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ORIGINAL RESEARCH

THE RELATIONSHIP BETWEEN SEX, SYMPTOM SEVERITY AND THE RISK OF EXERCISE INTOLERANCE IN ADOLESCENTS FOLLOWING SPORT-RELATED CONCUSSION

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ABSTRACT

Introduction: Exercise intolerance is a risk factor for prolonged recovery following sport-related concussion (SRC) in adolescents. Evidence suggests adolescent females are at increased risk of exercise intolerance and report higher symptom severity compared to males. Thus, this study examined if the association between sex and risk of exercise intolerance was either moderated or mediated by symptom severity.

Methods: Within 14-days of SRC, adolescents participating in the pan-Canadian SHRed Concussions study reported SCAT5 symptom severity score (SSS) and completed a Buffalo Concussion Treadmill Test (BCTT). The BCTT was terminated following a 3/10 increase in concussion symptoms (exercise intolerant) or volitional fatigue (>180bpm, >18/20 rating of perceived exertion; exercise tolerant). Moderation of sex effects on exercise intolerance risk by SSS were evaluated by likelihood ratio tests. Mediation by SSS was evaluated using the parametric g formula with bootstrap standard errors.

Results: 281 adolescents (126 male, 155 female) were included. 204 (100 male, 104 female) were tolerant to exercise and 77 (26 male, 51 female) were intolerant. Multivariable analysis revealed that 1 unit of square root SSS higher symptom severity was associated with increased risk (RR=1.16; 95% CI: 1.06, 1.27) while sex was associated with non-significant increased risk (RR=1.36; 95% CI: 0.90, 2.05) of exercise intolerance. Moderation assessed via likelihood ratio test was not significant ($X^2_{(1)}$=1.50, p=0.221). Mediation results showed significant indirect effects of sex through SSS (RR=1.131; 95% CI: 1.035, 1.272), accounting for 28% of the estimated total effects (RR=1.570; 95% CI: 0.986, 2.418) while direct effects, which explained a larger proportion of total effects (72%) were not significant (RR=1.36; 95% CI: 0.90, 2.05).

Conclusion: Potential sex differences in the risk of exercise intolerance following SRC are partially explained by differences SSS. The larger yet imprecisely estimated direct effects of sex on risk of exercise intolerance highlighting the presence of additional pathways which are distinct from symptomology and warrant further investigation.

KEYWORDS: Sport-Related Concussion, Exercise Intolerance, Sex Differences, Exercise Physiology

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1. INTRODUCTION

Adolescent sport participation is associated with a myriad of social, psychological and physiological benefits that promote development and are sustained throughout adulthood[1,2]. However, sport is also the principal context for adolescent injury[3]. Thus, there is a present need for prevention efforts in sport-injury, such that the benefits to adolescent sport participation can be amplified and the deleterious effects of sport-injury are minimised[4].

Sport-related concussion (SRC) is of particular interest, due the potential long-term consequences of neurological injury sustained during adolescence. SRC is a traumatic brain injury caused by force transmission to the brain following contact to the head or body[5]. Adolescents are at an increased risk for SRC and may be especially vulnerable to neurological consequences due to ongoing growth and development[6]. SRC is also known as a functional injury as it does not present on standard medical imaging as one sees with structural injuries. Instead SRC is associated with a wide and varied clinical symptomology, and functional limitations including reduced exercise tolerance[5].

While many adolescents return to sport by four weeks, approximately 30% may take many months to recover following SRC[7]. Early return to physical activity (such as with exercise prescription) has been identified as a key contributing factor to recovery following SRC. Those who engage in an early return to physical activity demonstrate shorter recovery time by ≥4 weeks compared to those who do not[8]. Thus, the former recommendation of complete cognitive and physical rest following SRC (*"Rest is Best"*) has been replaced with recommendations of a graduated return to work, school and/or activity even while symptomatic[5]. Physical activity following concussion is often prescribed by healthcare practitioners in the form of exercise. The intensity of this exercise is often set as a heart rate (HR) threshold determined using clinical graduated exertion testing. These exertion tests consist of an incremental ramp protocol with increasing exercise intensity, performed on either on a treadmill[9], cycle ergometer[10, 11] or arm ergometer for adapted athletes or athletes with concurrent lower limb injuries[12]. These tests assess HR threshold at which the overall condition (OC; concussion-related symptoms on a scale of 0-10) increase by 3 or more from baseline. Moreover, these tests are able to evaluate exercise tolerance. If the participant achieves volitional fatigue, defined as 180bpm HR (90% of age-predicted maximal HR) or 18 on the Borg 6-20 rating of perceived exertion (RPE) scale before seeing a 3 or more point increase in concussion-like symptoms, they are considered tolerant to exercise. If a 3-point symptom increase occurs before volitional fatigue, the participants is considered exercise intolerant. Between 30 and 50% of adolescents have been shown to be intolerant to exercise acutely following SRC[13, 14]. Exercise intolerance is associated with higher levels of clinical symptoms. Furthermore, there is mixed evidence across studies. One study demonstrated those who were exercise intolerant had longer (45.6 days) time to return to sport than those who were exercise tolerant (10.0 days) for males and females[13]. Another demonstrated exercise intolerant females had a longer recovery time than exercise tolerant females; a finding not observed in males[14]. Another study found no relationship between exercise intolerance and risk of prolonged recovery following SRC[15].

