Response to comment on: "The Effects of Menstrual Cycle Phase on Exercise Performance in Eumenorrheic Women: A Systematic Review and Meta-Analysis" and "The Effects of Oral Contraceptives on Exercise Performance in Women: A Systematic Review and Meta-analysis"

Kirsty J. Elliott-Sale[1], Kelly L. McNulty[2], Stuart Goodall[2], Paul Ansdell[2], Kevin Thomas[2], Paul A. Swinton[3], Eimear Dolan[4], Kirsty M. Hicks[2]

[1]Sport Health and Performance Enhancement (SHAPE) Research Centre, Department of Sport Science, Nottingham Trent University, Nottingham, UK.

[2]Department of Sport, Exercise & Rehabilitation, Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK.

[3]School of Health Sciences, Robert Gordon University, Aberdeen, UK.

[4]Applied Physiology and Nutrition Research Group, Escola de Educação Física e Esporte, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil.

Corresponding author: Dr Kirsty Elliott-Sale, Email: kirsty.elliottsale@ntu.ac.uk

Kirsty Jayne Elliott-Sale	ORCID ID: 0000-0003-1122-5099
Kelly Lee McNulty	ORCID ID: 0000-0001-6176-7983
Stuart Goodall	ORCID ID: 0000-0001-9029-2171
Paul Ansdell	ORCID ID 0000-0001-7542-1107
Kevin Thomas	ORCID ID: 0000-0003-2973-5337
Paul Alan Swinton	ORCID ID 0000-0001-9663-0696
Eimear Dolan	ORCID ID 0000-0002-1018-7601

Kirsty Marie Hicks ORCID ID: 0000-0002-5057-9191

Dear Editor,

We thank Lei *et al*. for their interest in our studies [1, 2]. In their letter, Lei *et al*. questioned why certain studies [3-7] had not been included in our reviews. The reason for this is because our research question pertained to the effects of ovarian steroids on exercise performance in eumenorrheic women [1] and oral contraceptive users [2] and was not intended to look at these relationships in response to ambient heat stress or other conditions. In this response, we will clarify the search and selection strategy of our reviews in order to address the misunderstanding between ourselves and Lei *et al*.

(i) Our search strategies reflected our research question and although the studies [3-7] listed by Lei *et al*. in their letter were not included, these omissions do not reflect an incomplete search in the context of our research aims. We admit that no search is entirely exhaustive, however, we respectfully disagree with Lei *et al.* that we have overlooked their studies [3-7], rather, they were outside of the scope of our reviews [1, 2]. As such, we stand by our search strategies which were aligned with our research questions and intended outcomes and were constructed according to Cochrane Library guidelines.

(ii) As identified by Lei *et al.* we included two studies [8,9] in our menstrual cycle review [1] that investigated the influence of menstrual cycle phase on exercise under thermally stressed conditions, but not others [3-7]. It is important to clarify, however, that only the thermoneutral data were extracted from these studies, in agreement with our research question. These studies were included as they were identified through our research specific, pre-defined search strategy, and were not specifically sought by using search terms related to thermoregulation (for a full list of search terms see section 2.2 [1]), and were deemed eligible based on our inclusion criteria, namely: (i) no specific interventions (*e.g.*, dry/humid heat) were investigated; and (ii) only studies that had the primary or secondary objective of assessing changes in exercise performance across the menstrual cycle were included (*e.g.*, not exercise performance during the menstrual cycle under different conditions of temperature). In contrast, the studies listed by Lei *et al.* were either (i) not identified using our

research specific, *a priori* search terms [7]; (ii) not indexed in the databases we searched [4]; or (iii) not deemed eligible based on our inclusion criteria [3, 5, 6]. As such, we believe that the scope of our review precluded the studies listed by Lei *et al*. In terms of future work, we agree that a more explicit list of eligibility criteria and/or some exemplars of certain criteria would be beneficial and help to avoid misinterpretation between authors and their audience. We note that Lei *et al*. are active researchers in the field of thermoregulation, and believe their work is more suited to a specific meta-analysis investigating the effects of menstrual cycle phase on exercise performance in eumenorrheic women and oral contraceptive users in response to ambient heat stress or as part of a wider review on the effects of menstrual cycle phase on performance in response to different environmental conditions.

