Canadian Science Publishing

EDITORIAL

Importance of considering sex and gender in exercise and nutrition research

Michaela C. Devries and Jennifer M. Jakobi

Introduction

In the last decade, scientists, professionals, consumers, and government organizations have elevated awareness on the adequate inclusion of diverse populations in scientific research. The intent is assurance that the research applies to all people. Increasingly, funding agencies (e.g., Tri-Agency Statement), academic institutions (e.g., Stanford University; Clow et al. 2009) and publishers (e.g., Coalition for Diversity & Inclusion in Scholarly Communications) are acknowledging that scientific evidence may be fundamentally flawed because there is an ongoing failure to include sex and gender approaches in study design and analysis (Holdcroft 2007). The inclusion, and delineation, of sex and gender is not just a trend in science, it is a shift to embrace a neoteric approach to research. *Applied Physiology, Nutrition, and Metabolism* (*APNM*) recognizes that sex and gender in research is critical to optimizing performance and health in both men and women. However, a retrospective analysis of papers published by *APNM* since its inception (as *Canadian Journal of Applied Physiology*; *CJAP*) underscore the need for increased identification and inclusion of women/females in research experimentation. Thus, the purpose of this virtual issue is to overview the historical context of sex/gender within *APNM* by featuring studies that have considered sex and gender to provide exemplars to elevate awareness of greater inclusion and appropriate approaches of sex and gender in applied science and nutrition research.

Retrospective analysis of *APNM* publications

Published articles from 1993–2021 were evaluated. Symposium papers, abstracts, theses and letters to the editor were excluded during the initial search. Straightaway, it became apparent in the original research that there was a historical conflation of the terms sex and gender, and thus for the purpose of this virtual issue sex and gender have been collapsed in reporting. The Canadian Institute of Health Research (CIHR) eloquently articulates sex and gender delineations (sex; biological attributes in humans and animals, gender; social constructs of individuals), and to continue to conflate these terms is inappropriate. It was only undertaken herein due to historical lack of clarity and general confusion surrounding these terms. These authors interpretation is that the original papers were evaluating sex-specific differences. Herein we draw attention to the gap in gender-based studies in applied science and nutrition research; gender-based studies are needed. There are substantially greater incidences of misapplication of the term gender in the literature, and situational corroboration where reviewers have requested that authors replace ‘sex’ with ‘gender’, when sex was the appropriate noun to use (observed and reported by Associate Editors of *APNM*). Overall, publication of gender-based differences are too few in *APNM* to build meaningful interpretation. Towards fostering better research and language approaches, *APNM* has moved to endorsing sex and gender equity in research (SAGER) guidelines (Heidari et al. 2016), and with Editorial Board education, *APNM* is working towards appropriate delineation of sex and gender terminology.

Evaluative approach

There were 2547 original papers, reviews and position papers evaluated. A substantial number of papers published did not report the sex or gender of the human and/or animal sample (381 papers; 15%). The majority of publications identified males as the human or animal in the investigation (39%) while very few papers identified females (278 papers; 11%) as the primary experimental group (Fig. 1). There were also 886 papers (35%) that included both males and females; however, of these publications only 245 (10% of all papers included) included sex as a bivariate measure. Notwithstanding that, low power or effect sizes limit the ability to detect statistical differences in many of the papers that measured outcomes in males and females. A further analysis of the total pool of papers (2547) revealed that there were 378 (15%) review papers, and most (231) did not identify sex or gender. This is problematic, as review papers tend to deliver quantitative, qualitative and narrative components conjointly to synthesize a body of work, reveal inconsistencies, gaps and insights towards building conceptual frameworks or future directions of research. Without identifying sex or gender a dimension of analysis that has critical impact on outcomes and future research and public information is overlooked.

Workplace and fitness testing

Remarkable is that of the 9 papers published in the first issue of the journal (*CJAP*; 1 review) 4 included females, and no issue since that time has achieved such high identification and/or inclusion of female subjects. The inaugural issue in 1993 set to propel forward global research in physical activity, exercise training, work and fitness. Ready et al. (1993), in her study of female nurses and back injury, was the first to identify the need for appropriate physical fitness measurements and job specific assessments. Since this original study on females, publications

Received 15 April 2021. Accepted 15 April 2021.

