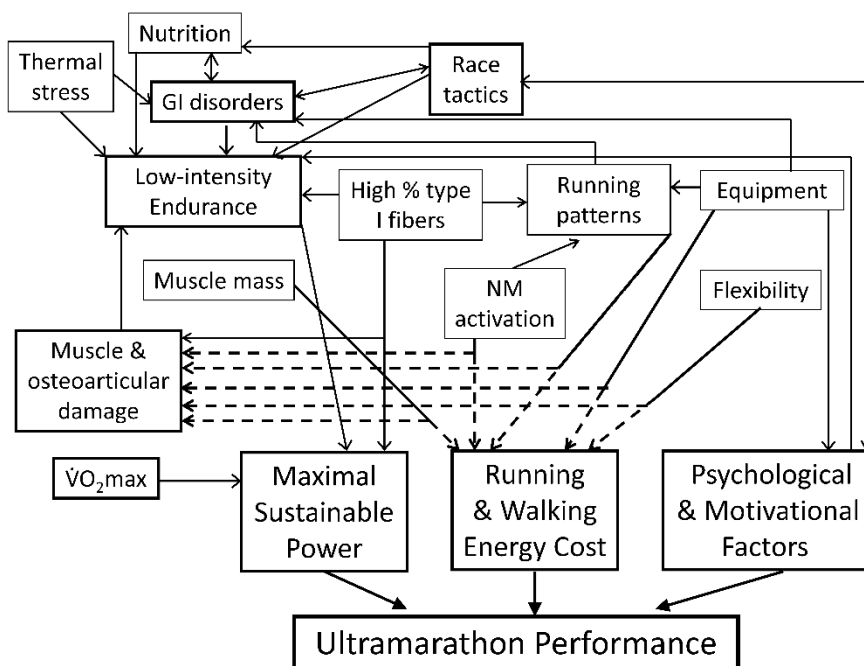


- ➖ Less in women than in men
- ➕ Greater in women than in men

1551

1552

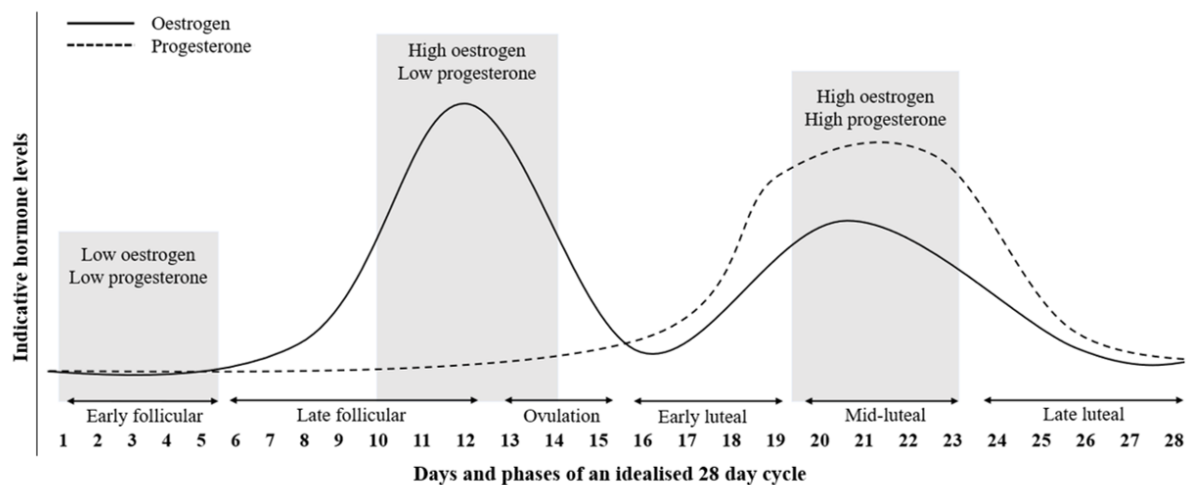
1553 Figure 2.



1554

1555

1556 Figure 3.



1557

1558