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# Sex-based comparison of the blood pressure, haemodynamic and cardiac autonomic adaptations following isometric exercise training in sedentary adults: a randomised controlled trial

Harry Swift [1,2] Damian Coleman [2] Charles Pedlar [1,3] Neil Andrew Smart [4] Chris Farmer [5] Jonathan Wiles [2]

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## ABSTRACT

**Objectives** We aimed to explore sex-specific differences in resting blood pressure (BP) reduction and associated cardiovascular adaptations following isometric exercise training (IET).

**Methods** 100 sedentary adults with normal to high-normal systolic BP volunteered for the study. Participants either performed home-based lower-body IET in the form of a wall squat three times a week for 4 weeks (each session comprised 4×2 min bouts) or were allocated to the control group. Cardiovascular variables, including BP, cardiac output, total peripheral resistance, stroke volume and heart rate variability (HRV), were measured at rest preintervention and postintervention.

**Results** Following 4 weeks of IET, there were no significant differences in resting systolic BP and diastolic BP between females (122.1±6.9 and 80.0±8.3 mm Hg) and males (119.6±7.2 and 77.4±8.6 mm Hg). However, female participants had a greater cardiac autonomic response following training, evidenced by a lower low-frequency to high-frequency HRV ratio (F: 1.38±1.27 and M: 2.1±1.5, p=0.004) and decreased and elevated low-frequency normalised units (F: 50.3%±16.2% and M: 60.9%±16.9%, p=0.015) and high-frequency normalised units (F: 49.7%±16.2% and M: 39.1%±16.9%, p=0.015), respectively.

**Conclusions** While resting BP reductions were comparable between female and male participants, there was a greater autonomic response and a higher incidence of clinically important BP reductions in females, which could indicate a greater cardioprotective effect following IET. These findings highlight the importance of considering sex differences in the prescription and evaluation of exercise interventions for hypertension management.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Isometric exercise training (IET) has effectively reduced resting blood pressure (BP), often outperforming other exercise modalities like aerobic and dynamic resistance training. While prior meta-analyses suggest no consistent sex differences in resting BP responses to IET, limited studies with small sample sizes have resulted in conflicting findings regarding sex-specific physiological adaptations.

### WHAT THIS STUDY ADDS

⇒ This study is the largest primary investigation that directly compares sex-based resting BP reductions and physiological adaptations following IET, using a robust sample size and validated methodology. It demonstrates that while BP reductions were comparable between sexes, females showed a greater improvement in cardiac autonomic modulation, highlighting potential sex-specific mechanisms of cardiovascular adaptation.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings call for further exploration of sex-specific mechanisms in exercise prescription, particularly in the context of autonomic regulation and hormonal influences. Sex-specific tailoring of exercise protocols could optimise cardiovascular outcomes, potentially influencing guidelines for hypertension management.

## INTRODUCTION

Cardiovascular disease (CVD) accounts for approximately 32% of all global deaths annually.[1] Hypertension (HTN) is a primary risk factor for CVD, as it increases the rates of atherosclerosis and other vascular changes that compromise cardiovascular function.[2] Recent data have demonstrated that age-standardised rates of HTN are similar between females and males (32% and 34%, respectively).[3] Current 2023 European Society of Hypertension (ESH) guidelines recommend that females and males with suboptimal blood pressure (BP) and low cardiovascular risk engage in non-pharmaceutical lifestyle interventions such as daily physical activity.[4] Notwithstanding this, the guidelines mention





For numbered affiliations see end of article.

**Correspondence to**
Dr Jonathan Wiles;
jim.wiles@canterbury.ac.uk

that there may be differences in the magnitude of BP reduction between females and males when following the exercise recommendations presented. However, evidence for this statement is based on a single meta-analysis conducted over a decade ago that found a greater BP-lowering effect following exercise training in males following aerobic (AT) and dynamic resistance training (DRT),[5] and there remains a lack of research in this area.

Recent data suggest that BP reductions following isometric exercise training (IET) are greater than following AT or DRT.[6] However, the existence of sex-related differences in BP adaptation following IET has also been under-researched, with inconsistent interpretations of the findings to date. Following critical evaluation of the IET literature, pooled data from a meta-analysis by Inder *et al*[7] and an individual participant data meta-analysis by Smart *et al*[8] indicated no differences in the BP responses between males and females following IET. Conversely, a systematic review and narrative synthesis by Bentley *et al*[9] demonstrated a greater IET effect for BP reductions in females, highlighting a lack of consensus regarding sex-related differences.

