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Matching mechanical load removes sex differences in creatine kinase response to intense eccentric exercise: a comparative study

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Abstract

Background

Men are frequently reported to exhibit greater creatine kinase (CK) responses to exercise-induced muscle damage (EIMD) than women, but the mechanisms underlying this apparent sex difference remain unclear. We investigated whether this difference reflects intrinsic sex-related biological mechanisms or is largely attributable to greater absolute mechanical loading in men resulting from sex-associated differences in maximal strength.

Methods

Two hundred participants (127 men and 73 women) performed a unilateral intense eccentric exercise (IEE) on a leg press at 85% of their theoretical maximal isometric strength for eight sets of 10 repetitions. Blood samples were collected before IEE, immediately post-IEE, and 24, 48, and 72 h after the IEE to assess CK activity. Principal component analysis was performed to explore the determinants of interindividual variability in peak CK increase, and CK response over time was analyzed using linear mixed-effects models. To examine the influence of absolute mechanical loading on the observed sex difference, men and women were matched for equivalent absolute mechanical loading.

Results

Men exhibited significantly greater CK response than women (*time, sex,* and *time* x *sex interaction*, all $p < 0.001$) and exercised against greater absolute resistance ($p < 0.001$). Applied resistance was the main determinant of interindividual variability in CK response and was positively associated with peak CK increase ($\rho = 0.52$, $p < 0.001$). However, when men and women were matched for equivalent applied resistance, the sex difference in CK response was no longer evident (sex effect, $p = 0.74$; *sex* x *time interaction*, $p = 0.35$).

Conclusions

The greater CK response observed in men was no longer evident when men and women were exposed to equivalent absolute resistance. These findings suggest that apparent sex difference in CK response may be largely mediated by sex-associated differences in strength and resulting mechanical loading, rather than by intrinsic sex-related mechanisms. Absolute loading should therefore be considered when investigating biological sex differences in EIMD.

Trial registration

This research is an ancillary study of the POLYGENDOMUS trial (NCT06740136 in clinicaltrials.gov, 2023-03-13).

Plain English Summary

After muscle-damaging exercise, men often show a larger increase than women in blood creatine kinase, a widely used biomarker of muscle damage. This difference is often attributed directly to biological sex, particularly to hormonal differences. However, men and women also differ in physical characteristics such as muscle mass and strength. As men are generally stronger, they exercise against greater absolute loads when exercise intensity is prescribed relative to maximal strength. In 200 physically active adults, men initially showed a greater creatine kinase response than women. However, when men and women were compared at the same mechanical loading, this difference was no longer detected. These findings suggest that differences in the mechanical load imposed during exercise may explain a substantial part of the apparent sex difference in creatine kinase response. Studies comparing muscle damage between men and women should therefore consider absolute as well as relative exercise loading.

Highlights

- Men exhibit greater CK response than women following eccentric exercise performed at the same relative intensity.
- Prescribing the same relative exercise intensity resulted in greater absolute mechanical loading in men because of their greater maximal strength.
- Mechanical loading was positively associated with CK response and contributed substantially to its interindividual variability.
- The apparent sex difference in CK response was no longer evident when men and women were matched for equivalent mechanical loading.
- In women, CK response was not associated with circulating sex hormones, menstrual cycle phase, or hormonal contraception.

Background

Eccentric contractions may trigger exercise-induced muscle damage (EIMD) due to the mechanical stress imposed on skeletal muscle [1,2]. During eccentric contractions, muscles lengthen while producing force, generating strain within sarcomeres and potentially disrupting weaker sarcomeres [2,3]. This can lead to structural, functional, and metabolic disturbances including sarcolemmal disruption, reductions in muscle strength and range of motion, altered Ca^{2+} homeostasis and redox balance, and immune activation [1,2,4–6]. These alterations can impair muscle function and performance, highlighting the need for reliable biomarkers to assess EIMD and monitor recovery [7].

Creatine kinase (CK) activity is widely used as a blood biomarker for EIMD because it reflects sarcolemmal disruption and the efflux of muscle proteins into the circulation [8–11]. However, the CK response to exercise-induced damage is highly variable [7,12]. Men generally exhibit greater increases in circulating CK than women following eccentric exercise, raising the question of the mechanisms underlying this apparent sex difference [13,14]. Intrinsic biological mechanisms have been proposed,

particularly a protective effect of estrogens on skeletal muscle membranes through membrane-stabilizing, antioxidant, and other cellular effects [13–15]. However, evidence supporting a direct role of sex hormones remains inconsistent, as circulating estrogen levels and menstrual cycle phase have not been consistently associated with CK responses to EIMD [13–17]. Importantly, men and women also differ in characteristics that determine the mechanical stimulus imposed during exercise. Men typically have greater muscle mass and absolute strength and, when exercise intensity is prescribed relative to individual maximal strength, consequently perform exercise against a greater absolute resistance [13,14,18–20]. Because both muscle mass and the magnitude of mechanical loading may influence CK release, these sex-associated phenotypic differences could contribute to the greater CK response observed in men [18,19,21,22]. It therefore remains unclear whether the male-female difference in CK response primarily reflects intrinsic sex-related biological mechanisms or is mediated by sex-associated phenotypic differences that influence the mechanical stimulus imposed on the muscle [14,19,21–24].