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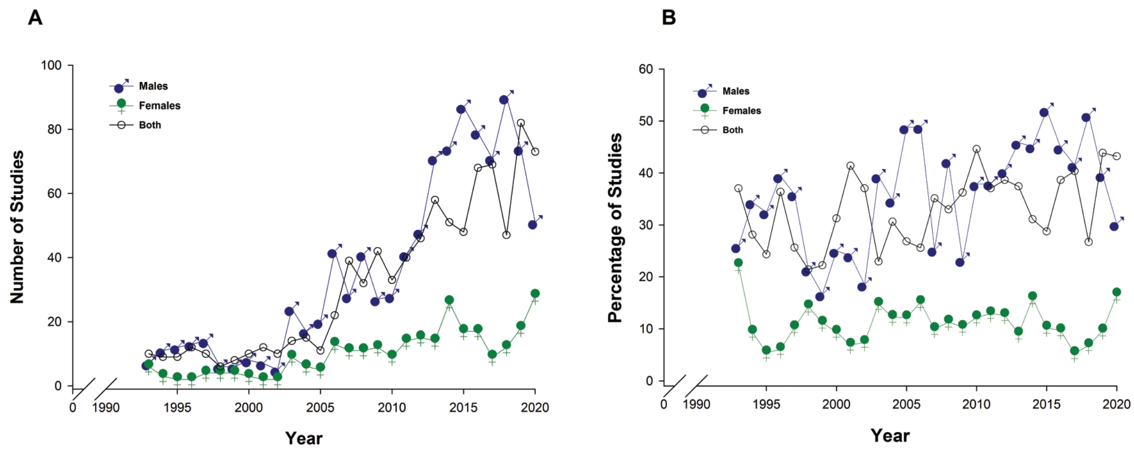
*Michaela C. Devries served as a Guest Editor at the time of manuscript review and acceptance; Jennifer M. Jakobi served as a Guest Editor and Associate Editor at the time of manuscript review and acceptance; peer review and editorial decisions regarding this manuscript were handled by Wendy Ward.

Fig. 1. (A) Number of studies published each year in *Applied Physiology, Nutrition, Metabolism* (*APNM*) between 1993–2021 that identified males, females or both as the study sample. Studies that did not report sex are not included. (B) Percentage of studies each year reporting males, females or both as the study sample. Studies that did not identify the sex of the sample are not reported. [Colour online.]



within *APNM* have led the field on work-specific fitness tests, validity and repeatability of such tests, inclusive of sex-related differences in workplace standard assessments. Jamnik and colleagues (2010), in response to the *Meiorin* Decision of the Supreme Court of Canada, identified that fitness tests for correctional officers had an adverse impact on both nonminority and minority females. However, they also discovered that when due diligence is applied to ensure that all persons are appropriately familiarized, it is possible for most to meet job-place work standards (Jamnik et al. 2010). Through a 6-week training program accommodation can occur to overcome the potential adverse impact of sex-specific differences in testing and ensure that female correctional officers are capable of meeting the physical demands encountered on the job.

Work-place fitness tests simulate on-the-job tasks, and testing has evolved to the inclusion of sex-related differences and consideration of hormonal fluctuations. Boyd and colleagues (2015) acknowledge the potential influence of menses; however, in the experimental design and scheduling approaches of the Canadian Forces Firefighter Physical Fitness Maintenance Evaluations they did not apply this consideration. Justification was that hormonal fluctuations are not applied in the workplace and therefore would threaten the validity of the experimental results. Nonetheless, identification of sex is necessary and contributes valuable information to physical performance standards (Roberts et al. 2016). Thusly, fitness related to job performance, as well as sport-related fitness need not always consider and align experimentation with phase specific testing of the menstrual cycle in females, as daily function and performance must occur irrespective of hormonal change. Ultimately, it is imperative that the design and inclusion of females and males, as well as hormonal measures, are dictated by the experimental question. Ultimately, measurement and reporting of these factors would elucidate aspects of data variability, and advance exercise and nutrition science.