A greater understanding of sex-related specificity in exercise prescription may help further enhance the implementation of IET as a therapeutic intervention in the management of BP. While there is growing evidence to support the efficacy of IET in reducing BP in females, any differences in the magnitude of BP reduction between females and males and the mechanistic pathways responsible for BP adaptation remain unclear. Therefore, this study aimed to engage female and male participants with an established IET protocol compared with control, then (1) explore any differences in the BP adaptations between female and male participants following IET and (2) investigate any differences in the associated physiological mechanisms between sexes.

## METHOD

### Participants

According to the ESH guidelines, participants with normal to high-normal systolic BP (sBP) (range 120–140 mm Hg) were recruited. A current physical activity level below the WHO recommendations of ≥150 min of moderate physical activity per week was also required for participation, which included low-level physical activity, such as walking, light cycling and general household activities.[10] Participants were free from injury or illness that may have affected the outcome variables of the study, were not taking any medication (or had a history of taking any anti-hypertensive medication), were non-smokers, consumed less than 14 units of alcohol per week and were not involved in purposeful exercise regimens. Screening was conducted using a standard Physical Activity Readiness Questionnaire, with an additional question added for females to assess whether they had regular menstruation, were taking oral contraception or were postmenopausal. At the time of testing, 12 female participants were taking hormonal contraception, 18 had regular menstruation and 6 were postmenopausal. For females with regular menstruation (approximately a 28-day cycle), laboratory data collection was timed around their self-reported early follicular phase (days 1–7 of their menstrual cycle).

### Study procedures

Recruitment was staggered on a rolling basis in batches of 10 to achieve the required sample size of 100 participants calculated using G*Power (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).[11] For a direct comparison of the primary outcome variable (sBP) between the sexes, based on an alpha level of 0.05, a power of 0.80, two groups (female and male) and one covariate (baseline BP values), a sample size of 80 participants (40:40) was able to detect a small-to-moderate effect (0.32 Cohen's d). For the first phase of the study comparing all 80 intervention participants (female and male) to a control group of 20 participants, the estimated power based on likely changes observed by Taylor *et al*[12] of 12 mm Hg sBP and 6 mm Hg diastolic BP (dBP) was in excess of 95% for both sBP and dBP.

Following screening, participants were randomly allocated (at a ratio of 4:1 within each batch) to either the IET intervention (n=80) or control (n=20). Randomisation was carried out by the lead researcher using the RAND function on Microsoft Excel. The study set out to recruit a 50:50 split of females and males. Thus, within each batch, four female and four male participants were allocated to the intervention group, and one female and one male were assigned to the control group. All intervention participants completed a 4-week home-based IET programme. Participants were asked to attend the laboratory on four separate occasions. The first visit was a familiarisation session where participants were exposed to the laboratory and exercise equipment. During the second visit, participants were asked to undertake an incremental IET test to determine their individualised knee joint angle used during training, as previously described.[13] As outlined below, the third and fourth visits recorded physiological data before and after the 4-week training period. Control participants were required to attend the laboratory twice for baseline and week-4 resting measures.

All participants were asked to maintain habitual dietary habits and daily routines throughout the study. Participants were asked to attend the laboratory at the same time (±2 hours), fast for 4 hours, and avoid caffeine and alcohol for 24 hours before testing. For the IET group, post-training measures were taken between 72–96 hours after the participant's final training session to avoid the influence of acute hypotension that may persist postexercise.

### Resting measures

All haemodynamic and cardiac autonomic variables were measured using a validated Task Force Monitor (TFM) (CNSystems, Medizintechnik, Graz, Austria).[14] All measurements were taken in a temperature-controlled room pre-IET and post-IET. To measure continuous BP, the TFM uses a vascular unloading technique at the proximal limb of the index or middle finger.[15] Continuous measurement of BP is then adjusted in accordance with oscillometric BP values from the brachial artery of the contralateral arm.[14] Heart rate (HR) was recorded using a six-channel ECG. Beat-to-beat stroke volume (SV) was measured with impedance cardiography via one electrode band applied to the nape of the neck and two placed on either side of the thorax, in line with the xiphisternum. Cardiac output ($\dot{Q}$) was then subsequently calculated as the product of HR and SV. Total peripheral resistance, a proxy for the resistance to blood flow caused by systemic vasculature, was measured according to Ohm's law as a function of mean arterial pressure (MAP) and $\dot{Q}$.

