Title

Do Sex Differences in Physiology Confer a Female Advantage in Ultra-Endurance Sport?

Journal

Sports Medicine, 51(5)

ISSN

0112-1642

Authors

Tiller, Nicholas B

Elliott-Sale, Kirsty J

Knechtle, Beat

et al.

Publication Date

2021-05-01

DOI

10.1007/s40279-020-01417-2

Peer reviewed

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

Nicholas B. Tiller[1], Kirsty J. Elliott-Sale[2], Beat Knechtle[3,4], Patrick B. Wilson[5], Justin D. Roberts[6], Guillaume Y. Millet[7,8]

[1]Institute of Respiratory Medicine and Exercise Physiology, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA.
[2]Musculoskeletal Physiology Research Group, Sport, Health, and Performance Enhancement Research Centre, School of Science and Technology, Nottingham Trent University, Nottingham, United Kingdom.
[3]Medbase St. Gallen Am Vadianplatz, 9001 St. Gallen, Switzerland.
[4]Institute of Primary Care, University of Zurich, 8091 Zurich, Switzerland.
[5]Department of Human Movement Sciences, Old Dominion University, Norfolk, VA 23529, USA
[6]Cambridge Centre for Sport and Exercise Sciences, School of Psychology and Sports Science, Anglia Ruskin University, Cambridge, UK.
[7]Univ Lyon, UJM-Saint-Etienne, Inter-university Laboratory of Human Movement Biology, EA 7424, F-40023, Saint-Etienne, France.
[8]Institut Universitaire de France (IUF).

Correspondence:
Nicholas B. Tiller, Ph.D. | 1124 W. Carson Street, CDCRC Building, Torrance, CA 90502 | Email: nicholas.tiller@lundquist.org | Tel: (+1) 310-980-8163 | Orchid: https://orcid.org/0000-0001-8429-658X

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

ABSTRACT

Ultra-endurance has been defined as any exercise bout that exceeds 6 h. A number of exceptional, record-breaking performances by female athletes in ultra-endurance sport has roused speculation that they might be predisposed to success in such events. Indeed, while the male-to-female performance gap in traditional endurance sport (e.g., marathon) remains at ~10%, the disparity in ultra-endurance competition has been reported as low as 4% despite the markedly lower number of female participants. Moreover, females generally outperform males in extreme-endurance swimming. The issue is complex, however, with many sports-specific considerations and caveats. This review summarizes the sex-based differences in physiological functions and draws attention to those which likely determine success in extreme exercise endeavors. The aim is to provide a balanced discussion of the female versus male predisposition to ultra-endurance sport. Herein, we discuss sex-based differences in muscle morphology and fatigability, respiratory-neuromechanical function, substrate utilization, oxygen utilization, gastrointestinal structure and function, and hormonal control. The literature indicates that while females exhibit numerous phenotypes that would be expected to confer an advantage in ultra-endurance competition (e.g., greater fatigue-resistance, greater substrate efficiency, and lower energetic requirements), they also exhibit several characteristics that unequivocally impinge on performance (e.g., lower O_2-carrying capacity, increased prevalence of GI distress, and sex-hormone effects on cellular function/ injury risk). Crucially, the advantageous traits may only manifest as ergogenic in the extreme endurance events which, paradoxically, are the races that females less often contest. The title question should be revisited in the coming years when/if the number of female participants increases.

KEY POINTS

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

1.0 INTRODUCTION

A 1992 correspondence published in the journal *Nature* posed the question '*Will women soon outrun men?*' The analysis of distance-running records throughout the 1900s revealed an essentially linear chronological increase in mean running velocity ($\bar{V}$-slope), which was considerably steeper in the women's marathon relative to the men's (~37.8 vs. 9.2 m[insert raised dot]min^{-1}[insert raised dot]decade^{-1}) [1]. From this historical trend, Whipp and Ward calculated that the intersection for the men's and women's marathon would occur in the late 1990s [1]. Although linear models have accurately described performance trends in ultra-distance swimming [2], their utility predicting the "gender" gap in other sports has been criticized on the basis that athletic adaptation and performance rarely, if ever, follow a linear progression [3]. In 1989, using a non-linear (hyperbolic) model, Peronnet *et al.* calculated a ~10% disparity between male and female running performances, owing primarily to greater maximal aerobic capacities ($\dot{V}O_2max$) in the former. The model also predicted that males would retain a biological distance-running advantage well into the future [4]. In point of fact, a contemporary analysis of ~92,000 marathon finishes revealed a ~10% discrepancy between non-elite male and female finish times (males = 4 h 28 min ± 53 min; females = 4 h 54 min ± 52 min; [5]). Thus, if females are to further diminish the endurance performance gap, it is most likely in those contests which depend less on maximal aerobic capacities.

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

Males and females compete side-by-side in ultra-endurance sport. Males are generally faster than females over any given distance [2,18,19], but the data may be confounded by the considerably lower number of female participants, particularly in the very long-distance races. For instance, while modern marathons comprise fairly equal numbers of males and females (54% and 46%, respectively; [20]), only 20% of ultra-marathon finishes since the 1970s have been accomplished by females [7,18]. In ultra-distance cycling (Race Across America; RAAM), females comprised only ~11% of finishers between 1982 - 2011 [19]. Notwithstanding, some have calculated the performance gap to be as low as 4% in ultra-marathon [21], 6% in ultra-distance open-water swimming [2], and negligible in cycling events of >200 miles [22]. In rare instances (yet, more often in ultra-endurance events than in shorter races) females may surpass their male counterparts [23]. Pertinently, the performance disparity between males and females is generally smallest in those events of greatest duration [19,21,24], and in those races with the highest number of female contestants [18,25]. At present, it is unclear what physical/physiological attributes underpin female ultra-endurance performance, and whether females might surpass males in this sport should their participation numbers equalize.

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

1.1 Performance Trends

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

When viewed in its entirety, the data show that males generally outperform females in most sports, irrespective of distance, although the range in the performance disparity is large (0 – 17%) and there are several notable exceptions. In an analysis of world-record running performances ranging from 100 m to 200 km, males were on average 12.4% faster than females [35]. Moreover, in 24-h ultra-marathon, a gap of ~17% was reported between the annual fastest male and female finishers, ~11% for the annual 10 fastest, and ~14% for the annual 100 fastest [24]. These data are likely confounded by the lower numbers of female contestants. Studies that account for the participation disparity show a slightly diminished performance gap. For example, in a multiple linear regression analysis of >93,000 ultra-marathon finishes between 1975 and 2013 (across the range of distances), the sex difference in performance was generally <10%, and the discrepancy in finish time was lowest in events where females participated in greater numbers [18].

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

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

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

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

2.0 PHYSIOLOGICAL CONSIDERATIONS

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

2.1 Muscle Morphology and Fatigability

Fatigue can be defined as a disabling symptom in which physical and cognitive function is limited by interactions between *perceived* fatigability and *performance* fatigability [50]. The latter of these, also known as neuromuscular fatigue (NMF), results from diminished voluntary activation (central component) and/or contractile function (peripheral component) [51]. We presently focus on the sex-differences in acute NMF, and how it might mediate performance in ultra-endurance competition. In controlled studies, females generally exhibit greater fatigue resistance than males [52,53]. Furthermore, in a detailed review of sex differences in fatigability, Hunter *et al.* made two specific observations: (i) females typically outperform males during exercise performed at submaximal intensities; and (ii) the magnitude of the difference is attenuated as contraction intensity increases [52].

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

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

Insert Table 1

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

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

When interpreting the data on NMF, an important consideration is that the magnitude and prevalence of fatigue is task-dependent; i.e., different neuromuscular sites will be stressed when the requirements of the task are altered, and the stress on these sites can differ for males and females [52]. As such, while females may exhibit less muscle fatigue than males during maximal voluntary (isometric) contractions [69], such localized responses may be of little relevance to dynamic, whole-body activities [70] including ultra-endurance exercise. The greater muscle mass involved in such activities evokes greater demands on cardiorespiratory and central nervous systems (e.g., greater afferent feedback and central drive), resulting in lower end-exercise impairments in contractile function [71] and, more generally, different NMF etiology compared to isolated exercises. In studies evaluating fatigue responses during dynamic, submaximal exercise, sex differences in fatigability are less consistent [72–74].

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

2.1.4 Respiratory muscle fatigue. Extending the fatigue data from the locomotor muscles, numerous studies support the notion of better fatigue resistance in the female respiratory muscles. The primary muscles of inspiration and expiration are the diaphragm and major abdominals, respectively, which have concurrent roles in ventilating the lungs and postural control. Respiratory muscle fatigue is a phenomenon whereby muscles attached to the thoracic cage exhibit a reduced force-generating capacity relative to baseline, usually following exhaustive exercise [75–78]. In male versus female comparisons, resistive breathing evoked a slower rate of inspiratory muscle fatigue in the latter, a finding that was independent of muscle strength [79], although both groups exhibited a similar relative decline in maximal inspiratory pressure (15%). In another study using cervical magnetic stimulation to artificially activate the diaphragm before and after constant work-rate cycling, diaphragm fatigue occurred in 11 out of 19 males (58%) and 8 out of 19 females (42%) [80]; however, contractile function diminished to a greater extent in the males (31 vs. 21%). Collectively, these data point to a female diaphragm that may be more fatigue-resistant, and this phenomenon might be partially attributed to a greater reliance on accessory inspiratory muscles for ventilation during dynamic exercise [81]. During high-intensity exercise, respiratory muscle fatigue may compromise ventilatory capacity and endurance, exacerbate dyspnea (sensations of breathlessness), and compromise limb-locomotor blood flow through “respiratory steal” [75]. However, its effects on ultra-endurance performance have not been adequately studied. Due to the expiratory muscles’ important role in postural control [82], it has been speculated that fatigue of the abdominals during ultra-marathon could place the runner at an increased risk of injury due to a relative inability to sustain the rigors of competition, particularly on challenging terrain [16]. A fatigue resistance in the respiratory muscles may, therefore, be advantageous to ultra-marathon performance.

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

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

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

Insert Fig. 1

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

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

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

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

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

2.3 Oxygen Utilization.

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

It is generally accepted that a lower $\dot{V}O_2$max in females is the result of sex-differences in fat mass, and hemoglobin and hematocrit levels [113,114]. When $\dot{V}O_2$max in males and females was adjusted to FFM, some showed the sex differences to disappear [115] while others found that males retained higher values [116]. Equalizing hemoglobin concentrations between sexes via blood withdrawal also failed to completely equalize absolute VO_2max [115], thus suggesting that the sex-differences in aerobic capacity are likely attributable to a combination of the aforementioned factors. The sex-mediated disparity in oxygen utilization may also be determined at a cellular level (see *2.1.1 Muscle fiber type*). For example, the rate of oxidative phosphorylation is influenced by mitochondrial density, and while respiration in isolated mitochondria is higher in female muscles compared to male [117], the latter tend to have a higher expression of genes encoding mitochondrial proteins [61]. Importantly, mitochondrial function, as well as membrane microviscosity, may depend to a large extent on estrogen concentrations, with lowered levels associated with diminished mitochondrial function [118] (See *2.4 Endocrine Function*).