The primary aim of this study was to determine whether the greater CK response reported in men persists when men and women are exposed to equivalent absolute mechanical loading during exercise. We additionally examined whether muscle mass and, in women, hormonal status and menstrual cycle phase contribute to the observed variability in CK response. We hypothesized a large sex effect in CK response in the overall cohort, with men exhibiting greater responses than women, but expected this difference to be markedly attenuated when men and women were matched for mechanical loading.

Distinguishing intrinsic sex-related mechanisms from effects mediated by sex-associated phenotypic characteristics may improve the interpretation of sex differences in EIMD and inform the design of future studies comparing physiological responses between men and women [24].

Methods

Participants

Ethics and recruitment

This research is an ancillary study of the POLYGENDOMUS trial. Briefly, athletes from the Lille metropolitan area were recruited through calls for participation distributed among local clubs and universities. Sex at birth was self-reported by participants at enrolment and was considered as a biological variable in accordance with the current recommendations for sex-responsive research [24]. Gender identity was not collected. Eligible participants were aged 18 to 35 years, weighing > 50 kg, practicing any sport for > 2 h per week, and able to comply with all study procedures. Each participant was informed about the procedure and provided written informed consent. The study was approved by the Île-de-France IV ethics committee (2022-A01308-35) and was in accordance with the Declaration of Helsinki.

Quality control

Quality control procedures were applied to assess participant eligibility. Participants were excluded if they: i) did not comply with the experimental protocol (i.e., withdrawal from the study, failure to perform the eccentric exercise within the required range of motion, and inadequate recovery before starting the protocol. Thresholds are described in Supplementary Methods S1), ii) did not exhibit EIMD after the eccentric exercise (i.e., peak increase in CK activity relative to baseline ≤ 0), iii) were suspected of having performed an additional unplanned bout of muscle-damaging exercise during the recovery period (i.e., participants showing a secondary increase in CK activity following an initial post-exercise peak and subsequent decline: CK activity at 72 h > 1.25 times the CK activity at 48 h), or iv) had missing data due to analytical measurement issues. Characteristics of the participants are presented in Table 1.

Sport activities classification

Participants' training characteristics (sports practiced, number of weekly training sessions, and weekly training time) were collected based on their oral statements. These data enabled us to classify participants according to their main sport activity in four categories: strength-based sports (e.g., bodybuilding, weightlifting, *CrossFit*, climbing, sprinting), endurance-based sports (e.g., running, swimming, trail running, cycling), mixed sports (e.g., team sports such as football, rugby, handball, basketball, and combat sports), and other sports (e.g., racket sports, horseback riding, golf, and dance).

Experimental design

The POLYGENOMUS study was an experimental comparative study primarily designed to assess the influence of genetic polymorphisms in EIMD. Each participant attended the laboratory on five separate visits. Participants were asked to: i) refrain from training throughout the experimental period and from any muscle-damaging physical activity for at least 48 h before the baseline blood sampling, ii) to avoid nutritional supplements, and iii) to avoid recovery strategies that could influence physiological responses (e.g., cold-water immersion, foam rolling, or anti-inflammatory drugs).

During the first visit, anthropometric measurements were collected. Total body mass and estimated muscle mass (eMM) of the dominant lower limb were assessed using a bioelectrical impedance scale (Tanita BC-418, Tanita Corporation, Tokyo, Japan), and body fat percentage was determined using a skinfold caliper (Harpenden skinfold caliper, Baty International, UK). Tanita BC-418 estimates muscle mass using proprietary regression equations based on height, body mass, age, sex, and segmental impedance measurements, developed against DXA-derived body composition. Participants were also familiarized during the first visit with the exercise protocol and performed an initial assessment to calibrate the intense eccentric exercise (IEE). After a minimum recovery period of 72 h, participants returned to the laboratory for four additional visits. The second visit comprised baseline pre-IEE assessments (including blood sampling), the IEE session, and post-IEE measurements (including blood sampling). Other blood samples were then collected 24, 48, and 72 h after the IEE.

Maximal strength determination

A general warm-up was first performed on a cycle ergometer (Monark 894E Peak Bike, Monark Exercise AB, Vansbro, Sweden) for 5 min at a self-selected moderate intensity. Maximal strength assessment and individualization of the unilateral IEE were conducted on a horizontal leg press (20040 - Eagle NX leg press, Cybex, Franklin Park, USA). Participants were seated with the knee flexed at 90°, and all positional parameters were recorded to ensure reproducibility. A standardized warm-up was then performed, consisting of two sets of 10 repetitions at a load corresponding to 60% of body mass. The first set was performed bilaterally, and the second set unilaterally with the dominant limb. Participants then completed a familiarization set of 5 unilateral repetitions, performed as explosively as possible.

A force-velocity profile was subsequently established using a linear positioning transducer recording velocities (Power analyzer, Tendo, London, UK). The initial load corresponded to 100% of body mass. At least four loading conditions were tested, each targeting a specific maximal velocity zone (0.3-0.5, 0.5-0.8, 0.8-1.1, and 1.1-1.4 $m \cdot s^{-1}$). For each load, participants completed three repetitions. Rest intervals were 30 s between repetitions in the two highest velocity zones and at least 45 s in lower velocity zones, with a minimum of 2 min between sets. Strong verbal encouragement was provided to ensure maximal concentric intent. The highest velocity obtained for each load was used to construct the force-velocity relationship, from which theoretical maximal isometric strength (F0) was derived as the y-intercept of the linear regression model [25]. At the end of the session, participants performed one set of 10 light-load repetitions to familiarize themselves with the eccentric tempo used during the IEE.