A six-channel ECG was used to measure R-R intervals, with the subsequent values used to calculate real-time HR variability (HRV) via an autoregressive model.[16] The ECG traces were manually screened to clear any erroneous data. High frequency (HF) (predominantly parasympathetic outflow) and low frequency (LF) (predominantly sympathetic outflow)[17] frequency parameters of HRV were automatically calculated by the TFM. These variables were expressed in absolute ($ms^2$) and normalised units (HFnu/LFnu). The sequence method automatically calculated baroreceptor reflex sensitivity (BRS) [18].

Resting haemodynamic and cardiac autonomic measures were measured at baseline and 4 weeks. Following 15 min of seated rest, haemodynamic and cardiac autonomic function were measured continuously in the seated position for 5 min. After this time, the mean for each variable was calculated offline for 5 min.

### IET intervention

The exercise training intervention consisted of an established lower-body IET programme[13] thrice weekly over 4 weeks, with 48 hours between sessions. Each training session comprised four bouts of IET exercise separated by 2 min of seated rest.[13] The training was performed at a participant-specific knee joint angle ascertained during an incremental IET test relative to 95% $HR_{peak}$ ($HR_{peak}$ relates to the mean HR evidenced during the final 30 s of the incremental test). Participants were required to record their HR during the last 30 s of each exercise bout using a wrist-mounted HR monitor and a Polar H10 chest strap (Polar Electro Oy, Kempele, Finland) and used to confirm adherence to training. If the HR data fell outside the target HR zone for more than two sessions, the knee angle was reduced or increased by 5° to ensure that the HR fell back within the correct range.

### Data analysis

Data were checked for normality assumptions. Where these were met, a one-way analysis of covariance (ANCOVA) was first carried out to explore the overall differences between all female and male participants (n=80) compared with a control group (n=20), with baseline measures as the covariate. Differences in each dependent variable (week-4 resting measures) between female (n=37) and male (n=43) participants were then explored using an ANCOVA with baseline measures as the covariate. Where data were not normally distributed, a Quade non-parametric test was used. An alpha level of <0.05 was set as the threshold for statistical significance.

### Patient and public involvement

Participants were not involved in the study design, conduct or dissemination of outcomes.

## RESULTS

113 participants were recruited to achieve a target sample size of 100 (table 1). The study experienced an 11.5% attrition rate, with 13 participants lost to follow-up. This included seven dropouts due to COVID-19-related reasons, three withdrawn participants for non-compliance with the protocol and three voluntarily withdrew. No adverse events were reported during the study. Of the 36 female participants allocated to the IET intervention, one missed a session (99.6% adherence). Two of the 44 male participants allocated to the IET intervention missed a single session each (99.8% adherence).

### Overall BP-lowering effect compared with control

Following the 4-week training period, resting sBP (M±SD) decreased (−9.45±6.69 mm Hg) and was significantly different to the control group (−0.79±3.97 mm Hg, p<0.001). Resting dBP reduced following IET (−5.62±9.92 mm Hg) and significantly differed from the control group (2.19±4.58 mm Hg, p=0.007). Reductions in MAP (−6.90±7.77 mm Hg) were also significantly different from the control group following IET (1.20±3.84 mm Hg, p<0.001) (figure 1).

**Table 1** Baseline characteristics of all participants used for analysis

| Variable | IET female (n=36) | IET male (n=44) | Control female (n=8) | Control male (n=12) |
|---|---|---|---|---|
| Age (years) | 39±12 | 36±12 | 33±5 | 32±6 |
| Height (cm) | 166±6 | 180±8 | 167±5 | 174±8 |
| Body mass (kg) | 72±9 | 88±13 | 64±7 | 74±12 |

Data are presented as mean±SD. Age, height and body mass were used for all intervention and control participants at baseline.
IET, isometric exercise training.