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

2.3.2 Oxygen economy and energy efficiency. Aside from $\dot{V}O_2$max, several other factors underpin middle-to-long distance endurance performance including velocity at $\dot{V}O_2$max (v$\dot{V}O_2$max), lactate threshold, and oxygen economy/work efficiency [108,122–124]. Although the greater relative adiposity in females would be expected to diminish their oxygen economy and work efficiency in weight-dependent sports, the data pertaining to sex-differences in these characteristics are inconsistent. Some suggest that females tend to have poorer oxygen economy at a given submaximal work rate [125,126] despite generally exhibiting a lower body mass. By contrast, at various relative intensities of lactate threshold, Fletcher *et al.* found no sex-mediated differences in running economy [127], and there are several reports of lower (better) values for running economy in trained adult females versus trained adult males [128,129]. In terms of gross energy efficiency - defined as the ratio of work accomplished to total energy expended – Yasuda *et al*. observed no sex-differences during cycling or arm-cranking across a range of submaximal relative exercise intensities, even in males and females who were matched for $\dot{V}O_2$ at the gas exchange threshold [130]. Similar observations of no sex-differences in energy efficiency have been made in cross-country skiing [131,132] and in distance running when comparing elite male and female athletes [133,134].

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

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

Finally, given that females generally outperform males in swimming events of extreme duration, the various factors that underpin ultra-distance swimming performance warrant independent consideration. It is unlikely that female success in this sport is due to a superior maximal oxygen uptake. Indeed, male open-water swimmers have been shown to exhibit considerably higher $\dot{V}O_2$max values than females (5.51 vs. 5.06 $L.min^{-1}$, respectively) [136]. Moreover, despite the lactate thresholds occurring at speeds equivalent to 89 and 95% $\dot{V}O_2$max for males and females, respectively, the absolute $\dot{V}O_2$ at lactate threshold was still higher in males (4.90 vs. 4.81 $L.min^{-1}$). Thus, female dominance in this sport is likely due to factors other than oxygen utilization, and may instead relate to differences in the energy cost of swimming, second to lower hydrodynamic resistance [137]. Indeed, although increases in body mass have been shown to diminish oxygen economy during running [138], a higher fat mass may be ergogenic in swimming. Fat has a lower density than muscle, and the greater relative female adiposity - as well as important differences in adipose tissue distribution - likely increases buoyancy and reduces drag [139]. The generally smaller body size of females confers a further decrease in hydrodynamic drag, as do shorter lower limbs that result in a more horizontal and streamlined position in the water [140,141]. Others speculate that female success in ultra-distance swimming may also be associated with better pacing strategies [44]. Evidently, the extent to which a biological trait (e.g., lower body fat) can be considered ergogenic, is determined by the specific demands and characteristics of the event in question.

Insert Fig. 2

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

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

In females, estrogen and progesterone exhibit large fluctuations throughout the monthly menstrual cycle [150] (Fig. 3). Estrogen augments muscle size, strength, and collagen content, all of which are conducive to sporting performance [151] (for a review of the effects of female sex hormones on the nervous system and muscle strength, see [152]). Paradoxically, elevated estrogen concentrations reduce tendon and ligament stiffness [151], which may impinge on ultra-endurance performance in two ways. First, there is a significant positive correlation between tendon stiffness and running economy in females [127], such that an estrogen-mediated decrease in stiffness might also deteriorate running economy. Second, there are cyclical changes in anterior knee laxity throughout the menstrual cycle [153], and while there is no consensus that female injury rates are necessarily hormone-mediated, it is possible that fluctuating sex-hormone concentrations may partially explain the higher prevalence of anterior cruciate ligament (ACL) ruptures in eumenorrheic females compared to males [154]. Worthy of note, the knee is one of the most frequently injured body parts in ultra-endurance athletes [155], and the risk may be greater when traversing technical/challenging terrain that increases impact and shear forces through the lower limbs. A greater propensity for injury would certainly attenuate the ability to both train and compete.

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

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

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

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

Insert Fig. 3

2.5 Gastrointestinal Distress. Ultra-endurance exercise is associated with widespread reporting of gastrointestinal symptoms [171–173]. The most well-documented, performance-altering GI disturbances are nausea/vomiting [174] and abdominal cramping [175,176], although other symptoms include reflux, bloating, loose stools, and flatulence [177]. GI distress is often cited as a reason for non-completion and/or attenuated performance, particularly in single stage running races [178]. The mechanisms that underpin GI distress during ultra-endurance exercise are complex and multi-faceted, but likely include impairments to gut perfusion and neuroendocrine alterations [179]. Gastrointestinal symptoms may also be triggered or exacerbated by aggressive and/or unaccustomed nutritional intake [180]. Certainly, a biological propensity for less frequent/severe GI distress, and/or a greater ability to tolerate/mitigate the symptoms, would be considered ergogenic in ultra-endurance competition.

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

2.5.2 Symptomology. In population-based research, females report a higher frequency of GI symptoms [197–199], most commonly nausea, bloating, abdominal pain, and constipation. While a greater prevalence of bloating and constipation in females may be due to slower whole-gut and colonic transit times [184,185] - thereby contributing to greater fermentation of dietary fiber and reabsorption of colonic water - the greater frequency of nausea and abdominal pain may be associated with the onset of monthly menses in individuals with eumenorrhea [200]. The observations of population-based studies generally extend to those made during exercise, although the most informative data stem from research in standard- as opposed to ultra-endurance competition [172,201–203]. For example, in a 1984 survey of >700 marathon runners (85% male), females more commonly reported symptoms of lower-GI distress (e.g., abdominal cramping, urge to defecate, diarrhea, bloody defecation) [203]. While interesting, these data may be confounded by external factors (e.g., training experience), particularly given that years of training associates negatively with GI symptoms [201]. A multivariate analysis of >1,200 endurance runners contesting races from 10 - 42 km also observed female sex to independently associate with increased prevalence of GI complaints [201].

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

2.5.3 Gut training. There is a growing interest in the concept of "training the gut" to enhance the digestion of, and tolerance to, exogenous carbohydrate and fluid intake during prolonged exercise. Such gut-training strategies are premised on the notion that high intakes of carbohydrate (at rest or during exercise) will increase the density and activity of intestinal glucose transports, thereby facilitating greater carbohydrate absorption and oxidation during exercise [206]. These adaptations would be expected to mitigate the magnitude and prevalence of GI distress during exercise. Gut training may be particularly relevant for ultra-endurance competition given the large energetic demands and nutritional intakes associated with training and racing [12]. Although anecdotal accounts of "speed eaters" show the GI tract to be highly adaptable [207], studies focused on the physiological and ergogenic appraisal of gut-training strategies are still relatively scarce. One such study on a group of trained cyclists and triathletes showed that a 28-d period of aggressive in-task fueling facilitated metabolic adaptations (including increased exogenous carbohydrate oxidation during exercise) [208]. Others report that gut-training evoked reductions in GI symptoms and carbohydrate malabsorption [209]. Nevertheless, the ergogenic effects of these strategies are mixed. The two studies that comprised mixed-sex cohorts showed that females were more likely to report GI symptoms during exercise when challenged with high rates of carbohydrate intake (90 $g \cdot h^{-1}$) [209,210]. Furthermore, following two weeks of gut training in a small group (5 male, 5 female), the magnitude of the reduction in GI symptoms associated with in-task fueling was lower in females relative to males [209]. Clearly, more data from larger samples are needed in order to make more robust direct comparisons.

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

A final consideration is the extent to which sex-differences in substrate efficiency and body mass impact on race nutrition and the propensity for nutrition-induced GI distress. Owing to their greater dependence on lipid oxidation during exercise (see *2.2 Substrate Utilization*), female endurance athletes may be less susceptible to glycogen degradation [212] and its debilitating effects. Better substrate efficiency may also explain, at least in part, the lower carbohydrate and general caloric intakes of females during ultra-endurance competition [213,214]. Lower caloric intakes in females is also a factor of a smaller average body size, smaller stomach, and possibly deliberate strategies aimed at mitigating GI symptoms. A lesser need to consume exogenous carbohydrate to sustain a given work rate may be pertinent given that the primary nutritional cause of GI distress during endurance exercise is the high intake of carbohydrate, particularly hyperosmolar solutions [171]. The lower average body mass of the female athlete may also explain their lower sweat rates at both absolute and relative work rates [215]. This may, in turn, attenuate their fluid requirements during exercise, and decrease the need to ingest high volumes that provoke GI distress. Therefore, while it may be that female athletes are more prone to GI distress during exercise, it remains unclear whether this extends to the durations typical of ultra-endurance and whether this might be partially mitigated by their reduced caloric, carbohydrate, and fluid requirements. More studies are needed to further explore this complex issue in the context of ultra-endurance performance.

3.0 BEYOND PHYSIOLOGY

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

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

Finally, this review discussed numerous physiological attributes that may facilitate or impede ultra-endurance performance. However, ultra-endurance events are highly variable in terms of the exercise mode (e.g., running, cycling, swimming, adventure racing, etc.), distance/duration, cumulative ascent/descent, terrain, and environmental extremes. It stands to reason, therefore, that the physical/physiological attributes of individuals will be differentially suited to different events. For instance, those contested on relatively flat, non-technical terrain may favor athletes with larger maximal aerobic capacities and higher ventilatory thresholds, whereas individuals with smaller frames and greater peripheral conditioning/robustness may excel on technical terrain with downhill running components. As such, the nuances of each event should be considered before arbitrarily designating a physical/physiological trait as advantageous. Certainly, optimal performances will stem from matching individual physiological profiles with individual race types.

4.0 CONCLUSION

When compared to their male counterparts, females exhibit numerous phenotypes that would be expected to confer an advantage in ultra- and/or extreme-endurance competition. These include a greater relative distribution of type-I (oxidative) fibers, greater fatigue-resistance owing to neuromuscular, contractile, and metabolic factors, better substrate efficiency (higher rates of lipid oxidation), lower energetic requirements, and higher subcutaneous body fat which is likely beneficial in ultra-distance swimming. The data also suggest that females may be better at pacing. These factors may explain why the sex-mediated performance disparity is lowest in ultra-endurance sport than in any other. However, there are two caveats. First, these collective traits may only manifest as ergogenic in the extreme endurance events which, paradoxically, are the races that females less-often contest. Second, several important characteristics of female physiology - including mechanical-ventilatory function, O_2-carrying capacity, prevalence of GI distress, and sex-hormone effects on both cellular function and injury risk – unequivocally impinge on female ultra-endurance performance, making it unlikely that the fastest females will ever outperform the fastest males (ultra-distance swimming a notable exception). In light of these caveats and the numerous considerations proposed in our discussion, we urge a skeptical approach to cursory or simplified answers to this complex question. We encourage more research into the physiological determinants of ultra-endurance sport, as well as more direct comparisons of male versus female ultra-endurance physiology, particularly when/if the number of female participants increases.

Acknowledgements

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

Declarations

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

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

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

REFERENCES

1. Whipp BJ, Ward SA. Will women soon outrun men? Nature. Nature Publishing Group; 1992. p. 25.

2. Zingg MA, Rüst CA, Rosemann T, Lepers R, Knechtle B. Analysis of sex differences in open-water ultra-distance swimming performances in the FINA World Cup races in 5 km, 10 km and 25 km from 2000 to 2012. BMC Sports Science, Medicine and Rehabilitation. BioMed Central Ltd.; 2014;6:7.

3. Reinboud W. Linear models can't keep up with sport gender gap [1]. Nature. Nature Publishing Group; 2004. p. 147.

4. Peronnet F, Thibault G. Mathematical analysis of running performance and world running records. Journal of Applied Physiology. J Appl Physiol (1985); 1989;67:453–65.