Intense Eccentric Exercise

To ensure reproducibility and minimize confounding factors, exercise variables were standardized across participants [26]. After the general warm-up, participants performed a specific warm-up on the leg press consisting of two sets of 10 repetitions at 40% and 60% of F0, using both lower limbs. The IEE was then performed unilaterally with the dominant limb and consisted of eight sets of 10 repetitions at 85% of F0 (i.e., the absolute applied resistance, AR). A 3-min rest interval was provided between sets. Each repetition consisted of a 5-s eccentric phase followed by a 3-s phase used to return to the starting position, performed with assistance from both lower limbs. This protocol was adapted from a previous study using eccentric leg press exercise to induce muscle damage [11].

Blood samples and analysis procedures

Venous blood samples were collected from the antecubital fossa just before and after the IEE, and at + 24, + 48, and + 72 h. The CK activity was determined using blood collected in heparinized tubes (BD Vacutainer, Plymouth, UK) by a colorimetric method according to the recommendations of the *International Federation of Clinical Chemistry* on the Roche Cobas 8000 platform (Roche Diagnostics GmbH, Mannheim, Germany). Myoglobin was measured from blood samples collected before IEE in dry tubes (BD Vacutainer, Plymouth, UK) using a nephelometric on a BN II System (Siemens Healthineers, Erlangen, Germany). Estradiol and progesterone levels were measured from blood samples collected before IEE in dry tubes (BD Vacutainer, Plymouth, UK) using a chemiluminescence immunoassay (Abbott Alinity system, Abbott Laboratories, Abbott Park, IL, USA).

Subgroups analysis

Additional matched-pair analyses were performed to further investigate the influence of AR, sex, menstrual cycle phases, and hormonal contraception. Subgroup matching procedures are detailed in Supplementary Methods S2.

Influence of AR in CK activity in subgroups of men

As AR emerged as the variable most strongly associated with CK response in the overall cohort and in men, men were divided into high- and low-AR subgroups to further examine its influence in CK response.

Men *vs*. women matched for AR

To directly test whether the observed sex difference in CK response persisted independently of absolute exercise loading, men and women were matched for AR.

Exploratory analyses of the influence of menstrual cycle phases

Exploratory analyses were performed in 35 women with regular menstrual cycles who were not using hormonal or invasive (i.e., copper intrauterine device) contraception. They were allocated to three groups according to the menstrual cycle phase in which they performed the IEE: follicular (early and late follicular phases), peri-ovulatory (ovulatory and early luteal phases), and luteal (mid and late luteal phases) [27].

Statistical analysis

Two primary outcomes were used to characterize the CK response to the IEE: i) the peak increase in CK activity relative to baseline (max_ΔCK), and ii) the CK fold change from baseline, used to express each participant's CK response relative to their own baseline. The latter was included to facilitate comparisons between individuals with markedly different baseline CK activity, particularly between men and women.

Data are presented as mean ± SD or mean (95% CI), as appropriate. Effect sizes were expressed as Hedges' *g* or eta squared (η^2) for group comparisons. Because max_ΔCK was not normally distributed, median and geometric mean values were also reported to facilitate data interpretation.

Normality was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots. Depending on data distribution and the number of groups, comparisons were performed using Welch's t-tests, Mann-Whitney U tests, Welch's ANOVA, or Kruskal-Wallis tests. Categorical variables were compared using χ^2 tests, and associations between variables were assessed using Spearman's rank correlation coefficient (ρ). Details of statistical procedures, effect size interpretation, and multiple-comparison corrections are provided in Supplementary Methods S3.

Changes in CK fold change over time were analyzed using linear mixed-effects models (LMM) with *time*, *group*, and their *interaction* included as fixed effects and participant as a random intercept. *Post hoc* comparisons were adjusted using Holm or Tukey corrections, as appropriate. A detailed description of the LMM specification is provided in Supplementary Methods S4.

Principal component analysis (PCA) was performed to explore the multivariate determinants of interindividual variability in max_ΔCK. The variables included, component selection criteria, and interpretation of PCA outputs are described in Supplementary Methods S5.

An *a priori* sample size calculation indicated that at least 25 participants per group were required to detect a large effect size with 80% power at an α level of 0.05. All statistical analyses were performed using RStudio (version 2026.05.1+225, Posit Software, Boston, MA, USA). Statistical significance was set at $p < 0.05$.

Results

Participants

Following quality control, 200 participants (127 men and 73 women) were included in the analyses (Table 1). Participants were excluded due to: evidence of additional muscle damage during recovery follow-up (n = 50), protocol non-compliance (n = 48), absence of CK response after IEE (n = 3), or missing CK data (n = 1).

Men and women did not differ in weekly training volume, training frequency, or primary sport activity. However, men exhibited greater AR ($g = 1.71$, $p < 0.001$), eMM ($g = 2.23$, $p < 0.001$), and max_ΔCK ($g = 0.62$, $p < 0.001$, Table 1). Median and geometric mean indicated that max_ΔCK was ± 3 times higher in men than in women (median in men *vs*. women: 187 *vs*. 64 (U/l); and geometric mean: 201 *vs*. 64 (U/l)).

