

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

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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 O₂-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⁻¹[insert raised dot]decade⁻¹) [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⁻¹). 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 $0.06 \text{ km}\cdot\text{h}^{-1}$ 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⁻¹), 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 β -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⁻¹ 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⁻¹, 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⁻¹). 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, progesterones, 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 eumenorrhic 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 β -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, O₂-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

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761

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771

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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.

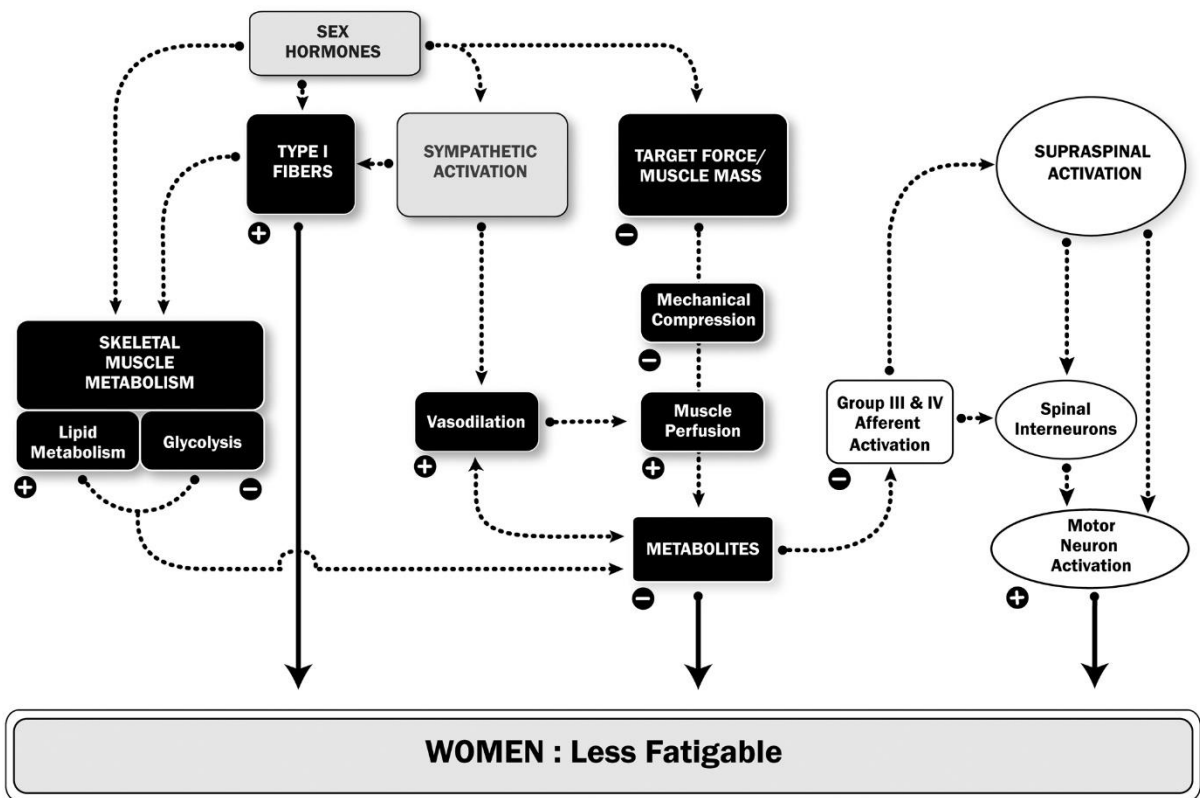
1547

Characteristic	ST Oxidative	FTa Oxidative	FTb Glycolytic
Contractile			
Time to peak tension	1.0	0.4	0.4
Ca ²⁺ myosin ATPase	1.0	3.0	3.0
Mg ²⁺ actomyosin ATPase	1.0	2.8	2.8
Enzymatic			
	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
Morphological			
Capillary density	1.0	0.8	0.6
Mitochondrial density	1.0	0.7	0.4
Metabolic			
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.