5. Deaner RO, Carter RE, Joyner MJ, Hunter SK. Men are more likely than women to slow in the marathon. Medicine and Science in Sports and Exercise. Lippincott Williams and Wilkins; 2014;47:607–16.

6. Zaryski C, Smith DJ. Training principles and issues for ultra-endurance athletes. Current Sports Medicine Reports [Internet]. Curr Sports Med Rep; 2005 [cited 2020 Jun 22];4:165–70. Available from: https://pubmed.ncbi.nlm.nih.gov/15907270/

7. Hoffman MD, Ong JC, Wang G. Historical analysis of participation in 161km ultramarathons in North America. International Journal of the History of Sport. 2010. p. 1877–91.

8. Scheer V. Participation Trends of Ultra Endurance Events. Sports Medicine and Arthroscopy Review [Internet]. Lippincott Williams and Wilkins; 2019 [cited 2020 Jun 17];27:3–7. Available from: http://journals.lww.com/00132585-201903000-00002

9. Millet GY, Banfi JC, Kerherve H, Morin JB, Vincent L, Estrade C, et al. Physiological and biological factors associated with a 24 h treadmill ultra-marathon performance. Scandinavian Journal of Medicine & Science in Sports [Internet]. John Wiley & Sons, Ltd; 2011 [cited 2020 Mar 3];21:54–61. Available from: http://doi.wiley.com/10.1111/j.1600-0838.2009.01001.x

10. Millet GY, Hoffman MD, Morin JB. Sacrificing economy to improve running performance - A reality in the ultramarathon? [Internet]. Journal of Applied Physiology. American Physiological Society Bethesda, MD; 2012 [cited 2020 Jun 10]. p. 507–9. Available from: https://www.physiology.org/doi/10.1152/japplphysiol.00016.2012

11. Hoffman MD, Lee J, Zhao H, Tsodikov A. Pain Perception After Running a 100-Mile Ultramarathon. Archives of Physical Medicine and Rehabilitation. Arch Phys Med Rehabil; 2007;88:1042–8.

12. Tiller NB, Roberts JD, Beasley L, Chapman S, Pinto JM, Smith L, et al. International Society of Sports Nutrition Position Stand: Nutritional considerations for single-stage ultra-marathon training and racing. Journal of the International Society of Sports Nutrition. Journal of the International Society of Sports Nutrition; 2019;16:1–23.

13. Knechtle B, Nikolaidis PT. Physiology and pathophysiology in ultra-marathon running. Frontiers in Physiology. Frontiers Media S.A.; 2018.

14. Cona G, Cavazzana A, Paoli A, Marcolin G, Grainer A, Bisiacchi PS. It's a Matter of Mind! Cognitive Functioning Predicts the Athletic Performance in Ultra-Marathon Runners. di Pellegrino G, editor. PLOS ONE [Internet]. Public Library of Science; 2015 [cited 2020 Jun 5];10:e0132943. Available from: https://dx.plos.org/10.1371/journal.pone.0132943

15. Thompson M. No TitlPhysiological and Biomechanical Mechanisms of Distance Specific Human Running Performancee. Integrative and comparative biology. 2017;57:293–300.

16. Tiller NB. Pulmonary and Respiratory Muscle Function in Response to Marathon and Ultra-Marathon Running: A Review. Sports Medicine. Springer International Publishing; 2019. p. 1031–41.

17. Tiller NB, Stewart GM, Illidi CR, Levine BD. Exercise is medicine? The cardiorespiratory implications of ultra-marathon. Current Sports Medicine Reports [Internet]. Lippincott Williams and Wilkins; 2020 [cited 2020 Sep 22];19:290–7. Available from: https://pubmed.ncbi.nlm.nih.gov/32769665/

18. Knechtle B, Valeri F, Nikolaidis PT, Zingg MA, Rosemann T, Rüst CA. Do women reduce the gap to men in ultra-marathon running? SpringerPlus. SpringerOpen; 2016;5.

19. Knechtle B, Abou Shoak, Knechtle, Rüst, Rosemann T, Lepers R. Participation and performance trends in ultracycling. Open Access Journal of Sports Medicine. Dove Medical Press Ltd.; 2013;4:41.

20. Knechtle B, di Gangi S, Rüst CA, Nikolaidis PT. Performance Differences Between the Sexes in the Boston Marathon From 1972 to 2017. Journal of strength and conditioning research. NLM (Medline); 2020;34:566–76.

21. Waldvogel KJ, Nikolaidis PT, di Gangi S, Rosemann T, Knechtle B. Women reduce the performance difference to men with increasing age in ultra-marathon running. International Journal of Environmental Research and Public Health. MDPI AG; 2019;16.

22. Baumgartner S, Victor Sousa C, Nikolaidis PT, Knechtle B. Can the performance gap between women and men be reduced in ultra-cycling? International Journal of Environmental Research and Public Health. MDPI AG; 2020;17.

23. Bam J, Noakes TD, Juritz J, Dennis SC. Could women outrun men in ultramarathon races? Medicine and Science in Sports and Exercise. Med Sci Sports Exerc; 1997;29:244–7.

24. Peter L, Rust CA, Knechtle B, Rosemann T, Lepers R, Peter L, et al. Sex differences in 24-hour ultra-marathon performance - A retrospective data analysis from 1977 to 2012. Clinics [Internet]. Faculdade de Medicina / USP; 2014 [cited 2020 Jun 22];69:38–46. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-59322014000100038&lng=en&nrm=iso&tlng=en

25. Senefeld J, Smith C, Hunter SK. Sex differences in participation, performance, and age of ultramarathon runners. International Journal of Sports Physiology and Performance [Internet]. Human Kinetics Publishers Inc.; 2016 [cited 2020 Jun 22];11:635–42. Available from: https://pubmed.ncbi.nlm.nih.gov/26561864/

26. Williams S. Are women better ultra-endurance athletes than men? [Internet]. BBC World News. 2019 [cited 2020 Jun 3]. Available from: https://www.bbc.co.uk/news/world-49284389

27. Carter K. 'Women have less ego. Men think: How hard can this be?': the female ultra-athletes leading the field. [Internet]. The Guardian. 2020 [cited 2020 Jun 3]. Available from:

https://www.theguardian.com/lifeandstyle/2020/jan/03/female-ultra-athletes-leading-field-women-less-ego

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

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

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

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

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

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

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

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

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

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

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

39. Knechtle B, Zingg M, Rosemann T, Rüst C. Performance differences between sexes in 50-mile to 3,100-mile ultramarathons. Open Access Journal of Sports Medicine [Internet]. Dove Medical Press Ltd.; 2015 [cited 2020 Aug 28];6:7. Available from: /pmc/articles/PMC4309798/?report=abstract

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

41. Speechly DP, Taylor SR, Rogers GG. Differences in ultra-endurance exercise in performance-matched male and female runners. Medicine and Science in Sports and Exercise. Med Sci Sports Exerc; 1996;28:359–65.

42. Ronto P. The state of ultra running 2020 [Internet]. RunRepeat. 2020 [cited 2020 Jun 11]. Available from: https://runrepeat.com/state-of-ultra-running

43. Knechtle B, Rosemann T, Lepers R, Rüst CA. Women outperform men in ultradistance swimming: The Manhattan Island Marathon Swim from 1983 to 2013. International Journal of Sports Physiology and Performance [Internet]. Human Kinetics Publishers Inc.; 2014 [cited 2020 Aug 31];9:913–24. Available from: https://pubmed.ncbi.nlm.nih.gov/24584647/

44. Knechtle B, Dalamitros AA, Barbosa TM, Sousa CV, Rosemann T, Nikolaidis PT. Sex differences in swimming disciplines—can women outperform men in swimming? International Journal of Environmental Research and Public Health [Internet]. MDPI AG; 2020 [cited 2020 Aug 31];17. Available from: https://pubmed.ncbi.nlm.nih.gov/32456109/

45. Sex & Gender | Office of Research on Women's Health [Internet]. [cited 2020 Jun 22]. Available from: https://orwh.od.nih.gov/sex-gender

46. IGH Learning - CIHR [Internet]. [cited 2020 Jun 22]. Available from: https://cihr-irsc.gc.ca/e/49347.html

47. Heidari S, Babor TF, de Castro P, Tort S, Curno M. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Research Integrity and Peer Review [Internet]. Springer Nature; 2016 [cited 2020 Jun 22];1:2. Available from: http://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6

48. Phillips SP. Defining and measuring gender: A social determinant of health whose time has come [Internet]. International Journal for Equity in Health. BioMed Central; 2005 [cited 2020 Jun 23]. p. 11. Available from: http://equityhealthj.biomedcentral.com/articles/10.1186/1475-9276-4-11

49. Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research? [Internet]. JAMA - Journal of the American Medical Association. American Medical Association; 2016 [cited 2020 Jun 22]. p. 1863–4. Available from: https://jamanetwork.com/journals/jama/fullarticle/2577142

50. Enoka RM, Duchateau J. Translating fatigue to human performance. Medicine and Science in Sports and Exercise [Internet]. Lippincott Williams and Wilkins; 2016 [cited 2020 Aug 4];48:2228–38. Available from: /pmc/articles/PMC5035715/?report=abstract

51. Millet GY. Can neuromuscular fatigue explain running strategies and performance in ultra-marathons?: The flush model [Internet]. Sports Medicine. Springer; 2011 [cited 2020 Aug 4]. p. 489–506. Available from: https://link.springer.com/article/10.2165/11588760-000000000-00000

52. Hunter SK. Sex differences in human fatigability: Mechanisms and insight to physiological responses. Acta Physiologica. Blackwell Publishing Ltd; 2014;210:768–89.

53. Hicks AL, Kent-Braun J, Ditor DS. Sex differences in human skeletal muscle fatigue. Exercise and Sport Sciences Reviews [Internet]. Lippincott Williams and Wilkins; 2001 [cited 2020 Jun 23];29:109–12. Available from: https://pubmed.ncbi.nlm.nih.gov/11474957/

54. Martin V, Kerhervé H, Messonnier LA, Banfi JC, Geyssant A, Bonnefoy R, et al. Central and peripheral contributions to neuromuscular fatigue induced by a 24-h treadmill run.