===== PLEASE, INSERT HERE TABLE 1=====

Sex differences in CK activity fold change

CK activity fold change increased significantly after the IEE in both men and women, reaching a peak 24 h after exercise (Table 2, Fig.1.A). Peak fold change was 2.4 in men (95% CI [2.24, 2.52]) and 1.7 (95% CI [1.57, 1.84]) in women. LMM revealed a significant *time* effect ($p < 0.001$), *sex* effect ($p < 0.001$), and *time ´ sex interaction* effect ($p < 0.001$). In both groups, CK activity fold change was significantly greater than baseline at all post-IEE time points ($p < 0.01$, Table 2). No significant sex difference in CK fold change was observed immediately after the IEE (fold change ratio (men/women) = 1.09, $p = 0.10$). However, men exhibited significantly greater CK fold changes than women at + 24 h (fold change ratio (men/women) = 1.39, $p < 0.001$), + 48 h (1.23, $p < 0.001$), and + 72 h (1.15, $p < 0.001$, Fig.1.A).

===== PLEASE, INSERT HERE FIGURE 1=====

===== PLEASE, INSERT HERE TABLE 2=====

Contributors to interindividual variability in max_ΔCK

A PCA was used descriptively to summarize the major axes of covariance of the interindividual variability in CK response. The first four PCs explained 70.2% of the total variance, with PC1 and PC2 accounting for 34% and 14.9% of the variance, respectively. The PC1-PC2 plot showed a clear separation of participants by sex, but not by their main practiced sport (Fig.2.A and 2.B). PC1 was primarily driven by AR and eMM, whereas PC2 mainly reflected weekly training volume and training frequency (Supplementary Table S1). Among the retained components, PC1 (r = 0.41, $p < 0.001$), PC3 (r = – 0.15, $p = 0.03$), and PC4 (r = 0.22, $p < 0.01$) were significantly associated with max_ΔCK, whereas PC2 was not (r < 0.01, $p = 0.98$). Correlation analyses confirmed that AR was the variable most strongly associated with max_ΔCK in the whole cohort (ρ = 0.52, $p < 0.001$), followed by eMM (ρ = 0.45, $p < 0.001$, Table 3). When analyses were stratified by sex, no significant correlation was observed in women, whereas AR (ρ = 0.37, $p < 0.001$) and AR normalized to eMM (ρ = 0.30, $p = 0.002$) remained significantly associated with max_ΔCK in men (Table 3).

===== PLEASE, INSERT HERE FIGURE 2=====

===== PLEASE, INSERT HERE TABLE 3=====

Influence of AR in CK response

To examine the association between AR and CK responses independently of the between-sex comparison, men were compared by AR. The high-AR and low-AR groups each included 30 participants and did not differ in body composition, training characteristics, or sport activity (Table 4). As expected, AR was higher in the high-AR group ($p < 0.001$), which also exhibited significantly greater max_ΔCK response than the low-AR group ($p < 0.01$), with median and geometric mean values approximately 2.5-fold higher. CK activity fold change peaked after IEE in both groups at + 24 h (2.9, 95% CI [2.51, 3.33] and 2.0, 95% CI [1.75, 2.32], respectively, for the high-AR and low-AR groups, Supplementary Table S2, Fig.1.B). LMM revealed significant effects of *time* ($p < 0.001$), *AR group* ($p < 0.01$), and a *time ´ AR group interaction* ($p < 0.01$). No between-group difference was observed immediately after exercise. In contrast, the magnitude of CK fold changes was significantly higher in the high-AR group at + 24, + 48, and + 72 h, with fold change ratios (high-AR/low-AR) of 1.44 ($p < 0.001$), 1.37 ($p < 0.01$), and 1.32 ($p < 0.01$), respectively.

===== PLEASE, INSERT HERE TABLE 4=====

Sex differences in CK response after matching for AR

To determine whether the sex difference persisted when the absolute exercise stimulus was controlled, 27 men were matched with 27 women for AR. By design, AR was similar between groups, as were training load and sport activity characteristics, whereas men exhibited a greater eMM (+ 26% in mean, *g*

= 2.10, $p < 0.001$; Table 5). Despite this difference in eMM, no significant sex difference was detected for max_ΔCK and CK fold change over time (Table 5, Fig.1.C). CK activity fold change peaked 24 h after IEE in both groups, with a 2.0-fold change for men (95% CI [1.77, 2.21]) and a 1.9-fold change for women (95% CI [1.70, 2.12], Table 6). LMM revealed a significant effect of *time* ($p < 0.001$), with no *sex* effect ($p = 0.74$) and no *time ´ sex* interaction ($p = 0.35$). Moreover, myoglobin fold change from pre- to post-IEE was significantly higher in the whole group of men *vs*. women (men/ women = 1.18, $p = 0.001$), but no significant difference was observed between men and women paired for AR (men paired/women paired = 1.05, $p = 0.56$). Thus, when men and women were exposed to equivalent AR, the previously observed sex differences in CK response were no longer evident.