With regards to the quality assessment used in the menstrual cycle paper; we cited two studies [10, 11] to underpin the inclusion of urinary ovulation detection kits in our approach. The purpose of urinary ovulation detection kits is to confirm ovulation, which is only part of the criteria to establish eumenorrhea. Eumenorrhea is a multifaceted term that reflects several concurrent requirements namely: menstrual cycle lengths between 21 and 35 days resulting in nine or more consecutive periods per year; evidence of the mid-cycle luteinising hormone surge; the correct hormonal profile (see Fig 1, [1]); and no hormonal contraceptive use in the three months prior to recruitment. As such, we believe that it is appropriate to downgrade an assessment of research quality of studies with serum hormone analysis, but without urinary ovulation detection kits. If we consider studies comparing the follicular (*i.e.*, low oestrogen and progesterone) with the luteal (*i.e.*, higher oestrogen and progesterone) phase, blood samples will have been drawn at these two timepoints and might show that ovarian steroid concentrations are within the correct ranges for these phases. However, this design would not confirm that ovulation has taken place, which is a key indicator of eumenorrhea, as the mid-luteal rise in oestrogen and progesterone can occur in the absence of ovulation [12]. Moreover, the phase "ranges" for serum oestrogen and progesterone are broad and overlapping; for example, the follicular, ovulatory and luteal phases are characterised by oestradiol concentrations of 72-529, 205-786 and 235-1309 $pmol \cdot L^{-1}$. As such, urinary ovulation detection kits provide additional context for interpreting hormonal data. Lastly, it is important to note that urinary ovulation detection kits are prospective (*i.e.*, are used to predict phases), whilst blood samples are retrospective (*i.e.*, used to confirm phases). Indeed, Janse de Jonge *et al.* [11] recommended that a combination of methods is used to verify menstrual cycle phase, namely calendar-based counting, urinary ovulation detection kits and serum oestrogen and progesterone

concentrations. Collectively, it is evident that urinary ovulation detection kits are an integral part of the research design of menstrual cycle studies.

We would like to clarify several points from the following statement made by Lei *et al.* based on the paper by Janse de Jonge *et al*. [11]:

> "The authors refer to a previous study as their reference for this , yet up to 50% of (highly) physically active women may have luteal phase-deficient and/or anovulatory cycles that would provide a false-positive result with this methodological recommendation ".

Firstly, Janse de Jonge *et al*. [11] cite one paper [12] that showed that it is not uncommon for false positive results to occur when participants interpret urinary ovulation detection kits at home. Secondly, Janse de Jonge *et al*. [11] state that there is a high prevalence (30%) of anovulation and luteal phase deficiency in physically active women. Thirdly Janse de Jonge *et al*. [11] state that the prevalence of anovulatory and luteal phase deficiency can be as high as 50% in heavily exercising women. As such, contrary to the statement by Lei *et al*. above, we do not believe that Janse de Jonge *et al.* [11] were stating that anovulatory and/or luteal phase deficient cycles result in false-positive urinary ovulation detection kit results. Instead, we agree with Janse de Jonge *et al.* [11], when they conclude that urinary ovulation detection kits are useful for determining ovulation and the mid-luteal phase, but do not preclude luteal phase deficient cycles. We assert that this conclusion further highlights the need for blood sample verification alongside urinary ovulation detection kits.

Our reviews [1,2] were intended to address a specific research question and we fully acknowledge that all systematic reviews and meta-analyses are limited by their scope. There is need for further studies, and reviews, in sport and exercise science with women as participants. Furthermore, a universal set of standards are required to improve the quality of future studies in this area and to consistently and appropriately appraise the quality of existing studies.

Declarations

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Conflicts of Interest

Kirsty Elliott-Sale, Kirsty Hicks, Kelly McNulty, Paul Ansdell, Stuart Goodall, Kevin Thomas, Paul Swinton and Eimear Dolan declare that they have no potential conflicts of interest relevant to the content of this letter.

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