Journal of Applied Physiology [Internet]. J Appl Physiol (1985); 2010 [cited 2020 Aug 4];108:1224–33. Available from: https://pubmed.ncbi.nlm.nih.gov/20167672/

55. Millet GY, Tomazin K, Verges S, Vincent C, Bonnefoy R, Boisson RC, et al. Neuromuscular consequences of an extreme mountain ultra-marathon. PLoS ONE [Internet]. Public Library of Science; 2011 [cited 2020 Aug 4];6:17059. Available from: /pmc/articles/PMC3043077/?report=abstract

56. Millet GY, Millet GP, Lattier G, Maffiuletti NA, Candau R. Alteration of neuromuscular function after a prolonged road cycling race. International Journal of Sports Medicine [Internet]. Int J Sports Med; 2003 [cited 2020 Aug 4];24:190–4. Available from: https://pubmed.ncbi.nlm.nih.gov/12740737/

57. TEMESI J, ARNAL PJ, RUPP T, FÉASSON L, CARTIER R, GERGELÉ L, et al. Are Females More Resistant to Extreme Neuromuscular Fatigue? Medicine & Science in Sports & Exercise [Internet]. Lippincott Williams and Wilkins; 2015 [cited 2020 Jun 10];47:1372–82. Available from: http://journals.lww.com/00005768-201507000-00007

58. Brooke MH, Kaiser KK. Muscle Fiber Types: How Many and What Kind? Archives of Neurology [Internet]. Arch Neurol; 1970 [cited 2020 Jun 22];23:369–79. Available from: https://pubmed.ncbi.nlm.nih.gov/4248905/

59. Zierath JR, Hawley JA. Skeletal Muscle Fiber Type: Influence on Contractile and Metabolic Properties. PLoS Biology [Internet]. Public Library of Science; 2004 [cited 2020 Jun 2];2:e348. Available from: https://dx.plos.org/10.1371/journal.pbio.0020348

60. Staron RS, Hagerman FC, Hikida RS, Murray TF, Hostler DP, Crill MT, et al. Fiber type composition of the vastus lateralis muscle of young men and women. Journal of Histochemistry and Cytochemistry [Internet]. Histochemical Society Inc.; 2000 [cited 2020 Jun 23];48:623–9. Available from: https://pubmed.ncbi.nlm.nih.gov/10769046/

61. Welle S, Tawil R, Thornton CA. Sex-related differences in gene expression in human skeletal muscle. PLoS ONE. PLoS One; 2008;3.

62. Parker BA, Smithmyer SL, Pelberg JA, Mishkin AD, Herr MD, Proctor DN. Sex differences in leg vasodilation during graded knee extensor exercise in young adults. Journal of Applied Physiology [Internet]. J Appl Physiol (1985); 2007 [cited 2020 Aug 4];103:1583–91. Available from: https://pubmed.ncbi.nlm.nih.gov/17717115/

63. Roepstorff C, Thiele M, Hillig T, Pilegaard H, Richter EA, Wojtaszewski JFP, et al. Higher skeletal muscle α2AMPK activation and lower energy charge and fat oxidation in men than in women during submaximal exercise. Journal of Physiology [Internet]. J Physiol; 2006 [cited 2020 Aug 4];574:125–38. Available from: https://pubmed.ncbi.nlm.nih.gov/16600998/

64. Miller AEJ, MacDougall JD, Tarnopolsky MA, Sale DG. Gender differences in strength and muscle fiber characteristics. European Journal of Applied Physiology and Occupational Physiology [Internet]. Springer-Verlag; 1993 [cited 2020 Aug 4];66:254–62. Available from: https://link.springer.com/article/10.1007/BF00235103

65. Barnes WS. The relationship between maximum isometric strength and intramuscular circulatory occlusion. Ergonomics [Internet]. Ergonomics; 1980 [cited 2020 Aug 28];23:351–7. Available from: https://pubmed.ncbi.nlm.nih.gov/7202390/

66. Martin PG, Rattey J. Central fatigue explains sex differences in muscle fatigue and contralateral cross-over effects of maximal contractions. Pflugers Archiv European Journal of

Physiology [Internet]. Springer; 2007 [cited 2020 Aug 4];454:957–69. Available from: https://link.springer.com/article/10.1007/s00424-007-0243-1

67. Russ DW, Kent-Braun JA. Sex differences in human skeletal muscle fatigue are eliminated under ischemic conditions. Journal of Applied Physiology [Internet]. American Physiological Society; 2003 [cited 2020 Aug 4];94:2414–22. Available from: https://pubmed.ncbi.nlm.nih.gov/12562681/

68. Millet GY, Martin V, Temesi J. The role of the nervous system in neuromuscular fatigue induced by ultra-endurance exercise [Internet]. Applied Physiology, Nutrition and Metabolism. Canadian Science Publishing; 2018 [cited 2020 Aug 29]. p. 1151–7. Available from: https://pubmed.ncbi.nlm.nih.gov/29726694/

69. Sato H, Ohashi J. Sex Differences in Static Muscular Endurance. Journal of Human Ergology. 1989;18:53.

70. Brownstein CG, Millet GY, Thomas K. Neuromuscular responses to fatiguing locomotor exercise. Acta Physiologica [Internet]. Blackwell Publishing Ltd; 2020 [cited 2020 Aug 4]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/apha.13533

71. Rossman MJ, Venturelli M, Mcdaniel J, Amann M, Richardson RS. Muscle mass and peripheral fatigue: A potential role for afferent feedback? Acta Physiologica [Internet]. Acta Physiol (Oxf); 2012 [cited 2020 Aug 4];206:242–50. Available from: https://pubmed.ncbi.nlm.nih.gov/22762286/

72. O'Leary TJ, Saunders SC, McGuire SJ, Izard RM. Sex differences in neuromuscular fatigability in response to load carriage in the field in British Army recruits. Journal of Science and Medicine in Sport [Internet]. Elsevier Ltd; 2018 [cited 2020 Aug 4];21:591–5. Available from: http://www.jsams.org/article/S1440244017316687/fulltext

73. Boccia G, Dardanello D, Tarperi C, Festa L, la Torre A, Pellegrini B, et al. Women show similar central and peripheral fatigue to men after half-marathon*. European Journal of Sport Science [Internet]. Taylor and Francis Ltd.; 2018 [cited 2020 Aug 4];18:695–704. Available from: https://pubmed.ncbi.nlm.nih.gov/29490592/

74. Glace BW, McHugh MP, Gleim GW. Effects of a 2-hour run on metabolic economy and lower extremity strength in men and women. Journal of Orthopaedic and Sports Physical Therapy [Internet]. Movement Science Media; 1998 [cited 2020 Aug 4];27:189–96. Available from: https://pubmed.ncbi.nlm.nih.gov/9513864/

75. Romer LM, Polkey MI. Exercise-induced respiratory muscle fatigue: Implications for performance. Journal of Applied Physiology. 2008. p. 879–88.

76. Taylor BJ, How SC, Romer LM. Exercise-induced abdominal muscle fatigue in healthy humans. Journal of Applied Physiology [Internet]. J Appl Physiol (1985); 2006 [cited 2020 Aug 31];100:1554–62. Available from: https://pubmed.ncbi.nlm.nih.gov/16424068/

77. Johnson BD, Babcock MA, Suman OE, Dempsey JA. Exercise-induced diaphragmatic fatigue in healthy humans. The Journal of Physiology [Internet]. John Wiley & Sons, Ltd; 1993 [cited 2020 Aug 19];460:385–405. Available from: https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/jphysiol.1993.sp019477

78. Tiller NB, Campbell IG, Romer LM. Influence of Upper-Body Exercise on the Fatigability of Human Respiratory Muscles. Medicine and Science in Sports and Exercise. 2017;49:1461–72.

79. Gonzales JU, Scheuermann BW. Gender differences in the fatigability of the inspiratory muscles. Medicine and Science in Sports and Exercise [Internet]. Med Sci Sports Exerc; 2006 [cited 2020 Jun 22];38:472–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16540834/

80. Guenette JA, Romer LM, Querido JS, Chua R, Eves ND, Road JD, et al. SEX DIFFERENCES IN EXERCISE-INDUCED DIAPHRAGMATIC FATIGUE IN 2 ENDURANCE-TRAINED ATHLETES 3 4. Articles in PresS J Appl Physiol. 2010;

81. Mitchell RA, Schaeffer MR, Ramsook AH, Wilkie SS, Guenette JA. Sex differences in respiratory muscle activation patterns during high-intensity exercise in healthy humans. Respiratory Physiology and Neurobiology [Internet]. Elsevier B.V.; 2018 [cited 2020 Sep 18];247:57–60. Available from: https://pubmed.ncbi.nlm.nih.gov/28890403/

82. Abraham KA, Feingold H, Fuller DD, Jenkins M, Mateika JH, Fregosi RF. Respiratory-related activation of human abdominal muscles during exercise. Journal of Physiology [Internet]. Wiley-Blackwell; 2002 [cited 2020 Jun 22];541:653–63. Available from: /pmc/articles/PMC2290343/?report=abstract

83. Dominelli PB, Molgat-Seon Y, Bingham D, Swartz PM, Road JD, Foster GE, et al. Dysanapsis and the resistive work of breathing during exercise in healthy men and women. Journal of Applied Physiology [Internet]. American Physiological Society; 2015 [cited 2020 Jun 22];119:1105–13. Available from: /pmc/articles/PMC4816413/?report=abstract

84. Sheel AW, Dominelli PB, Molgat-Seon Y. Revisiting dysanapsis: Sex-based differences in airways and the mechanics of breathing during exercise. Experimental Physiology. Blackwell Publishing Ltd; 2016. p. 213–8.

85. Dominelli PB, Render JN, Molgat-Seon Y, Foster GE, Romer LM, Sheel AW. Oxygen cost of exercise hyperpnoea is greater in women compared with men. The Journal of Physiology [Internet]. Blackwell Publishing Ltd; 2015 [cited 2020 Jun 15];593:1965–79. Available from: http://doi.wiley.com/10.1113/jphysiol.2014.285965

86. Nikolaidis P, Ćuk I, Knechtle B. Pacing of Women and Men in Half-Marathon and Marathon Races. Medicina [Internet]. MDPI AG; 2019 [cited 2020 Sep 1];55:14. Available from: http://www.mdpi.com/1010-660X/55/1/14

87. March DS, Vanderburgh PM, Titlebaum PJ, Hoops ML. Age, Sex, and Finish Time as Determinants of Pacing in the Marathon. Journal of Strength and Conditioning Research [Internet]. 2011 [cited 2020 Sep 1];25:386–91. Available from: http://journals.lww.com/00124278-201102000-00014

88. Renfree A, Crivoi do Carmo E, Martin L. The influence of performance level, age and gender on pacing strategy during a 100-km ultramarathon. European Journal of Sport Science. Taylor and Francis Ltd.; 2016;16:409–15.

89. Deaner RO, Lowen A. Males and Females Pace Differently in High School Cross-Country Races. Journal of Strength and Conditioning Research. NSCA National Strength and Conditioning Association; 2016;30:2991–7.

90. Hubble C, Zhao J. Gender differences in marathon pacing and performance prediction. Journal of Sports Analytics. 2016;2:19–36.

91. Deaner RO, Addona V, Hanley B. Risk taking runners slow more in the marathon. Frontiers in Psychology. Frontiers Media S.A.; 2019;10.

92. Goudriaan AE, Lapauw B, Ruige J, Feyen E, Kaufman J-M, Brand M, et al. The influence of high-normal testosterone levels on risk-taking in healthy males in a 1-week letrozole administration study. Psychoneuroendocrinology [Internet]. 2010 [cited 2020 Jun 9];35:1416–21. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0306453010000958

93. Waśkiewicz Z, Kápcińska B, Sadowska-Krępa E, Czuba M, Kempa K, Kimsa E, et al. Acute metabolic responses to a 24-h ultra-marathon race in male amateur runners. European Journal of Applied Physiology. Eur J Appl Physiol; 2012. p. 1679–88.

94. Bergström J, Hultman E. Muscle glycogen synthesis after exercise: An enhancing factor localized to the muscle cells in man [22]. Nature. Nature; 1966. p. 309–10.

95. Monaco C, Whitfield J, Jain SS, Spriet LL, Bonen A, Holloway GP. Activation of AMPKα2 Is Not Required for Mitochondrial FAT/CD36 Accumulation during Exercise. Moro C, editor. PLOS ONE [Internet]. Public Library of Science; 2015 [cited 2020 Jun 10];10:e0126122. Available from: https://dx.plos.org/10.1371/journal.pone.0126122

96. Ibrahimi A, Bonen A, Blinn WD, Hajri T, Li X, Zhong K, et al. Muscle-specific overexpression of FAT/CD36 enhances fatty acid oxidation by contracting muscle, reduces plasma triglycerides and fatty acids, and increases plasma glucose and insulin. Journal of Biological Chemistry. J Biol Chem; 1999;274:26761–6.