Contribution of muscle mass to sex difference in CK response

The persistence of greater eMM in men after matching for AR prompted complementary analyses accounting for the amount of muscle involved. In the whole cohort, eMM was positively associated with max_ΔCK ($\rho = 0.45$, $p < 0.001$, Table 3). However, despite the mean retaining approximately 26% greater eMM in the AR-matched comparison, no significant sex difference in CK response was observed. Complementary matching for AR normalized to eMM confirmed these findings: max_ΔCK normalized to eMM did not differ significantly between paired men and women (18.5 ± 17.4 *vs*. 16.7 ± 20.5 U/l/kg, respectively; $g = 0.09$, $p = 0.54$; n = 31 pairs, Supplementary Table S3).

===== PLEASE, INSERT HERE TABLE 5=====

===== PLEASE, INSERT HERE TABLE 6=====

Exploratory analyses of the influence of menstrual cycle phases

Participants were classified into follicular (n = 13), peri-ovulatory (n = 8), and luteal (n = 14) groups. Anthropometry, body composition, training load, sport activity characteristics, IEE characteristics, basal levels of biological variables, and max_ΔCK were similar between groups (Supplementary Table S4). As expected, estradiol and progesterone levels differed significantly across menstrual phases, confirming the biological relevance of the classification (Supplementary Table S4). However, neither max_ΔCK nor CK fold change differed between menstrual phases (Supplementary Table S4 and Fig.1.D). LMM revealed a significant effect of *time* ($p < 0.001$) without a significant *phase* effect ($p = 0.87$) or *time ´ phase interaction* ($p = 0.80$) in CK activity fold change (Supplementary Table S5). Likewise, estradiol and progesterone levels of this subpopulation of menstruating women were not significantly associated with the max_ΔCK (n = 35, $\rho = -0.16$, $p = 0.66$; and $\rho = -0.12$, $p = 0.75$, respectively).

The subpopulation of women not using hormonal or invasive contraception was considered irrespective of cycle phase and matched for AR with women using hormonal contraception, yielding two groups of 29 participants. Despite higher estradiol levels (112 ± 85 *vs*. 32 ± 21 pg/ml, $g = 1.28$, $p < 0.001$) and progesterone levels (3.7 ± 5.5 *vs*. 0.2 ± 0.1 ng/ml, $g = 0.88$, p-unadjusted < 0.01, $p = 0.07$) in women without hormonal contraception, no significant differences in CK response were observed

(Supplementary Table S6). Independently of the contraception strategy, estradiol and progesterone levels were not significantly correlated with the max_ΔCK activity (n = 58, ρ = − 0.14, *p* = 0.65 and ρ = − 0.15, *p* = 0.65, respectively).

Discussion

The principal finding of this study is that the greater CK response observed in men in the overall cohort was no longer evident when men and women were matched on equivalent mechanical loading. Although men exhibited greater max_ΔCK and greater CK fold changes than women before matching, they also exercised against substantially greater mechanical load. Together, our findings suggest that a sex-associated difference in mechanical loading can account for a substantial part of the apparent sex difference in CK response following eccentric exercise. Thus, differences observed between men and women should not necessarily be interpreted as evidence of a physiological intrinsic effect of sex without considering the mechanical stimulus imposed.

Apparent sex difference in CK response is strongly influenced by mechanical loading

Considering the whole cohort, the approximately threefold greater max_ΔCK observed in men than in women confirmed our initial hypothesis and is consistent with previous reports of greater CK response in men following eccentric exercise [13,14,28]. Men also performed the IEE with a higher mechanical load than women, despite similar training load and sport activity characteristics. However, one of the main findings of this study is that a higher mechanical loading, whether expressed as absolute or normalized to eMM, was consistently associated with a greater CK response. This relationship was observed both when comparing subgroups of men and when comparing men and women, suggesting that the influence of mechanical loading is independent of sex. These findings are in agreement with previous studies showing that the magnitude of mechanical loading is a major determinant of EIMD [21,22]. Indeed, Nosaka and Newton observed that maximal eccentric exercise induced significantly greater CK increases than contractions performed at 50% of maximal strength, even when the total amount of work was the same [22]. Similarly, Chen et al. demonstrated that higher-intensity eccentric contractions produced greater CK peaks than lower-intensity contractions, despite a lower total workload [21]. Together, these findings support the idea that the intensity of the eccentric load is a primary determinant of CK release following exercise. An important implication of these findings is that prescribing the same relative exercise intensity (*e.g.*, 85% of their F0) does not necessarily expose participants to the same mechanical stimulus. Individuals with greater maximal strength generate higher absolute forces and therefore experience greater mechanical tension during eccentric contractions. Consequently, although the relative intensity was standardized across participants in the present study, stronger individuals were exposed to a greater absolute mechanical load, which likely contributed to their larger CK response.

Importantly, when men and women were matched for equivalent mechanical loading sustained during the exercise, the sex difference in CK responses was no longer observed. This indicates that exercise

loading, rather than sex *per se*, largely explains the greater CK response observed in men. Although Hicks et al. reported a persistent *sex* effect after accounting for strength, they similarly found a significant correlation between max_ΔCK and maximal strength normalized to muscle mass [13]. Rather than statistically adjusting for mechanical load, we directly compared participants exposed to similar absolute mechanical stress through pair matching, which may explain this discrepancy in the results. Our results therefore suggest that controlling the exercise stimulus at the design stage may provide a more appropriate assessment of sex-related differences in CK response. These observations were confirmed by the lack of difference in myoglobin fold change from pre- to post-IEE between men and women paired; and are also consistent with the broader literature reporting similar responses between men and women for other markers of EIMD, including strength loss, delayed-onset muscle soreness, and histological muscle damage [14,29,30]. Collectively, our findings indicate that future studies investigating sex differences in EIMD should account for absolute mechanical loading and, whether possible, the amount of muscle involved in the exercise.