In the broader literature, there is also mixed evidence regarding the association between sex and time to return to sport following SRC, with some studies reporting that females take longer to return to sport and other studies finding no sex differences[16]. Furthermore, there is evidence that female adolescents report higher symptom severity at baseline and following SRC, which likely encapsulates both gendered (sociological) differences in reporting behaviours and sex (biological) differences in disease progression[17]. Thus, it has proved problematic to determine if SRC sustained by females tends to be more severe, or if females are more forthcoming with symptoms, leading to increased SSS scores and delays in medical clearance to return to sport. Moreover, symptom presentation following SRC is heterogeneous, and SSS can be elevated even in those who are exercise tolerant, suggesting that SSS and exercise intolerance are independent, rather than reflective of overlapping self-reported measurement techniques. A previous study reported that females are at 59% higher risk of exercise intolerance, based on a bivariate analysis[14]. This association was significantly attenuated following adjustment for initial post-injury Sport Concussion Assessment Tool 5 (SCAT5) symptom severity scores (SSS)[14]. Such adjustment implies that SSS is independently associated with sex and risk of exercise intolerance. While many studies adjust for symptom severity when assessing sex differences in certain injury presentations, it is unclear if the association between sex and exercise intolerance is confounded, moderated, or mediated by SSS. Moderation implies that a differential effect of sex on risk of exercise intolerance, depending on SSS. Moreover, it may be the case that elevated SSS, resulting from sex differences in injury presentation, may explain downstream differences in exercise intolerance. The purpose of this study was to use data collected for a previous study[14] to evaluate if the association between sex and risk of exercise intolerance was moderated or mediated by symptom severity. It was hypothesised that the relationship between sex and exercise intolerance would not depend on SSS but would be mediated by SSS.

2. METHODS

Participants were recruited in alignment with the broader Surveillance in High school to Reduce Concussions (SHRed Concussions) Longitudinal cohort study. The SHRed cohort recruited adolescent athletes in high risk for concussion sports at baseline and followed them prospectively using injury surveillance methods[18]. This study received approval from institutional ethics review board (CHREB: REB18-2107). Participants' guardians provided informed consent and participants provided informed assent. Participants older than 14 years of age were able to provide 'mature minor' consent to participate. Participants reported biological sex and gender pre-injury during baseline testing. In the event of a suspected SRC, participants were assessed by a study physician. Upon diagnosis of SRC, participants completed a multimodal testing battery performed at the sport injury prevention research centre (SIPRC) at the University of Calgary, including a Buffalo Concussion Treadmill Test (BCTT)[9]. Participants returned for weekly assessments until they were cleared to return to sport (RTS) by a sports medicine physician. Participants were included in the study if they had completed a BCTT within 14 days of SRC.