97. Kiens B, Roepstorff C, Glatz JFC, Bonen A, Schjerling P, Knudsen J, et al. Lipid-binding proteins and lipoprotein lipase activity in human skeletal muscle: Influence of physical activity and gender. Journal of Applied Physiology. J Appl Physiol (1985); 2004;97:1209–18.

98. Miotto PM, McGlory C, Holloway TM, Phillips SM, Holloway GP. Sex differences in mitochondrial respiratory function in human skeletal muscle. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology [Internet]. American Physiological Society; 2018 [cited 2020 May 30];314:R909–15. Available from: https://www.physiology.org/doi/10.1152/ajpregu.00025.2018

99. Devries MC. Sex-based differences in endurance exercise muscle metabolism: Impact on exercise and nutritional strategies to optimize health and performance in women. Experimental Physiology. Blackwell Publishing Ltd; 2016;101:243–9.

100. Melanson EL, Sharp TA, Seagle HM, Horton TJ, Donahoo WT, Grunwald GK, et al. Effect of exercise intensity on 24-h energy expenditure and nutrient oxidation. Journal of applied physiology (Bethesda, Md : 1985) [Internet]. American Physiological Society; 2002 [cited 2020 Jun 17];92:1045–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11842038

101. Tarnopolsky LJ, MacDougall JD, Atkinson SA, Tarnopolsky MA, Sutton JR. Gender differences in substrate for endurance exercise. Journal of Applied Physiology [Internet]. J Appl Physiol (1985); 1990 [cited 2020 Jun 22];68:302–8. Available from: https://pubmed.ncbi.nlm.nih.gov/2179207/

102. Chenevière X, Borrani F, Sangsue D, Gojanovic B, Malatesta D. Gender differences in whole-body fat oxidation kinetics during exercise. Applied Physiology, Nutrition and Metabolism. Appl Physiol Nutr Metab; 2011;36:88–95.

103. Venables MC, Achten J, Jeukendrup AE. Determinants of fat oxidation during exercise in healthy men and women: A cross-sectional study. Journal of Applied Physiology. American Physiological Society; 2005;98:160–7.

104. Lundsgaard A, Kiens B. Gender differences in skeletal muscle substrate metabolism - molecular mechanisms and insulin sensitivity. Frontiers in Endocrinology. 2014;5.

105. Jeukendrup AE, Jentjens RLPG, Moseley L. Nutritional Considerations in Triathlon. Sports Med. 2005.

106. Civitarese AE, Hesselink MKC, Russell AP, Ravussin E, Schrauwen P. Glucose ingestion during exercise blunts exercise-induced gene expression of skeletal muscle fat oxidative genes. American Journal of Physiology-Endocrinology and Metabolism [Internet]. American Physiological Society; 2005 [cited 2020 Jun 11];289:E1023–9. Available from: https://www.physiology.org/doi/10.1152/ajpendo.00193.2005

107. Henderson GC. Sexual dimorphism in the effects of exercise on metabolism of lipids to support resting metabolism. Frontiers in Endocrinology. Frontiers Media S.A.; 2014.

108. Coyle EF. Physiological regulation of marathon performance. Sports Medicine. Adis International Ltd; 2007. p. 306–11.

109. Tanaka H, Bassett DR, Swensen TC, Sampedro RM. Aerobic and anaerobic power characteristics of competitive cyclists in the United States cycling federation. International Journal of Sports Medicine [Internet]. Int J Sports Med; 1993 [cited 2020 Jun 22];14:334–8. Available from: https://pubmed.ncbi.nlm.nih.gov/8407064/

110. Emerick P, Teed K, Rusk G, Fernhall B. Predictors of marathon performance in female runners. Sports Medicine, Training and Rehabilitation. Taylor & Francis Group ; 1997;8:23–36.

111. Maughan RJ, Leiper JB. Aerobic capacity and fractional utilisation of aerobic capacity in elite and non-elite male and female marathon runners. European Journal of Applied Physiology and Occupational Physiology. Springer; 1983;52:80–7.

112. Loe H, Rognmo Ø, Saltin B, Wisløff U. Aerobic Capacity Reference Data in 3816 Healthy Men and Women 20-90 Years. 2013 [cited 2020 Jun 10]; Available from: www.ntnu.edu/hunt

113. Calbet JAL, Joyner MJ. Disparity in regional and systemic circulatory capacities: Do they affect the regulation of the circulation? [Internet]. Acta Physiologica. Blackwell Publishing Ltd; 2010 [cited 2020 Aug 14]. p. 393–406. Available from: /pmc/articles/PMC3011865/?report=abstract

114. Astrand P. Human Physical Fitness With Special Reference to Sex and Age From the Department of Physiology. Physiological Reviews. 1956;36:307–35.

115. Cureton KJ, Bishop P, Cureton K, Bishop P, Hutchinson P, Newland H, et al. Sex difference in maximal oxygen uptake Effect o f equating haemoglobin concentration. European Journal of Applied Physiology-and Occupat~onal Phys~ology O Spmger-Vedag [Internet]. 1986 [cited 2020 Sep 1];54:656–60. Available from: https://www.researchgate.net/publication/19212802

116. Barun Sharma H, Kailashiya J. Gender Difference in Aerobic Capacity and the Contribution by Body Composition and Haemoglobin Concentration: A Study in Young Indian National Hockey Players. Journal of Clinical and Diagnostic Research. 2016;10:CC09-CC13.

117. Cardinale DA, Larsen FJ, Schiffer TA, Morales-Alamo D, Ekblom B, Calbet JAL, et al. Superior intrinsic mitochondrial respiration in women than in men. Frontiers in Physiology. Frontiers Media S.A.; 2018;9.

118. Torres MJ, Kew KA, Ryan TE, Pennington ER, Lin C te, Buddo KA, et al. 17β-Estradiol Directly Lowers Mitochondrial Membrane Microviscosity and Improves Bioenergetic Function in Skeletal Muscle. Cell Metabolism. Cell Press; 2018;27:167-179.e7.

119. Davies CTM, Thompson MW. Aerobic performance of female marathon and male ultramarathon athletes. European Journal of Applied Physiology and Occupational Physiology. Springer-Verlag; 1979;41:233–45.

120. Whyte G, Lumley S, George K, Gates P, Sharma S, Prasad K, et al. Physiological profile and predictors of cycling performance in ultra-endurance triathletes. Journal of Sports Medicine and Physical Fitness. 2000;40:103–9.

121. Laursen PB, Rhodes EC. Factors affecting performance in an ultraendurance triathlon. Sports Medicine. Adis International Ltd; 2001. p. 195–209.

122. Ingham SA, Whyte GP, Pedlar C, Bailey DM, Dunman N, Nevill AM. Determinants of 800-m and 1500-m running performance using allometric models. Medicine and Science in Sports and Exercise. Med Sci Sports Exerc; 2008;40:345–50.

123. Joyner MJ. Modeling: Optimal marathon performance on the basis of physiological factors. Journal of Applied Physiology. J Appl Physiol (1985); 1991;70:683–7.

124. Joyner MJ. Physiological limits to endurance exercise performance: influence of sex [Internet]. Journal of Physiology. Blackwell Publishing Ltd; 2017 [cited 2020 Sep 21]. p. 2949–54. Available from: /pmc/articles/PMC5407964/?report=abstract

125. Helgerud J, Ingjer F, Strømme SB. Sex differences in performance-matched marathon runners. European Journal of Applied Physiology and Occupational Physiology. Springer-Verlag; 1990;61:433–9.

126. Daniels J, Daniels N. Running Economy of Elite Male and Elite Female Runners. Medicine & Science in Sports & Exercise. 1992;24:483–9.

127. Fletcher JR, Pfister TR, Macintosh BR. Energy cost of running and achilles tendon stiffness in man and woman trained runners. Physiological Reports [Internet]. American Physiological Society; 2013 [cited 2020 Aug 31];1. Available from: https://pubmed.ncbi.nlm.nih.gov/24744857/

128. Bourdin M, Pastene J, Germain M, Lacour JR. Influence of training, sex, age and body mass on the energy cost of running. European Journal of Applied Physiology and Occupational Physiology [Internet]. Springer-Verlag; 1993 [cited 2020 Aug 31];66:439–44. Available from: https://pubmed.ncbi.nlm.nih.gov/8330613/

129. Bielik V. Gender differences of running kinematics and economy in trained distance runners. Gazzetta Medica Italiana Archivio per le Scienze Mediche. Edizioni Minerva Medica; 2019;178:403–10.

130. Yasuda N, Gaskill SE, Ruby BC. No gender-specific differences in mechanical efficiency during arm or leg exercise relative to ventilatory threshold. Scandinavian Journal of Medicine and Science in Sports [Internet]. Scand J Med Sci Sports; 2008 [cited 2020 Sep 21];18:205–12. Available from: https://pubmed.ncbi.nlm.nih.gov/17490463/

131. Ainegren M, Carlsson P, Tinnsten M, Laaksonen MS. Skiing economy and efficiency in recreational and elite cross-country skiers. Journal of Strength and Conditioning Research [Internet]. J Strength Cond Res; 2013 [cited 2020 Sep 21];27:1239–52. Available from: https://pubmed.ncbi.nlm.nih.gov/22344058/

132. Hegge AM, Bucher E, Ettema G, Faude O, Holmberg HC, Sandbakk Ø. Gender differences in power production, energetic capacity and efficiency of elite cross-country skiers during whole-body, upper-body, and arm poling. European Journal of Applied Physiology [Internet]. Springer Verlag; 2016 [cited 2020 Sep 21];116:291–300. Available from: https://pubmed.ncbi.nlm.nih.gov/26476546/

133. Billat V, Lepretre PM, Heugas AM, Laurence MH, Salim D, Koralsztein JP. Training and bioenergetic characteristics in elite male and female Kenyan runners. Medicine and Science in Sports and Exercise [Internet]. Med Sci Sports Exerc; 2003 [cited 2020 Sep 21];35:297–304. Available from: https://pubmed.ncbi.nlm.nih.gov/12569219/

134. Lacour JR, Bourdin M. Factors affecting the energy cost of level running at submaximal speed [Internet]. European Journal of Applied Physiology. Springer Verlag; 2015 [cited 2020 Sep 21]. p. 651–73. Available from: https://pubmed.ncbi.nlm.nih.gov/25681108/

135. Balducci P, Clémençon M, Trama R, Blache Y, Hautier C. Performance Factors in a Mountain Ultramarathon. International Journal of Sports Medicine [Internet]. Georg Thieme Verlag; 2017 [cited 2020 Jun 10];38:819–26. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0043-112342

136. VanHeest JL, Mahoney CE, Herr L. Characteristics of elite open-water swimmers. Journal of Strength and Conditioning Research [Internet]. J Strength Cond Res; 2004 [cited 2020 Aug 31];18:302–5. Available from: https://pubmed.ncbi.nlm.nih.gov/15142018/

137. Toussaint HM, de Groot G, Savelberg HHCM, Vervoorn K, Hollander AP, van Ingen Schenau GJ. Active drag related to velocity in male and female swimmers. Journal of Biomechanics [Internet]. J Biomech; 1988 [cited 2020 Sep 21];21:435–8. Available from: https://pubmed.ncbi.nlm.nih.gov/3417695/

138. Cureton K, Sparling P, Evans B, Johnson S, Kong U, Purvis J. Effect of experimental alterations in excess weight on aerobic capacity and distance running performance. Medicine and Science in SPorts. 1978;10:194–9.