Hormonal influences

The data and reporting from Birch and Reilly (1997) underscores the importance of data inspection and critique. The data from their study suggests that during the luteal (postovulatory) phase of the menstrual cycle compared with menses in eumenorrheic females, heart rate was ∼10 bpm higher in response to lifting and moving, a weighted box 6×/min for 10 min, at shoulder height. Although this difference was not statistically significant, the low statistical power was suggestive of potential for a type II error. Upon further evaluation with paired t test and the effect sizes (0.61–0.85), authors suggested that although the ANOVA was statistically non-significant the differences were realistically meaningful (Birch and Reilly 1997). There is no doubt that statistical comparisons are challenged by greater data variability in females and that sex-based comparisons require consideration of timing of female measurements in the experimental design, which is generally unnecessary when measuring males. This does add experimental complexity, but it should not deter sex-based experimentation.

Oosthuyse et al. (2003) identified the importance of hormonal fluctuations in testing and applying correction factors in estimating free fatty acid oxidation with carbon-labeled tracers. In studies that administer carbon tracers to quantify substrate oxidation, the acetate correction factor determines the extent of carbon label retention in exchange reactions of the TCA cycle. In eumenorrhoeic, sedentary women, the acetate correction factor derived during submaximal exercise is consistently lower in the mid-luteal phase than in the early follicular phase. There were no differences in the correction factor between the middle and late follicular phase, or the late and early follicular phase. Authors suggest that the lower correction factor in the mid luteal phase would result in an ∼6% greater calculated rate of plasma free fatty acid oxidation. Given that both menstrual cycle and sex influence the contribution of fat and carbohydrate sources as a fuel during exercise reviewed by Beaudry and Devries (2019), accounting for the menstrual cycle when calculating plasma free fatty acid oxidation can reduce variability and increase the sensitivity of the measure. This study highlights the need to (re)consider the measurement tools when the internal physiological milieu inherently differs due to hormonal fluctuations.

Oral contraceptive (OC) use has also received consideration in exercise science. Parmar et al. (2018) reported that the increase in mean arterial pressure (MAP) during isometric handgrip exercise at 30% max force was lower in the follicular phase in women not taking OC (95 ± 4 mm Hg) compared with men (114 ± 4 mm Hg) and women taking OC (111 ± 3 mm Hg). Testing was conducted on 2 separate days and the rise in MAP in response to handgrip exercise on those days was correlated in men and women not taking OC, but not in women taking OC. These findings suggest that women not taking OCs have greater day-to-day variation in MAP, making the detection of changes in MAP in response to an intervention more difficult to detect in women not taking OC. Overall, OC use reduces variability in the muscle metaboreflex response, which arises because of fluctuating levels of ovarian hormones throughout the menstrual cycle. Consistent with prior research, authors reported that women not taking OC demonstrated a blunted blood pressure response to increased sympathetic activity. This study offers evidence of the sex-dependent physiological response as well as the variability that fluctuating hormones place upon physiological measurements. This research also lends insight into the inclusion of women using OC as participants where day-to-day variation in the cardiovascular response to exercise needs to be minimized (Parmar et al. 2018). Greater research is required to fully understand the influence of hormonal fluctuations and contraceptive use on applied physiology and performance.