A clinical exercise physiologist administered the BCTT on a SportsArt T635M Treadmill (SportsArt, Mukilteo, Washington). Participants were required to have a resting HR<100 bpm, a blood pressure (BP) <160/90mmHg, and an OC <6 on the wong-baker faces pain 0-10 scale[19] to be cleared for exercise testing. Participants who were too symptomatic during their initial visit, were eligible to complete a BCTT during the weekly follow up appointments. The BCTT started with 1 minute of walking on the treadmill at 3.2 miles per hour (mph) at 0% incline. Each minute the incline increased by 1% until a maximum 15% (reached in 15 minutes) was reached, after which the treadmill increased in speed by 0.2 mph per minute while maintaining the 15% incline. Each minute, the participants recorded their OC and RPE on a visual scale, and HR was recorded using a polar H10 heart rate strap (Polar Electro Oy, Kempele, Finland). The BCTT was terminated if participants experienced an increase of 3 or more (/10 on visual analogue scale) of concussion symptoms or reached volitional fatigue (>180bpm; approximately 90% of age-predicted HR_{max}), >18/20 rating of perceived exertion). Participants were encouraged to complete the test until a termination threshold was met. While participants were permitted to stop the test at any time, no participants in the present study stopped the test for reasons other than volitional fatigue or exercise intolerance. Participants were categorised as exercise tolerant if they achieved volitional fatigue, and exercise intolerant if the test was terminated due to an increase in OC. Following the initial visit, participants were followed prospectively until medical clearance to return to sport.

2.1 Analysis

All analysis were completed using Stata 19 (Stata Corp, USA). Participant characteristics were stratified by sex and compared using two-tailed between groups t-test. Bivariate associations between covariates and exercise tolerance status have been reported elsewhere, and the relative risk (RR) of exercise intolerance between females and males was reproduced, adjusted for age and time to BCTT[14]. Subsequently, RRs of exercise intolerance following SRC were estimated using generalised linear models with binomial family and long link including sex, pre-BCTT SSS, age and time between SRC and BCTT. SSS was square-root transformed prior to modelling to improve distributional characteristics Moderation of sex effects by SSS was evaluated by comparing models with an without a sex-by-SSS interaction term using likelihood ratio testing. Mediation by SSS was evaluated using the parametric g formula adapted from the work by Valeri and Vanderweele[20]. The mediator model was specified using a Gaussian identity-link model for transformed SSS conditional on sex, age, and time to BCTT, while the outcome model used a binomial log-link model conditional on sex, transformed SSS, age, and time to BCTT. Sex, age, and time to BCTT were included as covariates due to previous evidence suggesting these may influence risk of exercise intolerance[13, 21]. Natural direct, natural indirect, and total effects were defined using the counterfactual framework of[22] and estimated by g-computation: predicted outcomes under each exposure–mediator counterfactual scenario were averaged over the observed covariate distribution. Bias-corrected bootstrap confidence intervals were obtained using 5000 replications. The analysis was performed on the log-scale and only back-transformed after obtaining the means and CI's for convenience of interpretation. Analyses assumed no unmeasured exposure–outcome, exposure–mediator, or mediator–outcome confounding, correct model specification, and no exposure-induced mediator–outcome confounding. Analyses were conducted using complete cases. Data is presented as means and 95% Confidence Intervals (95% CI) unless otherwise specified.

3. RESULTS

In total, 347 participants were eligible to be recruited for the primary cohort study following a physician diagnosis of SRC. There were 25 participants who did not complete testing due to being too symptomatic (n=21) or other reasons (n=4) including not having appropriate footwear or having a concurrent musculoskeletal injury at time of testing. Of the remainder, 41 participants completed the BCTT >14 days following SRC and were excluded (14). A final sample included 281 adolescents (126 male, 155 female) that were either exercise tolerant (204; 100 male, 104 female) or exercise intolerant (77; 26 male, 51 female) completed the BCTT within 14 days of SRC (median: 5 days). All included participants in the final sample were cisgendered. The most common sports in the sample were rugby (n=98), football (n=46), ringette (n=36) and soccer (n=25). Participant demographics stratified by sex are reported in Table 1.

TABLE 1. Mean and 95% CIs demographics stratified by participant sex

	Male (n=126)	Female (n=155)	
	Mean (95% CI)	Mean (95% CI)	*p* value
Age (years)	16.05 (15.81, 16.29)	15.76 (15.50, 16.02)	0.115
Height (cm)	**177.05 (175.37, 178.73)**	**165.25 (163.98,166.51)**	**<0.001**
Mass (Kg)	**72.62 (69.79, 75.45)**	**60.30 (58.33, 62.27)**	**<0.001**
BMI (Kg/m^2)	**23.08 (22.37, 23.79)**	**21.90 (21.32, 22.48)**	**0.011**
SCAT5 SSS (/132)	**20.84 (17.50, 24.18)**	**26.76 (23.49, 30.04)**	**0.014**
Pre-test OC (1-10)	**1.57 (1.31, 1.83)**	**2.09 (1.83, 2.35)**	**0.006**
Time to BCTT (days)	4.63 (4.12, 5.14)	4.61 (4.15, 5.08)	0.968
BCTT Duration (minutes)	**14.29 (13.57, 15.02)**	**11.35 (10.74, 11.96)**	**<0.001**

NOTE: Body Mass Index (BMI), Sport Concussion Assessment Tool 5 (SCAT5) Symptom Severity Score (SSS), Overall Condition (OC), Buffalo Concussion Treadmill Test (BCTT).