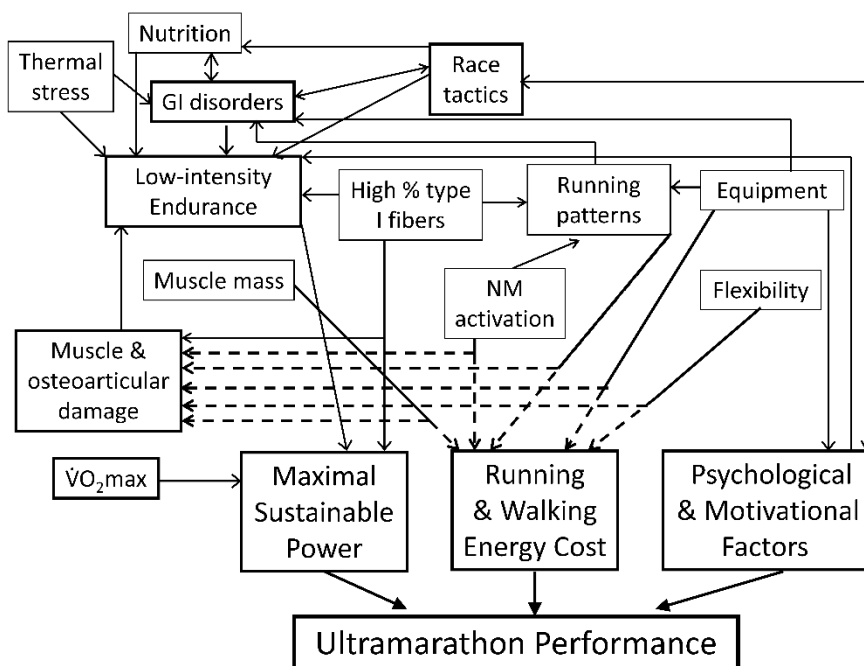


- ➖ Less in women than in men
- ➕ Greater in women than in men

1551

1552

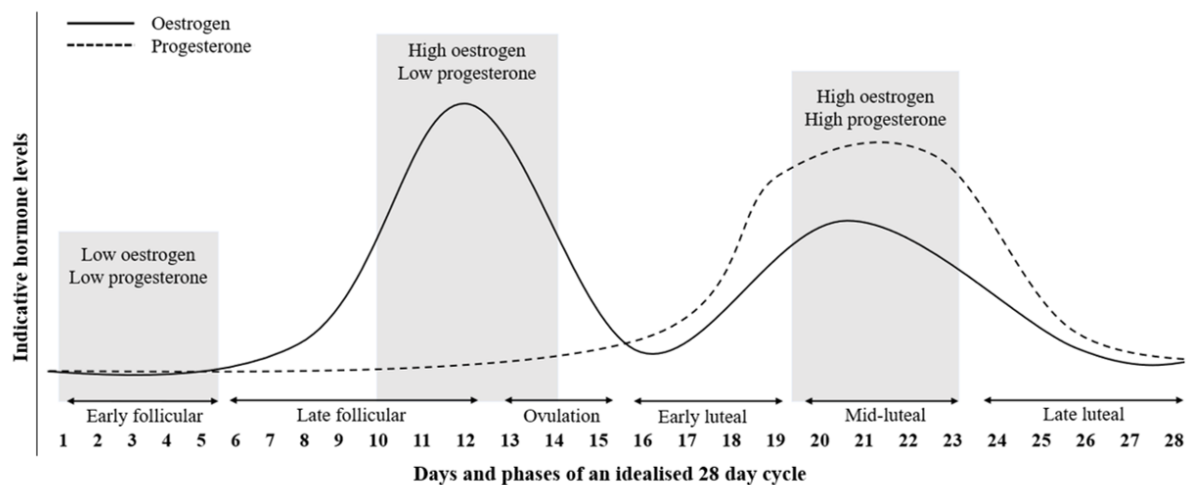
1553 Figure 2.



1554

1555

1556 Figure 3.



1557

1558