Sex as a bivariate measure

Notwithstanding the need to understand hormonal fluctuations and OCs in exercise and nutrition research, sex as a bivariate comparator is critical. As reviewed by Beaudry and Devries (2019), sex influences lipid storage within the liver and muscle and this sex-dependent difference is a primary contributor to sex-related differences in muscle metabolism and differential development of metabolic disease between males and females. Furthermore, sex has been found to influence fuel utilization during exercise with women relying to a greater extent on fat sources during exercise (Beaudry and Devries 2019; Sarafian et al. 2016). Understanding these metabolic differences in fuel storage and utilization between the sexes is essential in the application of dietary and exercise interventions. For example, high-fat, very low-carbohydrate ketogenic diets, which have received substantive attention in the mitigation and management of metabolic syndrome, induce different adaptations in male and female Wistar rats (Moore et al. 2020). Male and female Wistar rats were randomized to either standard chow, western diet or ketogenic diet with unlimited access to wheel running for 7 weeks. Interestingly, while both the ketogenic and western diets resulted in greater percent body fat than the standard chow diets, percent body fat was lower in female mice on the ketogenic diet compared with female mice on the western diet, a finding that was not seen in males. Similarly, while both western and ketogenic diets increased hepatic triglyceride content, hepatic triglyceride content was 30% lower in females following ketogenic diet compared with western diet, whereas there was no difference in hepatic triglyceride stores between western and ketogenic diet males. Despite these differences, serum TBARS concentration, an indicator of lipid peroxidation and a marker of oxidative stress, did not differ between diets in male rats, but was 2 times higher following the ketogenic diet compared with western and standard chow diets in female rats. Underlying differences in metabolism between male and female rats including the finding that female rats had lower hepatic CD36, indicative of lower hepatic fatty acid uptake, and higher ^{Thr172}AMPK phosphorylation, indicative of higher hepatic fatty acid oxidation, may underpin these differential responses to the dietary intervention and warrant further investigation. The authors of this paper are to be commended for including both male and female rats in their trial, particularly given the complex study design and numerous outcomes that were assessed. Unfortunately, due to the amount of data generated in this trial, the authors were likely limited in their ability to provide a comprehensive discussion of the meaning of these sex-related differences. Future research needs to ensure that when differences between the sexes are found that their meaning is interpreted.

Indeed, the importance of conveying sex-dependent differences in response to nutrition interventions was recently highlighted in a review by Wickham and Spriet (2019) when they signposted in their title "no longer beeting around the bush". The review focussed on an examination of existing chronic dietary nitrate supplementation (leafy green and root vegetables, particularly beetroots) and reported that supplementation has a positive effect on health and athletic performance in males, but less is known about females. Females, in exercise nutrition supplement research are an underrepresented research group, and throughout their paper, Wickham and Spriet (2019) offer suggestions for future research. That is not to say that women will always respond differently to a nutrition or supplement intervention. In fact, despite hypothesizing that women would have an exaggerated insulin desensitizing response to acute caffeine ingestion, Beaudoin et al. (2013) found no difference in the effect of different doses of caffeine on plasma glucose, insulin or C-peptide concentrations during an oral glucose tolerance test in young, lean, healthy men and women. Interestingly, insulin sensitivity index was lower in men following ingestion of 5 mg/kg caffeine compared with 3 mg/kg caffeine; however, insulin sensitivity did not differ from placebo in women following consumption of 1 mg/kg, 3 mg/kg or 5 mg/kg (Beaudoin et al. 2013). Thus, while not all trials will find a difference in the effect of an intervention between the sexes, it is still imperative that we conduct trials examining sex differences to identify, and appropriately attend to, the differences that do exist.

Animal models are incredibly useful when examining inherent physiological differences between the sexes. For example, in a study by Huot and colleagues (2016) there was a differential effect of maternal folic acid supplementation between male and female rat pups on body weight and expression of food intake regulatory genes. These findings highlight the importance of considering sex when conducting research as had the investigators not considered sex of the pups as a variable, the effects of high folic acid intake by female rats during pregnancy could have been completely missed.

Studying more than one cohort is a complex undertaking that requires greater sample size, methodological considerations (hormonal considerations) and statistical evaluation; among other considerations. Yet, there are a number of reports in *APNM* that indicate sex-related differences in force generation, muscle activation and fatigue. During repeated 5-s sprint cycling, the work decrement (18.9% vs. 29.6%; $p < 0.05$) calculated by integrating the power curve over the sprinting cycle was less in women compared with men. Summed muscle activity, measured with electromyography of 4 lower limb muscles, was less (11.4% vs. 19.4%; $p < 0.05$) in women compared to men despite both sexes achieving a similar perceived effort (Billaut and Smith 2009). Differences in motor unit recruitment strategies between the men and women were speculated as an underling cause of the sex-dependent difference in cycling work. Although little is known about recruitment strategies of motor units between female and male muscles, Inglis and Gabriel (2020) reported that compared with males, females have a higher motor unit discharge rate at low forces (<40% of maximal voluntary contraction; MVC), whereas males exhibit elevated discharge rates at higher forces. Females also have greater incidence of doublet discharges and rapid short trains of firing, and this observation of more variable and rapid firing was more cogent in a subset of males and females matched for strength. They suggest that the discharge behaviour of motor units may be a result of females needing to generate greater neural drive to achieve fused tetanus (Inglis and Gabriel 2020). The underlying influence of motor unit activity in sex-based differences is unclear, and greater knowledge would assist in understanding the greater age-related loss of force control in females compared with males (Jakobi et al. 2018).