139. Sandbakk Ø, Solli GS, Holmberg HC. Sex differences in world-record performance: The influence of sport discipline and competition duration [Internet]. International Journal of Sports Physiology and Performance. Human Kinetics Publishers Inc.; 2018 [cited 2020 Aug 31]. p. 2–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28488921/

140. Pendergast DR, di Prampero PE, Craig AB, Wilson DR, Rennie DW. Quantitative analysis of the front crawl in men and women. Journal of Applied Physiology Respiratory Environmental and Exercise Physiology [Internet]. J Appl Physiol Respir Environ Exerc Physiol; 1977 [cited 2020 Sep 21];43:475–9. Available from: https://pubmed.ncbi.nlm.nih.gov/914719/

141. Lavoie JM, Montpetit RR. Applied Physiology of Swimming [Internet]. Sports Medicine: An International Journal of Applied Medicine and Science in Sport and Exercise. Sports Med; 1986 [cited 2020 Sep 21]. p. 165–89. Available from: https://pubmed.ncbi.nlm.nih.gov/3520747/

142. Wierman ME. Sex steroid effects at target tissues: mechanisms of action. Advances in Physiology Education [Internet]. American Physiological Society; 2007 [cited 2020 Jun 18];31:26–33. Available from: https://www.physiology.org/doi/10.1152/advan.00086.2006

143. Storer TW, Magliano L, Woodhouse L, Lee ML, Dzekov C, Dzekov J, et al. Testosterone dose-dependently increases maximal voluntary strength and leg power, but

does not affect fatigability or specific tension. Journal of Clinical Endocrinology and Metabolism. J Clin Endocrinol Metab; 2003;88:1478–85.

144. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, et al. Testosterone dose-response relationships in healthy young men. American Journal of Physiology - Endocrinology and Metabolism. American Physiological Society; 2001;281.

145. Gleason ED, Fuxjager MJ, Oyegbile TO, Marler CA. Testosterone release and social context: When it occurs and why. Frontiers in Neuroendocrinology. Front Neuroendocrinol; 2009;30:460–9.

146. Rovira-Llopis S, Bañuls C, de Marañon AM, Diaz-Morales N, Jover A, Garzon S, et al. Low testosterone levels are related to oxidative stress, mitochondrial dysfunction and altered subclinical atherosclerotic markers in type 2 diabetic male patients. Free Radical Biology and Medicine. Elsevier Inc.; 2017;108:155–62.

147. Petersson SJ, Christensen LL, Kristensen JM, Kruse R, Andersen M, Højlund K. Effect of testosterone on markers of mitochondrial oxidative phosphorylation and lipid metabolism in muscle of aging men with subnormal bioavailable testosterone. European Journal of Endocrinology [Internet]. 2014 [cited 2020 Jun 22];171:77–88. Available from: www.eje-online.org

148. Griggs RC, Kingston W, Jozefowicz RF, Herr BE, Forbes G, Halliday D, et al. Effect of testosterone on muscle mass and muscle protein synthesis. J. Appl. Physiol. 1989.

149. Handelsman DJ, Hirschberg AL, Bermon S. Circulating testosterone as the hormonal basis of sex differences in athletic performance. Endocrine Reviews. Oxford University Press; 2018. p. 803–29.

150. McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, et al. The Effects of Menstrual Cycle Phase on Exercise Performance in Eumenorrheic Women: A Systematic Review and Meta-Analysis [Internet]. Sports Medicine. Springer; 2020 [cited 2020 Aug 17]. p. 1–15. Available from: https://doi.org/10.1007/s40279-020-01319-3

151. Chidi-Ogbolu N, Baar K. Effect of estrogen on musculoskeletal performance and injury risk. Frontiers in Physiology. Frontiers Media S.A.; 2019. p. 1834.

152. Tenan MS. Sex hormone effects on the nervous system and their impact on muscle strength and motor performance in women. Sex Hormones, Exercise and Women: Scientific and Clinical Aspects [Internet]. Springer International Publishing; 2016 [cited 2020 Jul 28]. p. 59–70. Available from: https://link.springer.com/chapter/10.1007/978-3-319-44558-8_4

153. Shultz SJ, Schmitz RJ, Beynnon BD. Variations in varus/valgus and internal/external rotational knee laxity and stiffness across the menstrual cycle. Journal of Orthopaedic Research. NIH Public Access; 2011;29:318–25.

154. The female ACL: Why is it more prone to injury? Journal of Orthopaedics [Internet]. Reed Elsevier India Pvt. Ltd.; 2016 [cited 2020 Aug 31];13:A1–4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4805849/

155. Almekinders LC, Engle CR. Common and uncommon injuries in ultra-endurance sports. Sports Medicine and Arthroscopy Review. Lippincott Williams and Wilkins; 2019. p. 25–30.

156. Hamadeh MJ, Devries MC, Tarnopolsky MA. Estrogen Supplementation Reduces Whole Body Leucine and Carbohydrate Oxidation and Increases Lipid Oxidation in Men during Endurance Exercise. The Journal of Clinical Endocrinology & Metabolism [Internet].

Oxford Academic; 2005 [cited 2020 Jun 17];90:3592–9. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2004-1743

157. Santosa S, Jensen MD. Adipocyte fatty acid storage factors enhance subcutaneous fat storage in postmenopausal women. Diabetes. Diabetes; 2013;62:775–82.

158. D'Eon TM, Sharoff C, Chipkin SR, Grow D, Ruby BC, Braun B. Regulation of exercise carbohydrate metabolism by estrogen and progesterone in women. American Journal of Physiology - Endocrinology and Metabolism [Internet]. American Physiological Society; 2002 [cited 2020 Jul 28];283:1046–55. Available from: http://www.ajpendo.orgE1046

159. Isacco L, Boisseau N. Sex hormones and substrate metabolism during endurance exercise. Sex Hormones, Exercise and Women: Scientific and Clinical Aspects [Internet]. Springer International Publishing; 2016 [cited 2020 Jul 28]. p. 35–58. Available from: https://link.springer.com/chapter/10.1007/978-3-319-44558-8_3

160. Valencia AP, Schappal AE, Matthew Morris E, Thyfault JP, Lowe DA, Spangenburg EE. The presence of the ovary prevents hepatic mitochondrial oxidative stress in young and aged female mice through glutathione peroxidase 1. Experimental Gerontology. Elsevier Inc.; 2016;73:14–22.

161. Baltgalvis KA, Greising SM, Warren GL, Lowe DA. Estrogen regulates estrogen receptors and antioxidant gene expression in mouse skeletal muscle. PLoS ONE. PLoS One; 2010;5.

162. Vezzoli A, Dellanoce C, Mrakic-Sposta S, Montorsi M, Moretti S, Tonini A, et al. Oxidative Stress Assessment in Response to Ultraendurance Exercise: Thiols Redox Status and ROS Production according to Duration of a Competitive Race. Oxidative Medicine and Cellular Longevity. Hindawi Limited; 2016;2016.

163. Heikura IA, Uusitalo ALT, Stellingwerff T, Bergland D, Mero AA, Burke LM. Low energy availability is difficult to assess but outcomes have large impact on bone injury rates in elite distance athletes. International Journal of Sport Nutrition and Exercise Metabolism [Internet]. Human Kinetics Publishers Inc.; 2018 [cited 2020 Jul 28];28:403–11. Available from: https://pubmed.ncbi.nlm.nih.gov/29252050/

164. Miller S, Kukuljan S, Turner A, van der Pligt P, Ducher G. Energy Deficiency, Menstrual Disturbances, and Low Bone Mass: What Do Exercising Australian Women Know About the Female Athlete Triad? International Journal of Sport Nutrition and Exercise Metabolism. 2012;22:131–8.

165. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP. The female athlete triad. Medicine and Science in Sports and Exercise [Internet]. Med Sci Sports Exerc; 2007 [cited 2020 Jul 28];39:1867–82. Available from: https://pubmed.ncbi.nlm.nih.gov/17909417/

166. Riggs BL. The mechanisms of estrogen regulation of bone resorption. Journal of Clinical Investigation. The American Society for Clinical Investigation; 2000. p. 1203–4.

167. Chen YT, Tenforde AS, Fredericson M. Update on stress fractures in female athletes: Epidemiology, treatment, and prevention. Current Reviews in Musculoskeletal Medicine. Springer; 2013;6:173–81.

168. Papageorgiou M, Elliott-Sale KJ, Parsons A, Tang JCY, Greeves JP, Fraser WD, et al. Effects of reduced energy availability on bone metabolism in women and men. Bone

[Internet]. Elsevier Inc.; 2017 [cited 2020 Jul 28];105:191–9. Available from: https://pubmed.ncbi.nlm.nih.gov/28847532/

169. Elliott-Sale KJ, Tenforde AS, Parziale AL, Holtzman B, Ackerman KE. Endocrine effects of relative energy deficiency in sport. International Journal of Sport Nutrition and Exercise Metabolism [Internet]. Human Kinetics Publishers Inc.; 2018 [cited 2020 Jul 28];28:335–49. Available from: https://pubmed.ncbi.nlm.nih.gov/30008240/

170. Martin D, Sale C, Cooper SB, Elliott-Sale KJ. Period prevalence and perceived side effects of hormonal contraceptive use and the menstrual cycle in elite athletes. International Journal of Sports Physiology and Performance [Internet]. Human Kinetics Publishers Inc.; 2018 [cited 2020 Jul 28];13:926–32. Available from: https://pubmed.ncbi.nlm.nih.gov/29283683/

171. de Oliveira EP, Burini RC, Jeukendrup A. Gastrointestinal complaints during exercise: Prevalence, etiology, and nutritional recommendations. Sports Medicine. Springer International Publishing; 2014;44:79.

172. Riddoch C, Trinick T. Gastrointestinal disturbances in marathon runners. British journal of sports medicine. BMJ Publishing Group; 1988;22:71–4.

173. Stuempfle KJ, Hoffman MD. Gastrointestinal distress is common during a 161-km ultramarathon. Journal of Sports Sciences. Routledge; 2015;33:1814–21.