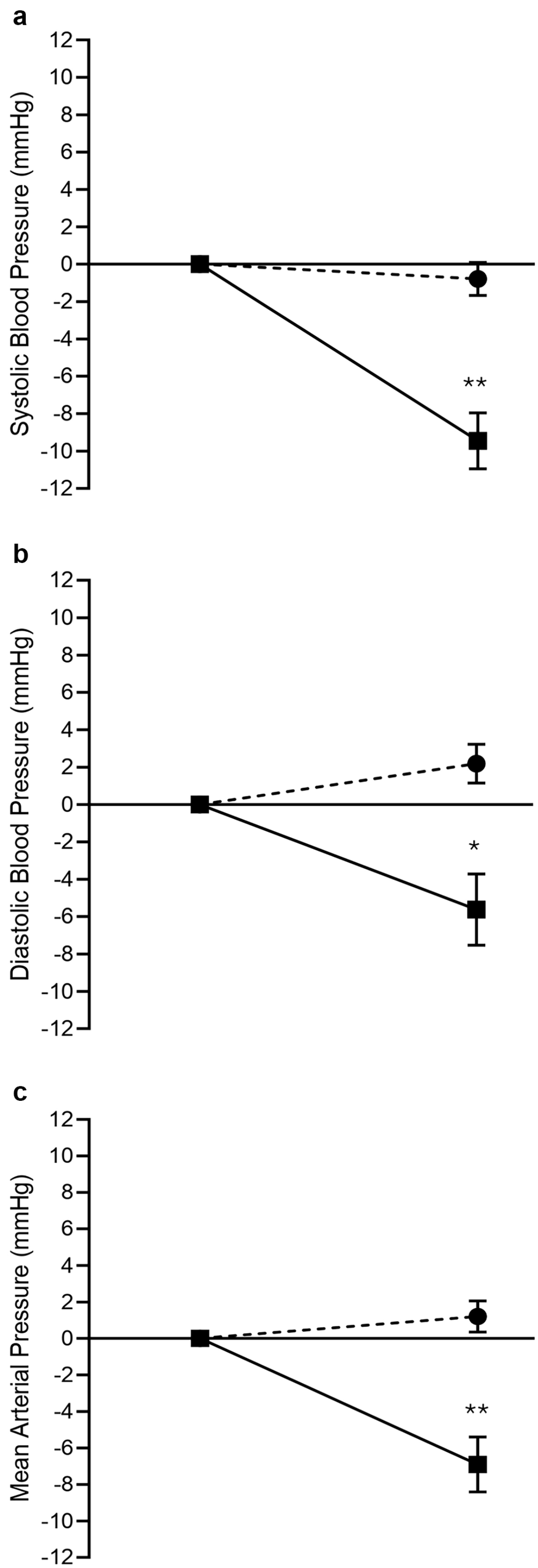


**Figure 1** The mean systolic (a), diastolic (b) and mean arterial (c) pressure changes for the control (●) and training (■) conditions. Error bars indicate the SE of the mean. *p<0.05, **p<0.01 for the difference between experimental and control conditions.

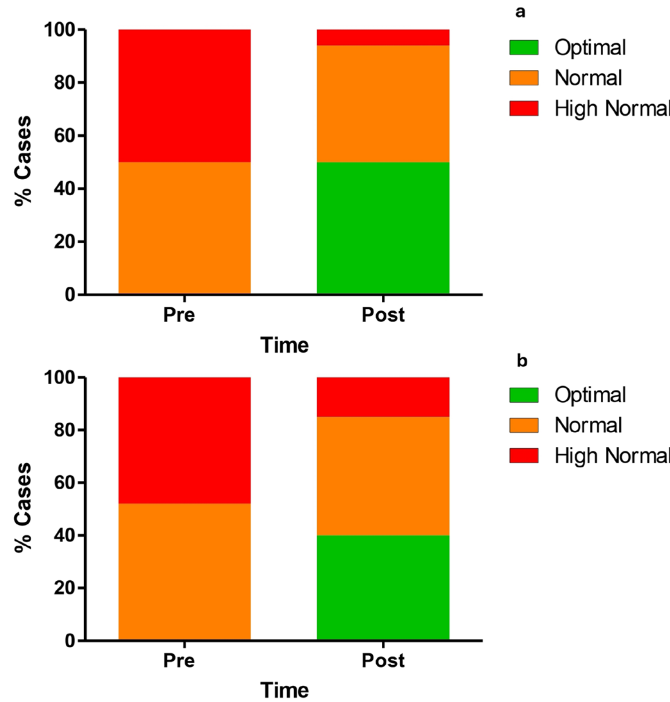


**Figure 2** Percentage distribution of BP categories in females (a) and males (b) pre-IET and post-IET. BP, blood pressure; IET, isometric exercise training.