Muscle mass as a sex-associated contributor to CK response

Muscle mass represents another sex-associated characteristic that may contribute to differences in CK response. In the present study, eMM was greater in men and was positively associated with max_ΔCK, indicating that individuals with a greater muscle mass could exhibit greater muscle damage following EIMD. This finding aligns with Swaminathan et al., who reported a significant correlation between CK activity and fat-free mass in both men and women [19,31].

However, our findings suggest that muscle mass alone does not explain the observed male-female difference. Men retained approximately 26% greater estimated muscle mass after matching for applied resistance, yet no significant sex effect in CK response was observed. Moreover, matching participants for mechanical load normalized to eMM resulted in negligible differences in normalized max_ΔCK between sexes. These observations are consistent with previous evidence showing that an increase in the amount of muscle mass involved in eccentric exercise does not necessarily result in a proportional increase in CK response [31].

Together, strength and muscle mass should therefore not simply be considered confounding variables when investigating sex differences in EIMD. Rather, they represent sexually dimorphic phenotype characteristics that may influence the mechanical stimulus and subsequent CK response. Our findings support a pathway whereby sex-associated differences in strength translate into differences in absolute mechanical loading, which in turn contribute to the apparent sex difference in CK response.

Limited evidence for an influence of female hormones in CK response

An alternative explanation for sex difference in EIMD involves intrinsic biological mechanisms, particularly the potential protective effect of estrogen against EIMD. Although several studies have suggested that estrogen may reduce CK release through antioxidant, membrane-stabilizing, or receptor-mediated mechanisms [13,14,28,32], other investigations have reported no association between

estrogen and CK response [16,33,34]. Our results provide limited support for a major influence of circulating female hormones on CK response. Neither circulating estradiol nor progesterone was associated with max_ΔCK or CK fold change. Moreover, CK responses did not significantly differ across menstrual cycle phases. Similarly, women using and not using hormonal contraception showed similar CK responses when matched for mechanical loading, despite marked differences in circulating hormone levels. These findings should nevertheless be interpreted cautiously. A single measurement of circulating sex hormones provides only a limited representation of hormonal exposure across the menstrual cycle and may not reflect local estrogen synthesis and signaling within skeletal muscle [35,36]. Therefore, while our findings suggest that circulating hormonal status was not a major determinant of the interindividual variability in CK response observed under the present experimental conditions, they do not rule out a possible biological influence of female sex hormones on muscle damage.

Limitations

Several limitations should be acknowledged. First, although matching men and women for mechanical loading allowed an important component of the exercise stimulus to be controlled, the absence of a statistically significant difference does not demonstrate biological equivalence. Our findings should therefore be interpreted as providing limited evidence for a large independent sex effect under equivalent mechanical loading rather than demonstrating the absence of any sex effect. Second, eMM was estimated using bioelectrical impedance analysis, a practical field method whose estimates can be influenced by measurement conditions and the prediction equation used [37]. Importantly, the proprietary equation used to estimate muscle mass incorporates sex among predictors, which should be considered when interpreting analyses of sex differences. Future studies should confirm our findings using reference methods such as DXA or MRI. Third, analyses involving menstrual cycle phases were exploratory and included a limited number of participants in each subgroup. Although the expected differences in estradiol and progesterone levels supported the biological relevance of the menstrual phases classification, the study was not specifically powered to detect small differences in CK response between menstrual cycle phases. Consequently, the absence of significant differences between phases should not be interpreted as evidence of absence of a menstrual cycle effect. Larger cohorts will be required to confirm these findings. Finally, CK is an indirect marker of muscle damage and exhibits substantial interindividual variability. Although the similar findings observed for myoglobin support our interpretation, additional factors, including biomechanical characteristics or genetic polymorphisms, are also likely to contribute to individual susceptibility to EIMD [10,38]. Future studies combining circulating biomarkers with functional, imaging, or direct assessments could further clarify whether the influence of absolute mechanical loading extends to other dimensions of muscle damage.

Perspectives and Significance

The present findings have methodological implications for the interpretation of sex differences in exercise physiology. An observed difference between men and women does not necessarily reflect a

direct biological effect of sex, because sex-associated phenotypic characteristics may modify both exercise stimulus and the ensuing physiological response [20]. In this context, prescribing an exercise intensity relative to maximal strength controls relative intensity but simultaneously exposes stronger individuals to greater absolute mechanical loading. This distinction is consistent with current recommendations to move beyond treating sex as a simple stratification variable and instead investigate the biological pathways through which sex-associated characteristics may influence physiological outcomes [24]. Sex encompasses multiple biological attributes, including hormonal and physiological characteristics, which may contribute directly or indirectly to an observed difference between men and women. In the present study, the greater CK response observed in men at the same relative exercise intensity was no longer evident when men and women were exposed to equivalent applied resistance. Thus, rather than considering strength and mechanical loading merely as confounding factors to be statistically controlled, our findings suggest that they may represent part of the pathway through which sex-associated phenotypic differences contribute to CK response. This distinction may be particularly important for CK response, given its large interindividual variability and sensitivity to the characteristics of the exercise stimulus [7,21,22]. Studies investigating sex differences in EIMD should therefore report both relative and absolute mechanical loading and consider differences in strength and muscle mass when interpreting male-female comparisons. When the objective is to identify an independent effect of sex, a complementary approach such as matching participants for absolute mechanical load may help to distinguish intrinsic sex-related mechanisms from effects mediated by sexually dimorphic phenotype characteristics.