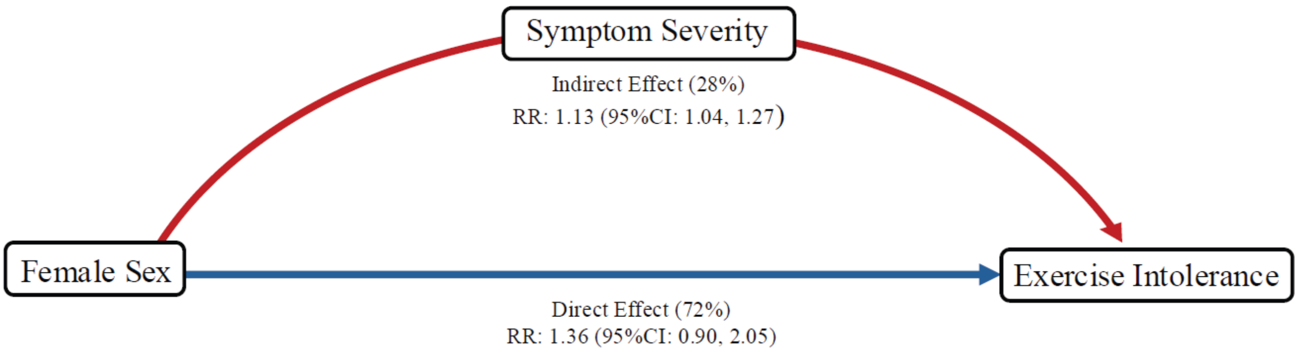

FIGURE 1. Direct and indirect effects of female sex on the risk of exercise intolerance, including Risk Ratios (RR) with male sex as the reference level.

A multivariable model, including adjustment for time to BCTT and age, but not SSS demonstrated a 57% higher risk of exercise intolerance in female participants (RR=1.57, 95% CI: 1.04, 2.37)[21]. The multivariable model including sex and SSS indicated a non-significant effect of sex (RR=1.36; 95% CI: 0.90, 2.05) and a significant effect of SSS (RR=1.16; 95% CI: 1.06, 1.27). Moderation as evaluated by the likelihood ratio test and was not significant ($^{2}_{(1)}$=1.50, p=0.22) with an estimated mean difference in the SSS-exercise tolerance relationship of 0.89 (95% CI: 0.76, 1.05) between females and males. The mediation analysis showed significant indirect effects of sex through SSS (RR=1.13; 95% CI: 1.04, 1.27) which account for 28% of the estimated total effects (RR=1.57; 95% CI: 0.99, 2.42) while direct effects were not significant (RR=1.36; 95% CI: 0.90, 2.05) despite explaining a larger proportion of total effects (72%).

4. DISCUSSION

The present study investigated whether symptom differences between males and females mediated sex differences in the risk of exercise intolerance. We observed that 28% of the estimated potential total effects of sex on risk of exercise intolerance was mediated by SSS, while direct effects accounted for 72% of the total estimated effect, based on a point-estimate, suggesting an imprecisely specified direct pathway, with other mediating factors which were not captured in the present study.

Debate is ongoing regarding increased susceptibility to SRC in female adolescents compared to males. Evidence for this includes higher rates of SRC for females in sports such as rugby[23], basketball and soccer[24], and similar rates of SRC in female hockey in non-body-checking leagues compared to male hockey leagues which permit body checking (24). Moreover, a recent systematic review reported that while many studies report longer recovery in females compared to males, a similar number of studies find no sex difference in recovery duration with age-adjusted meta-analysis demonstrating no significant recovery time differences between sexes[16]. However, evidence suggests female adolescents are at greater risk of developing persisting symptoms after concussion (PSaC; symptoms which are present for longer than one-month post injury) compared to adolescent males[7]. Moreover, studies also indicate that females experience higher total symptom severity following SRC compared to males[17]. Given reported sex differences in concussion susceptibility, recovery, and severity, the need for research to investigate the underlying modifiable factors is clear. Investigation of these differences supports the development of precision treatments and prevention efforts for female adolescent SRC[25, 26].