## BP variables (females vs males)

There were no significant differences in sBP (p=0.256), dBP (p=0.119) or MAP (p=0.066) reductions between male and female participants following the 4-week training period. Despite no significant differences between the groups, it was found that 89% of females experienced a clinically important 5 mm Hg drop in sBP[19] following IET compared with 76% of males. A 5 mm Hg reduction can be considered a clinically important difference as it reduces the risk of major cardiovascular events by about 10%, even among individuals with normal or high-normal BP values.[19] Mean values for sBP, dBP and MAP can be found in online supplemental table 2.

## BP reclassification

Before training, 50% of the female participants were categorised as having normal BP and 50% as having high-normal BP. After 4 weeks of IET, 50% had optimal (<120/80 mm Hg) BP, 44% had normal (120–129/80–84 mm Hg) BP and 6% had high-normal (130–139/85–89 mm Hg) BP. For male participants before training, 52% were categorised as having normal BP and 48% as having high-normal BP. After 4 weeks of IET, 38% had optimal BP, 45% had normal BP and 15% had high-normal BP (figure 2). The number needed to treat (NNT) to recategorise one female from normal to optimal BP is 2, and the NNT to recategorise one female from high-normal to normal BP is 3. For males, the NNT to recategorise one male from normal to optimal BP is 3 and the NNT to recategorise one male from high-normal to normal BP is 4.

### Haemodynamic and cardiac autonomic variables (females vs males)

Following the 4-week training period, there were significant differences between the male and female participants in LF:HF ratio (p=0.004), LFnu (p=0.015) and HFnu (p=0.015) (online supplemental table 3). There were no significant differences in any of the other measured variables.

## DISCUSSION

The primary aim of this study was to explore any differences in BP reduction and the associated underpinning physiological mechanisms between females and males following 4 weeks of IET. It was found that IET was effective in reducing resting BP compared with the control and that there were no significant differences in the magnitude of BP reduction between female and male participants. This is in agreement with previous meta-analytic findings by Inder *et al*[7] and Smart *et al*.[8] However, to the best of our knowledge, this is the largest primary research study to date with a high representation of both females and males to specifically investigate the efficacy of IET for BP reduction. Previous studies have used sample sizes of <30 participants to compare sex-based differences[7 8] compared with 80 in the current study. Therefore, these findings provide robust evidence for the utility of IET as an effective intervention for BP reduction in both sexes.

Despite no significant difference between females and males in BP reduction, the current study found statistically significant differences in specific HRV parameters. Following the 4-week training period, females were found to have lower LFnu and higher HFnu and a lower LF:HF ratio, which is known to represent sympathovagal balance[20] compared with male participants. These responses indicate increased cardiac vagal tone and parasympathetic modulation.[21] It has been documented that lower-body IET, specifically the IET protocol used in the present study, enhances HRV and sympathovagal balance in males.[12] However, the greater autonomic response observed in females in the current investigation may be linked to sex-related differences in hormonal and vascular biology that are known to influence cardiovascular regulation.[22] Females typically show greater parasympathetic activity affecting the heart and have less sympathetic input in vascular tone.[23] Female sex hormones, specifically oestrogen and progesterone, are known to improve HRV and vascular function, respectively. Together, these hormones provide vascular protective effects that are mediated through a complex interplay of physiological mechanisms, such as modulation of L-type calcium channel activity,[24] upregulation of the nitric oxide (NO) pathway[25 26] and greater expression of neuronal NO synthase in vagal neurons.[27] Moreover, oestrogen has been shown to affect higher brain centres, including the hypothalamus and amygdala, which regulate autonomic functions and enhance parasympathetic activity.[28] Furthermore, it has been shown that beta-adrenergic receptors are influenced by oestrogen, which can lead to an overall reduction in sympathetic drive.[29 30] Although oestrogen and progesterone levels were not measured in the current study, it is possible that the cardioprotective effects from these female sex hormones augmented the autonomic adaptations specifically seen in the female participants following the 4-week IET period. This is an important finding as increased HRV and vagal function are associated with a decreased risk of morbidity and mortality, independent of traditional risk factors.[31]