Conclusions

The greater CK response observed in men was no longer evident when men and women were exposed to equivalent absolute resistance. These findings suggest that apparent sex difference in CK response may be largely mediated by sex-associated differences in strength and resulting mechanical loading, rather than by intrinsic sex-related mechanisms. Absolute loading should therefore be considered when investigating biological sex differences in EIMD.

Abbreviations

AR
applied resistance
CK
creatine kinase
EIMD
exercise-induced muscle damage
eMM
estimated muscle mass of the dominant limb
F0
theoretical maximal isometric strength

IEE
intense eccentric exercise
LMM
linear mixed model
max_ΔCK
peak CK activity – baseline CK activity
PC
principal component
PCA
principal component analysis
RPE
rate of perceived exertion

Declarations

Conflict of interest

The authors report no conflict of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the Île-de-France IV ethics committee (2022-A01308-35) in accordance with the Declaration of Helsinki. Each participant was informed about the procedure and provided written informed consent.

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests: The authors report no conflict of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Tables

Table 1 Participants' characteristics.

	Men (n = 127)	Women (n = 73)	*p*-value adjusted	Hedges' *g*
Anthropometry and body composition				
Age (years)	23.2 ± 4.2	22.8 ± 3.7	0.77	0.09
Height (cm)	180.0 ± 7.2	166.6 ± 5.9	***	**1.99**
Body mass (kg)	77.5 ± 11.0	65.0 ± 9.8	***	**1.18**
eMM (kg)	10.9 ± 1.2	8.1 ± 1.3	***	**2.23**
Body fat (%)	16.4 ± 4.4	28.1 ± 5.8	***	**– 2.35**
Basal level of biological variables				
Basal CK activity (U/l)	187 ± 99	117 ± 58	***	**0.81**
Basal Mb (µg/l)	38 ± 12	27 ± 11	***	**0.87**
Training load and sport activity characteristics				
Weekly sport activity sessions (n)	4.9 ± 2.2	4.3 ± 1.8	0.11	0.25
Weekly training time (h)	7.7 ± 4.0	7.6 ± 4.5	0.51	0.04
Strength-based activity (n, % per sex)	43 (33.9)	20 (27.4)	0.09	Na
Endurance-based activity (n, % per sex)	29 (22.8)	18 (24.7)		
Mixed activity (n, % per sex)	48 (37.8)	23 (31.5)		
Other activity (n, % per sex)	7 (5.5)	12 (16.4)		
IEE characteristics				
AR (N)	1264 ± 268	871 ± 137	***	**1.71**
AR normalized to eMM (N/kg)	116 ± 20	109 ± 19	**0.01**	**0.38**
RPE (score)	7.1 ± 1.5	5.8 ± 2.0	***	**0.78**
Max_ΔCK (U/l)	339 ± 466	105 ± 123	***	**0.62**

AR, applied resistance during the IEE; *CK*, creatine kinase; *eMM*, estimated muscle mass of the dominant lower limb; *IEE*, intense eccentric exercise; *max_ΔCK*, peak blood – basal CK activity; *Mb*, myoglobin; *Na*, not applicable; *RPE*, rate of perceived exertion from 0 to 10, based on the Foster method [39]. *p*-values were adjusted with the Benjamini-Hochberg procedure: ***, *p*-adjusted < 0.001. Hedges' |*g*|, with $g < 0.2$, $g < 0.5$, $g < 0.8$, and $g \geq 0.8$, represented a negligible, small, medium, and large effect, respectively. For $g > 0$, men > women, and for $g < 0$, women > men. Descriptive data are presented as mean ± SD.

Table 2 CK activity fold change from baseline in men and women.

	Measure	Fold-change [95% CI]	*p*-value adjusted *vs.* Pre
Women (n =73)	Pre (baseline)	1.00 [0.92, 1.08]	Na
	Post	1.13 [1.05, 1.23]	**
	+ 24 h	1.70 [1.57, 1.84]	***
	+ 48 h	1.40 [1.30, 1.52]	***
	+ 72 h	1.20 [1.11, 1.30]	***
Men (n = 127)	Pre (baseline)	1.00 [0.94, 1.06]	Na
	Post	1.23 [1.16, 1.31]	***
	+ 24 h	2.38 [2.24, 2.52]	***
	+ 48 h	1.74 [1.64, 1.85]	***
	+ 72 h	1.38 [1.30, 1.47]	***

Na, not applicable. *p*-values were adjusted with the Holm correction: **, *p*-adjusted < 0.01; ***, *p*-adjusted < 0.001.

Table 3 Correlations between the max_ΔCK and variables of interest.