Similar to motor unit properties, sex-related differences in contractile properties remain uncertain, and potentially overlooked due to conventional statistical evaluation. In training and fatigue studies, the baseline contractile properties of young and old females are generally slower compared to males, albeit these differences are not always statistically significant. Although not statistically significant, isometric twitch contraction and relaxation time of the elbow flexors and dorsiflexors ranged from 4%–30% slower in older females than males (Hicks and McCartney 1996), and tetanic rate of force development and relaxation of the knee extensors were statistically 10%–40% slower in females than males for young and old healthy adults (Yacyshyn and McNeil 2020). Similar to the disparate outcomes in isometric and tetanic contractile properties, there is also a misalignment between fatigue studies. The intricacies of findings are unsurprising given the known task and muscle specificity nature of fatigue, and alongside these accepted factors the interaction of sex and statistical power requires further consideration as it has important implications for determining age-related differences in performance between males and females. For example, Rüst et al. (2014) evaluated performance of open water ultra-distance swimming and found that female participation in the race increased exponentially over time between 1955 and 2012 and that during that time the male to female performance difference declined from ∼>10% to 3%. The mitigation of performance differences between the sexes is important to consider given that females experience an earlier and accelerated decline in isokinetic strength as compared with men (Haynes et al. 2020), suggesting that women may see a more rapid decline in sport performance.

APNM is well known for providing evidence-informed research for the development of position stands and activity guidelines. The influence of sex is not only gaining increased recognition within performance, exercise and nutrition research but within the development of activity guidelines. The need for consistent and enhanced physical activity monitoring, analysis and reporting procedures to lessen confusion among researchers, policy-makers and the public was previously identified (Katzmarzyk and Tremblay 2007); however, a decade ago there was little acknowledgement of sex and gender in physical activity. Evidence informed consideration and approaches of sex are mounting in the development of guidelines (Saunders et al. 2020). There is a need for greater sex-specific research to inform recommendations in physical activity.

Conclusions

Consideration of these studies as a progress report suggest that the field of applied exercise, nutrition and metabolism is progressing slowly to advance inclusive sex-based research. Despite national and international efforts, research inclusion remains low for females/women and a positive change here would likely lend favour to addressing participation of racial/ethnic minorities and other underrepresented groups in research that were not addressed within this historical overview but should not be ignored. Irrespective of historical rate of change, there is identifiable progress and optimism gained from a historical understanding. The inclusion of females in research is increasing and scientists are becoming more resolute in accurate reporting of sex, gender, hormonal supplementation and phase of menstrual cycle. To further knowledge of gender- and sex-specific differences in applied exercise and nutrition, authors are encouraged to identify appropriately, whether the sample is inclusive of men and women, or males and females. When groups studied are classified either through sex or gender the statistical approach that was used to reveal (or not) differences should be identified with effect sizes and statistical power reported. Ultimately, these facts should be highlighted in Key Findings. It goes without saying that there are many areas where sex and gender has not been investigated (or identified in this short overview), and it should also be stated that not all studies should consider sex or gender. What remains necessary and pertinent to defining meaningful differences is consideration and justification of sex and gender within the initial stages of research design, appropriate statistical evaluation, and subsequent reporting and recognition within the Results and Discussion of the publication.

Conflict of interest statement

J.M. Jakobi is an Associate Editor of *APNM*. The invitation, and decision-making was jointly held by the Co-Editors and members of the Editorial Board. There are no potential financial competing interests for M.C. Devries and J.M. Jakobi.

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