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Dear Professor Barrett,

Please find attached our reply (JP-RL-2019-279085) to the letter written by Denadai & Greco (JP-LE-2019-279016) in regard to our manuscript entitled "*Sex differences in fatigability and recovery relative to the intensity-duration relationship*"; which we would like to submitted for review and editorial checking.

We appreciate the chance to respond to the points raised by Denadai & Greco and confirm that our initial conclusions remain valid. However, if you believe our original submission should be altered, I would be happy to discuss this further.

We hope that you find our response satisfactory and would like thank you for taking the time to handle our manuscript.

Yours faithfully,



**Dr Stuart Goodall**

**Reply to JP-LE-2019-279016 from Paul Ansdell, Callum Brownstein, Jakob Skarabot, Kirsty Hicks, Glyn Howatson, Kevin Thomas, Sandra Hunter and Stuart Goodall**

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We express thanks to Denadai & Greco (2019) for their comments regarding our recent study identifying sex differences in fatigability during, and recovery following exercise normalised to the intermittent, isometric critical intensity (CI). The authors identified that the CI we calculated was lower than expected. The linear regression between force impulse and *time*, originally performed by Burnley (2009), used the total contraction time for the time to task failure to calculate CI, rather than the total time (i.e. including rest periods between contractions). In our original calculations we used the latter, which, as described by Denadai & Greco (2019), led to a lower estimation of CI, and a consequent error in predicting exercise intensities that were intended to be above and below the CI. However, as we outline in this letter, our conclusions that 1) females demonstrate a greater relative CI, and 2) females demonstrate greater fatigue resistance when exercise is normalised to the intensity-duration relationship are still valid, and our experimental approach has allowed us to study the sex differences in fatigability in two distinct exercise domains relative to the intensity-duration relationship, which was the primary purpose of the experiment.

***Conclusion 1: Females demonstrate a greater relative critical intensity.***

Our original findings demonstrated a sex difference in the relative CI ( $24.7 \pm 2.5$  vs.  $20.8 \pm 2.3\%$  MVC,  $P = 0.003$ ), and showed that females are able to maintain a greater relative exercise intensity compared to males. When these data were re-analysed excluding rest periods, the estimated CI increases, and females still exhibit a higher relative value compared with males. Indeed, the recalculated absolute values are greater in males compared to females ( $264 \pm 31$  vs.  $205 \pm 38$  N,  $P = 0.001$ ), but when these data are expressed relative to maximal strength, the female values are greater ( $42.4 \pm 4.5$  vs.  $34.9 \pm 3.9\%$  MVC,  $P = 0.003$ ; Figure 1). Therefore, our original conclusion that females are able to maintain a greater relative exercise intensity for an intermittent isometric contraction task, remain valid.

**\*\*FIGURE 1 HERE\*\***

***Conclusion 2: Females demonstrate greater fatigue resistance when exercise is normalised to the intensity-duration relationship.***

Given that our original calculation of CI led to a lower estimation of the maximal sustainable exercise intensity, the interpretation of subsequent exercise trials that were dependent on this threshold were affected. Originally, we normalised intensities to +10% and -10% of the calculated CI, intending that the +10% trial would result in an unsustainable exercise intensity, whilst the -10% trial would permit a metabolic steady-state. As a result of the lower CI, both +10% and -10% in the original paper were

below the re-calculated CI (-12 and -20%, respectively). Whilst the +10% trial was not in the intended 'severe' intensity domain, it did induce an unsustainable work rate, evidenced by progressive declines in MVC, potentiated twitch amplitude ( $Q_{tw,pot}$ ), and  $VA_{MNS}$ , along with an increase in EMG activity (rmsEMG) (Figure 2). Considering these responses, and the exercise time of this trial (~30 mins in the male group), it is likely that participants were exercising in the heavy exercise domain (Brickley et al. 2002; Thomas et al. 2016). In contrast, the neuromuscular responses to the -10% trial indicate a sustainable exercise intensity consistent with moderate domain exercise, with indices of neuromuscular function reaching a far smaller nadir in comparison (Figure 2). Thus, our data demonstrate that females are more fatigue-resistant during distinct, metabolically matched exercise at sustainable and unsustainable intensities in the heavy and moderate exercise domains.