174. Wilson PB. ‘I think I’m gonna hurl’: A Narrative Review of the Causes of Nausea and Vomiting in Sport. Sports [Internet]. MDPI AG; 2019 [cited 2020 Sep 15];7:162. Available from: https://pubmed.ncbi.nlm.nih.gov/31277403/

175. Rowlands DS, Swift M, Ros M, Green JG. Composite versus single transportable carbohydrate solution enhances race and laboratory cycling performance. Applied Physiology, Nutrition and Metabolism [Internet]. Appl Physiol Nutr Metab; 2012 [cited 2020 Sep 15];37:425–36. Available from: https://pubmed.ncbi.nlm.nih.gov/22468766/

176. O’Brien WJ, Stannard SR, Clarke JA, Rowlands DS. Fructose-maltodextrin ratio governs exogenous and other cho oxidation and performance. Medicine and Science in Sports and Exercise [Internet]. Med Sci Sports Exerc; 2013 [cited 2020 Sep 15];45:1814–24. Available from: https://pubmed.ncbi.nlm.nih.gov/23949097/

177. Costa RJS, Hoffman MD, Stellingwerff T. Considerations for ultra-endurance activities: part 1- nutrition [Internet]. Research in Sports Medicine. Taylor and Francis Inc.; 2019 [cited 2020 Sep 15]. p. 166–81. Available from: https://pubmed.ncbi.nlm.nih.gov/30056753/

178. Hoffman MD, Fogard K. Factors related to successful completion of a 161-km ultramarathon. International Journal of Sports Physiology and Performance [Internet]. Human Kinetics Publishers Inc.; 2011 [cited 2020 Sep 15];6:25–37. Available from: https://pubmed.ncbi.nlm.nih.gov/21487147/

179. Costa RJS, Snipe RMJ, Kitic CM, Gibson PR. Systematic review: exercise-induced gastrointestinal syndrome—implications for health and intestinal disease [Internet]. Alimentary Pharmacology and Therapeutics. Blackwell Publishing Ltd; 2017 [cited 2020 Sep 15]. p. 246–65. Available from: https://pubmed.ncbi.nlm.nih.gov/28589631/

180. Wilson PB. Does carbohydrate intake during endurance running improve performance? A critical review [Internet]. Journal of Strength and Conditioning Research. NSCA National Strength and Conditioning Association; 2016 [cited 2020 Sep 15]. p. 3539–59. Available from: https://pubmed.ncbi.nlm.nih.gov/27045602/

181. Cox AJ. Variations in Size of the Human Stomach. California and western medicine [Internet]. BMJ Publishing Group; 1945 [cited 2020 Sep 15];63:267–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18747178

182. Bouras EP, Delgado-Aros S, Camilleri M, Castillo EJ, Burton DD, Thomforde GM, et al. SPECT imaging of the stomach: Comparison with barostat, and effects of sex, age, body mass index, and fundoplication. Gut [Internet]. BMJ Publishing Group; 2002 [cited 2020 Sep 15];51:781–6. Available from: /pmc/articles/PMC1773479/?report=abstract

183. Monrroy H, Borghi G, Pribic T, Galan C, Nieto A, Amigo N, et al. Biological response to meal ingestion: Gender differences. Nutrients [Internet]. MDPI AG; 2019 [cited 2020 Sep 15];11. Available from: /pmc/articles/PMC6471145/?report=abstract

184. Probert CJS, Emmett PM, Heaton KW. Intestinal transit time in the population calculated from self made observations of defecation. Journal of Epidemiology and Community Health [Internet]. BMJ Publishing Group; 1993 [cited 2020 Sep 15];47:331–3. Available from: /pmc/articles/PMC1059804/?report=abstract

185. Rao SSC, Kuo B, McCallum RW, Chey WD, DiBaise JK, Hasler WL, et al. Investigation of Colonic and Whole-Gut Transit With Wireless Motility Capsule and Radiopaque Markers in Constipation. Clinical Gastroenterology and Hepatology [Internet]. Clin Gastroenterol Hepatol; 2009 [cited 2020 Sep 15];7:537–44. Available from: https://pubmed.ncbi.nlm.nih.gov/19418602/

186. Mori H, Suzuki H, Matsuzaki J, Taniguchi K, Shimizu T, Yamane T, et al. Gender Difference of Gastric Emptying in Healthy Volunteers and Patients with Functional Dyspepsia. Digestion [Internet]. S. Karger AG; 2017 [cited 2020 Sep 15];95:72–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28052285/

187. Datz F, Christian P, Moore J. Gender-related differences in gastric emptying. Journal of Nuclear Medicine. 1987;28:1204–7.

188. Gangula PRR, Sekhar KR, Mukhopadhyay S. Gender bias in gastroparesis: Is nitric oxide the answer? [Internet]. Digestive Diseases and Sciences. NIH Public Access; 2011 [cited 2020 Sep 16]. p. 2520–7. Available from: /pmc/articles/PMC3170494/?report=abstract

189. Kim YS, Unno T, Kim BY, Park MS. Sex differences in gut microbiota [Internet]. World Journal of Men?s Health. Korean Society for Sexual Medicine and Andrology; 2020 [cited 2020 Sep 15]. p. 48–60. Available from: /pmc/articles/PMC6920072/?report=abstract

190. Pires W, Veneroso CE, Wanner SP, Pacheco DAS, Vaz GC, Amorim FT, et al. Association Between Exercise-Induced Hyperthermia and Intestinal Permeability: A Systematic Review [Internet]. Sports Medicine. Springer International Publishing; 2017 [cited 2020 Sep 21]. p. 1389–403. Available from: https://link.springer.com/article/10.1007/s40279-016-0654-2

191. Stuempfle KJ, Valentino T, Hew-Butler T, Hecht FM, Hoffman MD. Nausea is associated with endotoxemia during a 161-km ultramarathon. Journal of Sports Sciences [Internet]. Routledge; 2016 [cited 2020 Sep 15];34:1662–8. Available from: https://www.tandfonline.com/doi/full/10.1080/02640414.2015.1130238

192. Brock-Utne J, Gaffin S, Wells M, Gathiram P, Sohar E, James M, et al. Endotoxaemia in exhausted runners after a long-distance race. South African Medical Journal. 1988;73:533–6.

193. Jeukendrup A, Vet-Joop K, Sturk A, Stegen J, Senden J, Saris W, et al. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. Clinical Science (London, England). 2000;98:47–55.

194. Edogawa S, Peters SA, Jenkins GD, Gurunathan S v., Sundt WJ, Johnson S, et al. Sex differences in NSAID-induced perturbation of human intestinal barrier function and microbiota. The FASEB Journal [Internet]. FASEB; 2018 [cited 2020 Sep 21];32:6615–25. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1096/fj.201800560R

195. Mujagic Z, Ludidi S, Keszthelyi D, Hesselink MAM, Kruimel JW, Lenaerts K, et al. Small intestinal permeability is increased in diarrhoea predominant IBS, while alterations in gastroduodenal permeability in all IBS subtypes are largely attributable to confounders. Alimentary Pharmacology and Therapeutics [Internet]. Blackwell Publishing Ltd; 2014 [cited 2020 Sep 21];40:288–97. Available from: https://pubmed.ncbi.nlm.nih.gov/24943095/

196. Suenaert, Bulteel, den Hond, Hiele, Peeters, Monsuur, et al. The effects of smoking and indomethacin on small intestinal permeability. Alimentary Pharmacology and Therapeutics [Internet]. John Wiley & Sons, Ltd; 2000 [cited 2020 Sep 21];14:819–22. Available from: http://doi.wiley.com/10.1046/j.1365-2036.2000.00754.x

197. Haug TT, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? Scandinavian Journal of Gastroenterology [Internet]. Taylor & Francis; 2002 [cited 2020 Sep 15];37:294–8. Available from: https://www.tandfonline.com/doi/abs/10.1080/003655202317284192

198. Bytzer P, Howell S, Leemon M, Young LJ, Jones MP, Talley NJ. Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: A population based study in 15 000 Australian adults. Gut [Internet]. Gut; 2001 [cited 2020 Sep 15];49:66–72. Available from: https://pubmed.ncbi.nlm.nih.gov/11413112/

199. Tibblin G, Bengtsson C, Furunes B, Lapidus L. Symptoms by age and sex: The population studies of men and women in gothenburg, Sweden. Scandinavian Journal of Primary Health Care [Internet]. Informa Healthcare; 1990 [cited 2020 Sep 15];8:9–17. Available from: https://www.tandfonline.com/doi/abs/10.3109/02813439008994923

200. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? BJOG: An International Journal of Obstetrics and Gynaecology [Internet]. John Wiley & Sons, Ltd; 1998 [cited 2020 Sep 15];105:1322–5. Available from: http://doi.wiley.com/10.1111/j.1471-0528.1998.tb10014.x

201. ter Steege RWF, van der Palen J, Kolkman JJ. Prevalence of gastrointestinal complaints in runners competing in a long-distance run: An internet-based observational study in 1281 subjects. Scandinavian Journal of Gastroenterology [Internet]. Scand J Gastroenterol; 2008 [cited 2020 Sep 15];43:1477–82. Available from: https://pubmed.ncbi.nlm.nih.gov/18777440/

202. Rehrer NJ, Janssen GME, Brouns F, Saris WHM. Fluid intake and gastrointestinal problems in runners competiting in a 25-km race and a marathon. International Journal of Sports Medicine [Internet]. Int J Sports Med; 1989 [cited 2020 Sep 15];10. Available from: https://pubmed.ncbi.nlm.nih.gov/2744925/

203. Keeffe EB, Lowe DK, Goss JR, Wayne R. Gastrointestinal symptoms of marathon runners. Western Journal of Medicine [Internet]. BMJ Publishing Group; 1984 [cited 2020 Sep 15];141:481–4. Available from: /pmc/articles/PMC1021858/?report=abstract

204. Wilson PB, Rhodes GS, Ingraham SJ. Saccharide Composition of Carbohydrates Consumed during an Ultra-endurance Triathlon. Journal of the American College of Nutrition [Internet]. Routledge; 2015 [cited 2020 Sep 15];34:497–506. Available from: https://pubmed.ncbi.nlm.nih.gov/25941980/

205. Costa RJ, Swancott AJ, Gill S, Hankey J, Scheer V, Murray A, et al. Compromised energy and macronutrient intake of ultra-endurance runners during a multi-stage ultra-marathon conducted in a hot ambient environment. International Journal of Sports Science [Internet]. Scientific & Academic Publishing Co.; 2013 [cited 2020 Sep 15];3:51–62. Available from: https://www.researchgate.net/publication/256846395

206. Jeukendrup AE. Training the Gut for Athletes [Internet]. Sports Medicine. Springer International Publishing; 2017 [cited 2020 Sep 15]. p. 101–10. Available from: https://pubmed.ncbi.nlm.nih.gov/28332114/

207. Levine MS, Spencer G, Alavi A, Metz DC. Competitive Speed Eating: Truth and Consequences. American Journal of Roentgenology [Internet]. American Roentgen Ray Society; 2007 [cited 2020 Sep 15];189:681–6. Available from: http://www.ajronline.org/doi/10.2214/AJR.07.2342

208. Cox GR, Clark SA, Cox AJ, Halson SL, Hargreaves M, Hawley JA, et al. Daily training with high carbohydrate availability increases exogenous carbohydrate oxidation during endurance cycling. Journal of Applied Physiology [Internet]. American Physiological Society; 2010 [cited 2020 Sep 15];109:126–34. Available from: https://pubmed.ncbi.nlm.nih.gov/20466803/

209. Miall A, Khoo A, Rauch C, Snipe RMJ, Camões-Costa VL, Gibson PR, et al. Two weeks of repetitive gut-challenge reduce exercise-associated gastrointestinal symptoms and malabsorption. Scandinavian Journal of Medicine and Science in Sports [Internet]. Blackwell Munksgaard; 2018 [cited 2020 Sep 15];28:630–40. Available from: https://pubmed.ncbi.nlm.nih.gov/28508559/

210. Costa RJS, Miall A, Khoo A, Rauch C, Snipe R, Camões-Costa V, et al. Gut-training: the impact of two weeks repetitive gut-challenge during exercise on gastrointestinal status, glucose availability, fuel kinetics, and running performance. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme [Internet]. Appl Physiol Nutr Metab; 2017 [cited 2020 Sep 15];42:547–57. Available from: https://pubmed.ncbi.nlm.nih.gov/28177715/

211. Viribay A, Arribalzaga S, Mielgo-Ayuso J, Castañeda-Babarro A, Seco-Calvo J, Urdampilleta A. Effects of 120 g/h of carbohydrates intake during a mountain marathon on exercise-induced muscle damage in elite runners. Nutrients [Internet]. MDPI AG; 2020 [cited 2020 Sep 15];12. Available from: https://pubmed.ncbi.nlm.nih.gov/32403259/

212. Impey S, Jevons E, Mees G, Cocks M, Strauss J, Chester N, et al. Glycogen Utilization during Running: Intensity, Sex, and Muscle-specific Responses. Medicine and Science in Sports and Exercise. 2020;Online ahe.