Sex is often a surrogate measure which represents an unmeasured underlying biological, androgenic, biomechanical, anatomical and/or psychosocial mechanism(s). Moreover, while sex is not a modifiable risk factor, the mediators of the reported sex differences in SRC outcomes may be. Thus, investigation of mediating factors of sex differences following SRC, including the risk of certain symptomatic presentations such as exercise intolerance, may provide more clinically actionable conclusions. Given the association between exercise intolerance and longer recovery following SRC[13, 14], it is important to understand which pathways may be clinically targeted to improve recovery in female adolescents. Moreover, when studies do not investigate mediating factors, they may perform statistical adjustment(s) for covariates that are mediating rather than confounding an association. In the analysis previously reported[14], risk of exercise intolerance was not different between sexes following adjustment for SSS, with point-estimates suggesting a 36% greater risk in females[14]. Conversely, risk of exercise intolerance was 57% higher in females compared to males when not adjusted by SSS, suggesting statistical confounding by SSS. However, as we have demonstrated in the current study, a significant indirect effect of sex on risk of exercise intolerance is present, and importantly is mediated by SSS. Thus, the interpretation of the previous analysis is potentially influenced by the statistical adjustment, especially given potential gender influence associated with symptom reporting differences between sexes. Caution should be taken, however in forgoing adjustment for SSS all together until a more definitive causal structure is established. Post-injury symptomology, therefore, may be more meaningfully treated as a concussion outcome rather than a confounding factor requiring adjustment in statistical analyses. Statistically controlling for sex differences in SSS may disguise differences between males and females in other concussion outcomes, especially if symptom severity mediates the relationship such as shown in the present study (Figure 1).

Furthermore, SSS captures multiple elements of the SRC severity and recovery. While elevated symptoms in female adolescents may be representative of a more 'severe' injury, reported symptoms encompass sociocultural factors as well. Herein lies a challenge in interpreting subjective symptom reporting. The underlying symptoms are related to the objective pathophysiology of the ongoing injury, yet the reporting of the clinical symptoms is filtered by an individual's attitudes and experiences. As such, it is quite possible gendered norms are one of many factors that could influence symptom reporting following concussion as well as during exertion testing. A systematic review investigated sex differences in symptom reporting at baseline and following concussion. It was found that females were 42% more likely to report baseline symptoms compared to males[17]. Following concussion, total number of symptoms reported were higher in females compared to males regardless of age or symptom scale used[25]. Taken together, it appears that a difference in concussion symptom reporting exists between males and females, and is even independent of the presence of concussion.

Exercise intolerance is also identified by change in self-reported OC. Thus, it is plausible that the observed sex increase in SSS is related to symptom reporting behaviours, which manifest in increased OC reporting as well, leading to a higher likelihood of being classified as exercise intolerant. Moreover, pre-injury anxiety is more common in female youth, and is associated with increases symptoms and risk of exercise intolerance following SRC[27]. However, these factors relate predominantly to 28% of the total effect which is mediated by SSS. Moreover, indirect effects reported in the present study likely account for a combination of the gendered reporting differences and the underlying pathophysiological sex-differences which combine to increase reported SSS and risk of exercise intolerance. Investigation of potential mechanisms that are not mediated by SSS (direct effects) are therefore of considerable interest, as these might be missed by studies which use SSS as a primary outcome or statistically adjust for differences in SSS. Future research is needed to address other indirect pathways which might mediate sex differences in the risk of exercise intolerance following SRC in adolescents.

