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Editorial

What's the difference? Understanding sexual dimorphism in physiology

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Despite the fact that women had been playing Australian Rules Football for over 150 years in local competitions, it was not until 2010 that the Australian Football League (AFL) commissioned a review of women's football in Australia that led to a recommendation to develop a professional national women's competition. It was proposed that the first competitions should begin in 2020 but due to increasing public support the inaugural season was brought forward to 2017. The AFL moved cautiously and planned the initial match at a smaller oval with a capacity of 7,000 people. However, increasing demand would outstrip seating capacity and the match was moved to a larger stadium that could seat 22,000 people. On the night more than 24,500 people attended with many standing in the aisles, sitting on the fences or waiting outside. It was the largest crowd ever recorded for a women's only sporting event in Australia with the exception of the Olympic Games and Commonwealth Games.

This historical imbalance in public attitude in sporting competitions is also impeding progress in understanding female specific responses to exercise, as well as preventing injuries among female players not only in Australia but in many countries around the world. One driver for this is the large amount of money, in areas such as sponsorship and salaries, in men's sport. Another reason for this is that research in exercise and injuries is skewed towards male athletes leaving large gaps in knowledge about female sports and sports related injuries. A recent systematic review of 669 papers published between 2017 and 2021 compared the number of studies evaluating male versus

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female athletes and the co-ed sports that underrepresent females (ref 1). Most studies included male athletes only (70.7%) while 8.8% of studies examined female athletes only. Female athletes were researched primarily in the sports of volleyball and softball. Male athletes were studied in sports such as baseball, soccer, American football, basketball, rugby, hockey, and Australian football. It is clear that sports medicine studies favour the study of male athletes.

In this issue of *The Journal of Physiology* the role of sexual dimorphism is examined in physiology including skeletal muscle fatigability and exercise training. This knowledge is important for developing sex specific training routines particularly at the elite level of competition with the aim of enhancing performance, but a deeper understanding may also assist in protecting the individual from sports related injuries. In the article by Landen et al (Paul et al, 2022), it is clear that sex differences in exercise physiology are not only underpinned by the sex chromosome complement and sex hormones, but also posttranscriptional regulation and epigenetic changes such as skeletal muscle DNA methylation and histone modifications that contribute to muscle phenotype. Although many of the studies have concentrated on male subjects, there is increasing evidence that females respond to exercise differently at the molecular level. Factors influencing exercise such as the menstrual cycle, use of contraceptive hormones and menopause need to be considered and studies should account for sex as a covariate in analysis of data.

Sexual dimorphism also extends to pathological states. The development of cardiovascular risk associated with excess adiposity and obesity differs between men and women. The contributing factors are complex and multifactorial. De Jesus and Henry (cite paper) examine the biological basis for alterations in energy balance in men and women. Although energy balance is dependent upon caloric intake and energy expenditure, this is also influenced by the effects of leptin and insulin, thermogenic activity and sex steroid concentration. Young women are protected against weight gain and cardiometabolic disease but this changes post menopause when oestrogen drops and adipose deposition increases. Oestrogens regulate energy balance by altering melanocortin signalling in the hypothalamus thereby influencing satiety. The deposition and amount of brown adipose tissue differs also in females and is important in regulating thermogenesis. Understanding the physiological mechanisms that underpin these differences will be important for managing weight gain and reducing cardiometabolic risk in older women. A greater understanding will also inform the use of steroidal treatments such as hormone replacement therapy and gender affirming hormonal therapy.

Interestingly, in the last 20 years a mouse (and now rat) model has been developed which allows the investigation of differences in phenotypes between males and females caused by sex chromosomes

JP-E-2023-284342 **COMMISSIONED**

or gonadal hormones (Ref De Vries et al, 2002). This model has been used to test simultaneously the effects of hormones on a particular trait, and the interaction of sex chromosomes and hormonal effects in the development of a trait or disease risk.

It will be necessary to address the sex bias in research by designing large robust studies that include women and diverse cohorts. A greater proportion of studies focusing solely on women can be realised with an increase in awareness by the researchers and incentives provided by funding agencies such as the National Institutes of Health (NIH) that now require the clinical studies they fund to include data on the different sexes. More rigorous studies that understand the physiology of the female body and do not extrapolate from male studies will lead to a better understanding of injuries, treatment options and interventions while enhancing performance in sport. In addition, there are sex specific differences in pharmacokinetics and pharmacodynamics of multiple drugs which also requires consideration (Mauvais-Jarvis et al, 2021). Thus, a greater understanding of the physiological differences will also enable sex specific preventative measures to reduce morbidity and mortality in women and diverse cohorts.

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JP-E-2023-284342 **COMMISSIONED**