**\*\*FIGURE 2 HERE\*\***

One additional consideration that Denadai and Greco (2019) raised was the pattern of neuromuscular fatigue differed between our data and those of Burnley et al. (2012). Specifically, the decline in voluntary activation was lower in our original data set. However, when our data are considered in the context of the re-calculated CI (Table 1), the decline in neuromuscular function exhibited in the original "-10%" trial is similar to the CT-20% trial in Burnley et al. (2012). Another similarity between our data and that of Burnley et al. (2012) is both demonstrate that below CI, neuromuscular function does indeed progressively decline, with both central and peripheral contributing factors. However, this decline occurs at a slower rate than exercise performed above CI, indicating that task failure occurs below CI; a notion supported by data presented in Ansdell et al. (2019).

**\*\*TABLE 1 HERE\*\***

One method to assess fatigability in the 'severe' intensity domain from the present study is to consider the data collected during the estimation trials when determining CI. By sex-matching the percentage of CI *post-hoc*, we can identify trials at which males (n=8) and females (n=5) were exercising at ~160% of CI displayed in Figure 1 of this letter. Using this approach, it is clear that when exercise is metabolically matched above CI in the severe domain, females remain more fatigue resistant than males; not only was the time to task failure longer, the rate of decline in  $Q_{tw,pot}$  was lower (Table 2).

**\*\*TABLE 2 HERE\*\***

To summarise, our data demonstrate that females are able to maintain a greater relative intensity of exercise than males, and demonstrate a greater fatigue resistance during metabolically-matched exercise in heavy and moderate exercise domains. We acknowledge the points raised by Denadai & Greco (2019), however, the original conclusions presented in Ansdell et al. (2019) remain valid and provide mechanistic insight into the sex difference of fatigability during intermittent exercise performed with the knee extensors.

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### Table & Figure Legends

**Table 1.** A comparison of the rate of change ( $\Delta\text{value}/\Delta\text{time}$ ) for indices of neuromuscular function from pre-post equivalent fatiguing tasks in the male group from Ansdell et al. (2019) and all participants from Burnley et al. (2012).

**Table 2.** Sex-matched data demonstrating a sex difference in fatigability at 160% of critical intensity.

**Figure 1.** Critical intensities for males and females, re-calculated according to Burnley et al. (2009).

**Figure 2.** The decline in neuromuscular function for males in the +10% trial (filled circles) and the -10% trial (unfilled circles). Panel A: maximum voluntary contraction, Panel B: Potentiated twitch force; Panel C: Voluntary activation; Panel D: root-mean-squared electromyographical activity. \* = different from baseline ( $P < 0.05$ ).

Table 1. A comparison of the rate of change ( $\Delta\text{value}/\Delta\text{time}$ ) for indices of neuromuscular function from pre-post equivalent fatiguing tasks in the male group from Ansdell et al. (2019) and all participants from Burnley et al. (2012).

	Ansdell et al. (2019)		Burnley et al. (2012)	
	"+10"	"-10%"	Severe 1	CT-10%
Time to task failure (min)	30.4	45.0	17.6	57.1
$\Delta\text{MVC}/\Delta\text{time}$ ( $\% \cdot \text{min}^{-1}$ )	-2.1	-0.2*	-3.2	-0.6
$\Delta\text{Q}_{\text{tw.pot}}/\Delta\text{time}$ ( $\% \cdot \text{min}^{-1}$ )	-1.8	-0.6**	-2.2	-0.5
$\Delta\text{VA}/\Delta\text{time}$ ( $\% \cdot \text{min}^{-1}$ )	-1.5	-0.1*	-4	-0.4
$\Delta\text{EMG}/\Delta\text{time}$ ( $\% \cdot \text{min}^{-1}$ )	+2.8	+0.3**	+2.2	+0.5

\* = significantly lower rate than unsustainable ( $P < 0.05$ ); \*\* = significantly lower rate than unsustainable ( $P < 0.001$ )

Table 1. Sex-matched data demonstrating a sex difference in fatigability at 160% of critical intensity.

Post-hoc matched severe trials							
% critical intensity		TTF (s)		Q <sub>tw.pot</sub> change (%)		Rate of change (%·min <sup>-1</sup> )	
Male	Female	Male	Female	Male	Female	Male	Female
158 ± 4	159 ± 2	328 ± 142	624 ± 255	-47 ± 17	-31 ± 5	-9 ± 4	-3 ± 1
P value:		0.732	<b>0.020</b>	0.066		<b>0.009</b>	

TTF: time to task failure; Q<sub>tw.pot</sub> = potentiated quadriceps twitch