Furthermore, studies that have compared sex-based differences following acute bouts of exercise have also reported greater parasympathetic activity in females. Kappus *et al*[32] found greater vagal reactivation in females during recovery from maximal aerobic exercise. Teixeira *et al*[33] also found a greater increase in cardiac BRS (used as a measure of reflexive vagal modulation) following an acute bout of isometric handgrip training. Arguably, these findings are expected since strong associations have previously been observed between acute and chronic responses during exercise, which has led to the suggestion that chronic adaptations may result from the temporal summation of acute responses.[34]

### Clinical and cost effectiveness of IET delivery

Although there were no significant differences in the BP reductions following the 4 weeks, it should be acknowledged that 89% of females experienced a clinically important 5 mm Hg drop in sBP compared with 76% of males. A 5 mm Hg reduction in sBP reduces the risk of major cardiovascular events by approximately 10%, even among individuals with normal or high-normal BP values.[19] Moreover, more female participants were reclassified into the optimal BP category following IET (figure 2), which may be related to further reductions in cardiovascular risk.[35] The higher incidence of a clinically important reduction in BP and greater reclassification into the optimal BP category may be related to the autonomic adaptations evidenced and could indicate a greater cardioprotective effect for females following IET.

We also found that the NNT to recategorise one female from normal to optimal BP is 2, and the NNT to recategorise one female from high-normal to normal BP is 3. For males, we found the NNT to recategorise one male from normal to optimal BP is 3, and the NNT to recategorise one male from high-normal to normal BP is 4.[36] Related to this, our mean reduction in sBP of 10.5 mm Hg for females and 8.8 mm Hg for males exceeds the 7 mm Hg reported in the meta-analysis by Xie *et al*.[36] These authors demonstrated that a reduction of 7 mm Hg in sBP equated to a 13% risk reduction for myocardial infarction and a 22% risk reduction for stroke. Intuitively, we could expect similar or even greater reductions in these events in women and men with HTN who accomplish a reduction in sBP of 7 mm Hg or more from undertaking IET. Of course, these benefits should be considered regarding treatment delivery costs, especially as the expected sBP reduction from IET is similar to antihypertensive monotherapy.[37] The cost of a single antihypertensive medication to healthcare services in the UK can be up to £370 for direct renin inhibitors.[38] Based on a direct comparison of end-user products only (ie, home-based equipment used for IET), the IET intervention would have an estimated cost of £10 per annum per patient.[39]

## Limitations

We did not measure oestrogen levels in participants, and therefore, inferences based on its effect on the cardiovascular system lack physiological verification. Moreover, the type of contraceptive pill used was not controlled in this study. Although previous research has shown no differences in autonomic modulation throughout a full cycle while using oral contraceptive pills,[40] there are data to suggest fluctuations in endogenous and exogenous hormone levels throughout the pill cycle, which may have affected HRV.[41] Results from the current study are also only applicable to a 4-week training period, and it remains to be established whether there are sex differences with a more prolonged training dose.

## CONCLUSIONS

Our findings support the efficacy of lower-body IET in equally reducing BP in females and males. However, the greater autonomic response seen in females and a higher prevalence of clinically significant BP reductions may indicate a greater cardioprotective effect. These findings may have important implications for future IET prescription and could help practitioners develop sex-specific protocols to optimise cardiovascular outcomes.

**Author affiliations**
[1]School of Sport, Health and Applied Science, St Mary's University Twickenham, Twickenham, UK
[2]Sport, Exercise, and Rehabilitation Sciences, Canterbury Christ Church University, Canterbury, Kent, UK
[3]Institute of Sport, Exercise and Health, Division of Surgery and Interventional Science, University College London, London, UK
[4]School of Science and Technology, University of New England, Armidale, New South Wales, Australia
[5]University of Kent Centre for Health Services Studies, Canterbury, UK

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**ORCID iDs**
Harry Swift http://orcid.org/0000-0003-0499-5706
Damian Coleman http://orcid.org/0000-0003-1861-322X
Charles Pedlar http://orcid.org/0000-0002-3075-9101
Neil Andrew Smart http://orcid.org/0000-0002-8290-6409
Chris Farmer http://orcid.org/0000-0003-1736-8242
Jonathan Wiles http://orcid.org/0000-0002-7790-8063

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