213. Costa RJS, Gill SK, Hankey J, Wright A, Marczak S. Perturbed energy balance and hydration status in ultra-endurance runners during a 24 h ultra-marathon. British Journal of Nutrition [Internet]. Cambridge University Press; 2014 [cited 2020 Sep 15];112:428–37. Available from: https://pubmed.ncbi.nlm.nih.gov/24818799/

214. Wardenaar FC, Dijkhuizen R, Ceelen IJM, Jonk E, de Vries JHM, Witkamp RF, et al. Nutrient intake by ultramarathon runners: Can they meet recommendations? International

Journal of Sport Nutrition and Exercise Metabolism [Internet]. Human Kinetics Publishers Inc.; 2015 [cited 2020 Sep 15];25:375–86. Available from: https://pubmed.ncbi.nlm.nih.gov/25811196/

215. Gagnon D, Kenny GP. Does sex have an independent effect on thermoeffector responses during exercise in the heat? [Internet]. Journal of Physiology. Wiley-Blackwell; 2012 [cited 2020 Sep 15]. p. 5963–73. Available from: /pmc/articles/PMC3530110/?report=abstract

216. Hajali V, Andersen ML, Negah SS, Sheibani V. Sex differences in sleep and sleep loss-induced cognitive deficits: The influence of gonadal hormones. Hormones and Behavior. Academic Press Inc.; 2019. p. 50–61.

217. Deaner RO, Balish SM, Lombardo MP. Sex Differences in Sports Interest and Motivation: An Evolutionary Perspective. 2015 [cited 2020 Jun 23]; Available from: http://dx.doi.org/10.1037/ebs0000049

TABLES AND FIGURES

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

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

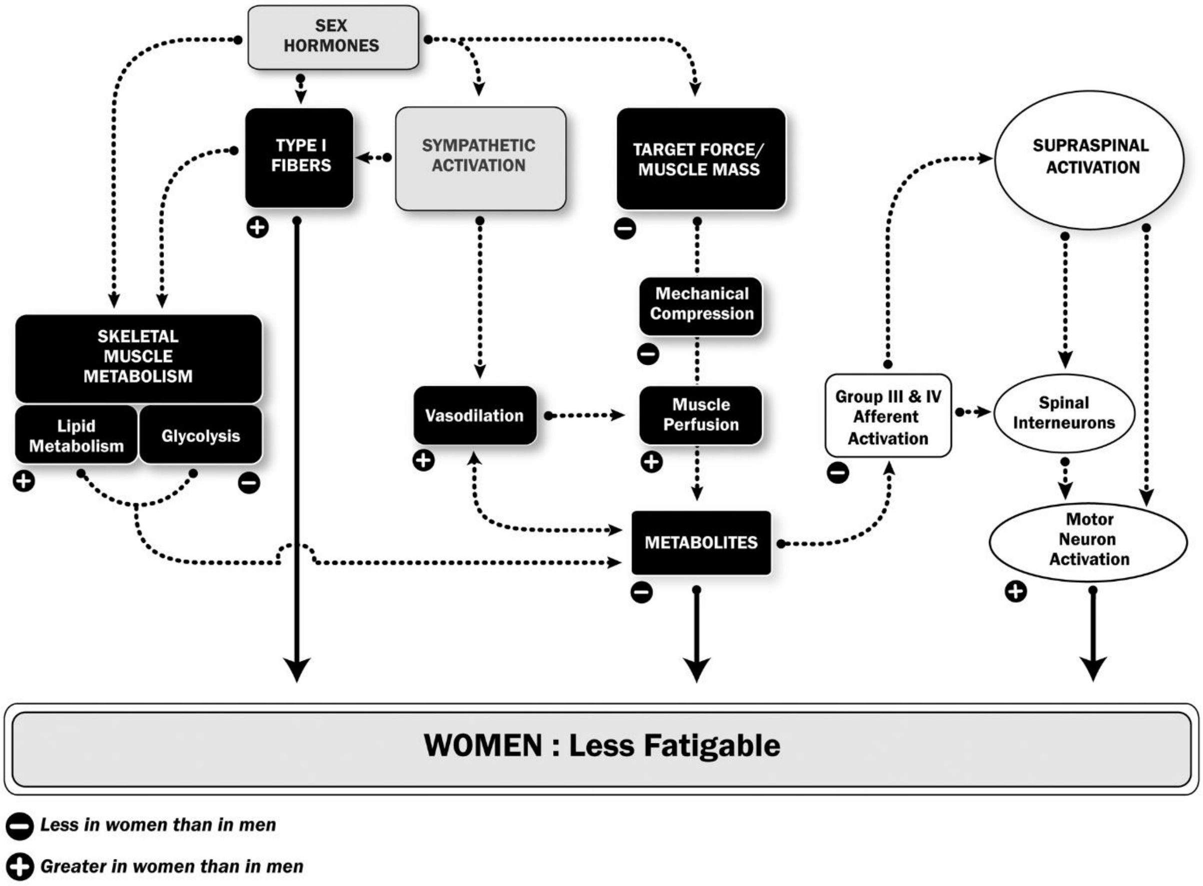
Fig. 2. Determinants of performance in ultra-endurance events, and the compromise between energy cost and lower-limb tissue damage (dashed lines). The principal determinants are in bold. Reproduced from Millet et al [10], with permission. GI = gastrointestinal; NM = neuromuscular; $\dot{V}O_2max$ = maximal oxygen uptake.

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

Table 1.

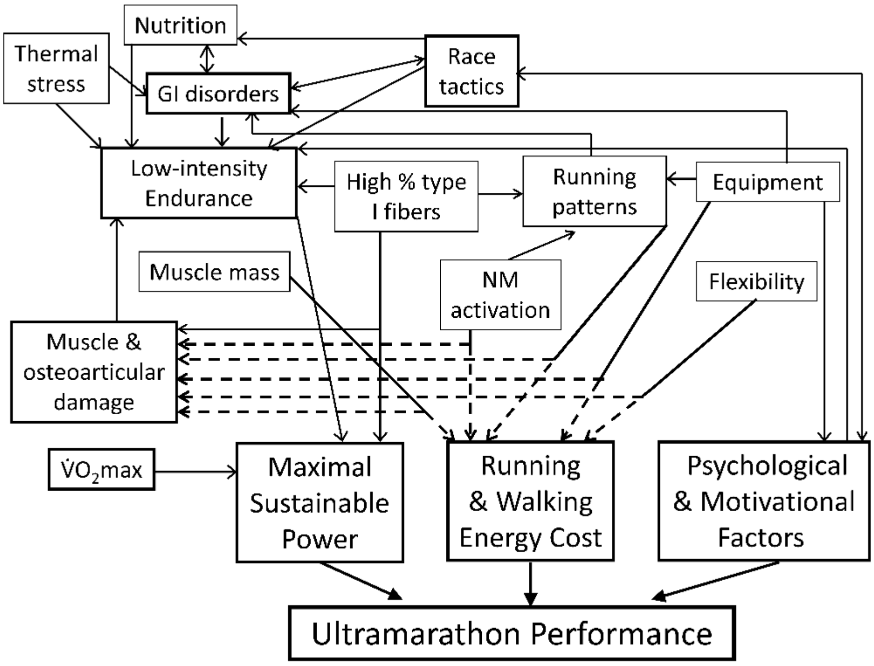
Characteristic	ST Oxidative	FTa Oxidative	FTb Glycolytic
Contractile			
Time to peak tension	1.0	0.4	0.4
Ca^{2+} myosin ATPase	1.0	3.0	3.0
Mg^{2+} actomyosin ATPase	1.0	2.8	2.8
Enzymatic	1.0		
Creatine phosphokinase	1.0	1.3	1.3
Phosphofructokinase	1.0	1.5	2.1
Glycogen phosphorylase	1.0	2.1	3.1
Citrate 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
Triacyglycerol	1.0	0.4	0.2

Figure 1.



SEX HORMONES
TYPE I FIBERS
SYMPATHETIC ACTIVATION
TARGET FORCE/ MUSCLE MASS
SUPRASPINAL ACTIVATION
SKELETAL MUSCLE METABOLISM
Lipid Metabolism
Glycolysis
Mechanical Compression
Vasodilation
Muscle Perfusion
Group III & IV Afferent Activation
Spinal Interneurons
Motor Neuron Activation
METABOLITES
WOMEN : Less Fatigable
Less in women than in men
Greater in women than in men

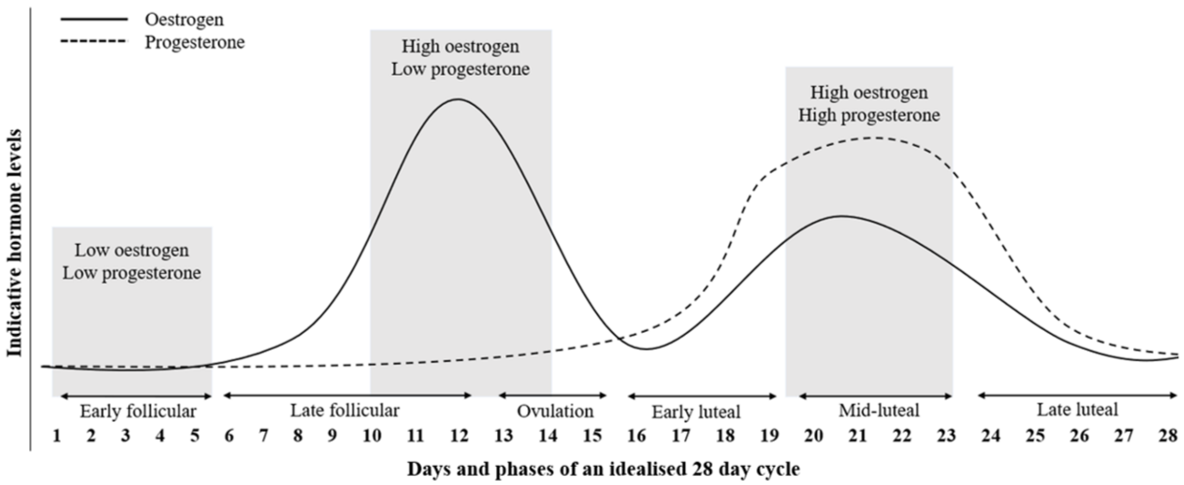
1553 Figure 2.



1554

1555

Figure 3.



Oestrogen
Progesterone
High oestrogen
Low progesterone
High oestrogen
High progesterone
Low oestrogen
Low progesterone
Indicative hormone levels
Early follicular
Late follicular
Ovulation
Early luteal
Mid-luteal
Late luteal
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Days and phases of an idealised 28 day cycle