The direct effects reported in the present study may be partially explained by differences in the physiological response to SRC and exercise responses between males and females. Disruptions to Cerebral Blood Flow (CBF) regulation as well as autonomic nervous system (ANS) function have been reported as plausible mechanisms underpinning exercise intolerance following SRC[28]. Evidence suggests sex differences in ANS function relate to differences in SSS, whereas impairments in CBF regulatory mechanisms (e.g. dynamic cerebral autoregulation [dCA], cerebrovascular reactivity [CVR], neurovascular coupling) can be present beyond clinical symptom resolution following SRC[28]. Moreover, CBF increases during exercise due to a multitude of changes including, increases in neural activity, augmented BP, regulation by the ANS, altered arterial carbon dioxide levels, and elevated cardiac output[29]. Additionally it has been shown, post-pubescent female adolescents exhibit higher CBF at rest and during exercise compared to their male counterparts, due to differences in cerebrovascular structure, maturation, hormonal influences and function[30]. Another consideration is ANS function, which is impaired following SRC and also assists in regulating the adaptive cerebrovascular responses to internal and external stimuli, including the influence of exercise[31]. Inadequate dynamic buffering of exercise-induced changes in BP by the cerebrovasculature, termed dCA, might permit higher cerebral profusion during exercise following SRC, potentially exacerbating symptoms when exercising following concussion[32]. Although not directly measured in the current investigation, this is plausible since there is evidence dCA is impaired following SRC[28, 33] and females exhibit greater dCA responses than males when uninjured[34, 35]. Conversely, changes in the arterial concentration of carbon dioxide are also known to induce potent vasoconstrictive (during hypocapnia) and vasodilatory (during hypercapnia) responses[36, 37], termed CVR. Female sex is associated with an increased CVR response compared to males[38]. It has been suggested that blunted CVR during exercise might explain exercise intolerance following SRC[28, 39]. This is supported by evidence that those with greater CVR also displayed greater tolerance for exercise following concussion[40]. Furthermore, evidence in a sample of female patients with PSaC demonstrated a blunted ventilatory responses to exercise-induced increases in arterial carbon dioxide, perhaps operating in concert with altered CVR which resulted in increased symptoms, and reduced exercise tolerance[41]. Thus, healthy females appear to have higher CBF levels and importantly more tightly regulated CBF, perhaps reducing tolerance to cerebrovascular dysfunction which occurs following SRC, and therefore increasing vulnerability to exercise-induced increases in CBF[28]. The extent to which cerebrovascular and ANS differences between male and female adolescents, which were not measured in the present study, contribute to the risk of exercise intolerance and whether these contributions are captured by differences in symptomology remains unclear and should be a priority area of future investigations. Future research is therefore required to better understand sex differences with respect to the underlying mechanisms associated with the pathophysiology of concussion as they relate to sex, exercise intolerance and recovery trajectories following SRC.

As highlighted above, there are many plausible, albeit not yet fully explored mechanisms that might further explain the difference in exercise tolerance between males and females following SRC, beyond the 28% mediated by SSS. Thus, there is a pressing need for future work to investigate the cerebrovascular, autonomic and psychological factors which likely contribute to the difference in risk of exercise intolerance which is not explained by differences in concussion symptoms. Mediation analysis is an informative and underutilised approach in SRC research, which should be leveraged in future research to identify underlying modifiable clinical targets to inform individualised treatment approaches[42].

4.1 Limitations

Participants who reported 6 or greater OC were excluded from completing the BCTT. While this was imperative to ensure participant safety, it may have biased the sample towards less symptomatic individuals. There is no practical and safe way to test exercise tolerance in those who are highly symptomatic, as eliciting even a mild symptom provocation would lead to an untenable overall symptom score. Nevertheless, the sample in the present study does not represent those who report an OC of 6 or more. Moreover, tendencies in self-reporting symptoms could have influenced both SSS and the risk of being classified as exercise intolerance. The present study cannot in principle distinguish differences in symptom experience, perception and reporting, which may have influenced the results. Other potential factors such as pre-injury symptom burden, menstrual cycle phase, psychological conditions, and activity level were not collected, and thus could not be considered despite potentially influencing results. Furthermore, as a secondary data analysis from another study, this study was not designed with an a priori power and sample size analysis and may not be adequately powered to fully parameterize the natural direct (and total) effects. However, instead of treating these results as definitive and final answers to a specific research question, we hope that these can be viewed as hypothesis-generating and provide some justification for future larger studies.

5. CONCLUSION

Sex differences with respect to the risk of exercise intolerance following SRC appear to operate through SSS rather than a direct pathway. The direct effects of sex, although proportionately larger, do not significantly directly influence risk of exercise intolerance, suggesting other unmeasured pathways affecting the differential risk for exercise intolerance in females post-concussion. Future studies assessing sex or gender differences in injury presentation in adolescents following SRC should consider whether adjustment for symptom severity biases the sex or gender comparisons towards the null, by treating a mediator of the relationship as a confounder. Furthermore, future research is warranted investigating the underlying mechanisms which may mediate sex differences in the risk of exercise intolerance, and recovery following SRC broadly.

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