	Men and women (n = 200)		Men (n = 127)		Women (n = 73)	
	ρ / η²	*p*-value adjusted	ρ / η²	*p*-value adjusted	ρ / η²	*p*-value adjusted
Anthropometry and body composition						
Age (years)	– 0.07	0.38	– 0.05	0.66	– 0.18	0.32
Height (cm)	**0.32**	***	– 0.02	0.83	0.03	0.79
Body mass (kg)	**0.35**	***	**0.22**	**0.04**	– 0.05	0.77
eMM (kg)	**0.45**	***	0.19	0.07	0.06	0.77
Body fat (%)	**– 0.33**	***	0.12	0.24	– 0.18	0.32
Basal level of biological variables						
Basal CK activity (U/l)	**0.45**	***	**0.34**	***	0.21	0.32
Basal Mb (µg/l)	**0.49**	***	**0.40**	***	0.12	0.51
Training load and sport activity characteristics						
Weekly sport activity sessions (n)	– 0.01	0.90	– 0.05	0.66	– 0.12	0.51
Weekly training time (h)	0.03	0.77	0.05	0.66	– 0.03	0.79
Main type of sport activity	0.03	0.06	0.03	0.16	0.06	0.32
IEE characteristics						
AR (N)	**0.52**	***	**0.37**	***	0.13	0.51
AR normalized to eMM (N/kg)	**0.28**	***	**0.30**	**	0.11	0.51
RPE (score)	**0.34**	***	**0.21**	**0.04**	0.28	0.20

AR, applied resistance during the IEE; *CK*, creatine kinase; *eMM*, estimated muscle mass of the dominant lower limb; *IEE*, intense eccentric exercise; *max_ΔCK*, peak blood – basal CK activity; *Mb*, myoglobin; *RPE*, rate of perceived exertion from 0 to 10, based on the Foster method [39]. Spearman's coefficient (*ρ)* and eta squared (*η²,* only for the main type of sport activity*)* represented the effect size, with *|ρ| < 0.10, |ρ| < 0.30, |ρ| < 0.50*, and *|ρ| ≥ 0.50,* representing a negligible, weak, moderate, and strong correlation, respectively, and *η²* = 0.06 representing a moderate correlation. *p*-values were adjusted with the Benjamini-Hochberg procedure: **, *p*-adjusted < 0.01; ***, *p*-adjusted < 0.001.

Table 4 Characteristics of men having sustained a high- or a low-AR.

	High-AR (n = 30)	Low-AR (n = 30)	*p*-value adjusted	Hedges' *g*
Anthropometry and body composition				
Age (years)	23.2 ± 3.6	24.0 ± 5.6	0.57	− 0.16
Height (cm)	179.7 ± 7.5	180.4 ± 6.3	0.74	− 0.10
Body mass (kg)	80.1 ± 9.4	75.7 ± 8.0	0.10	0.50
eMM (kg)	11.2 ± 1.1	10.9 ± 1.0	0.32	0.29
Body fat (%)	15.6 ± 3.9	17.2 ± 4.3	0.15	− 0.39
Basal level of biological variables				
Basal CK activity (U/l)	212 ± 102	162 ± 79	0.09	0.55
Basal Mb (µg/l)	42 ± 14	36 ± 12	**0.04**	**0.49**
Training load and sport activity characteristics				
Weekly sport activity sessions (n)	4.8 ± 1.5	5.0 ± 2.7	0.74	− 0.11
Weekly training time (h)	8.2 ± 3.5	7.0 ± 4.2	0.10	0.30
Strength-based activity (n, % per AR type)	12 (40.0)	7 (23.3)	0.25	Na
Endurance-based activity (n, % per AR type)	5 (16.7)	11 (36.7)		
Mixed activity (n, % per AR type)	12 (40.0)	9 (30.0)		
Other activity (n, % per AR type)	1 (3.3)	3 (10.0)		
IEE characteristics				
AR (N)	1599 ± 228	1017 ± 144	***	**3.01**
AR normalized to eMM (N/kg)	143.2 ± 14.5	93.7 ± 9.8	***	**3.94**
RPE (score)	7.9 ± 1.3	6.4 ± 1.2	***	**1.14**
Max_ΔCK (U/l)	595 ± 825	200 ± 226	**0.01**	**0.65**
Max_ΔCK normalized to eMM (U/l/kg)	54.1 ± 77.8	18.0 ± 19.1	**0.01**	**0.63**

AR, applied resistance during the IEE; *CK*, creatine kinase; *eMM*, estimated muscle mass of the dominant lower limb; *IEE*, intense eccentric exercise; *max_ΔCK*, peak blood – basal CK activity; *Mb*, myoglobin; *Na*, not applicable; *RPE*, rate of perceived exertion from 0 to 10, based on the Foster method [39]. *p*-values were adjusted with the Benjamini-Hochberg procedure: ***, *p*-adjusted < 0.001. Hedges' |*g*|, with $g < 0.2$, $g < 0.5$, $g < 0.8$, and $g \geq 0.8$, representing a negligible, small, medium, and large effect, respectively. For $g > 0$, high-AR > low-AR, and for $g < 0$, low-AR > high-AR. Descriptive data are presented as mean ± SD.

Table 5 Characteristics of men and women paired for AR.

	Men paired (n = 27)	Women paired (n = 27)	*p*-value adjusted	Hedges' *g*
Anthropometry and body composition				
Age (years)	23.3 ± 5.0	23.0 ± 3.9	0.68	0.07
Height (cm)	177.9 ± 6.7	168.1 ± 5.1	***	**1.61**
Body mass (kg)	72.2 ± 8.3	68.8 ± 11.7	0.29	0.34
eMM (kg)	10.3 ± 1.0	8.2 ± 0.9	***	**2.11**
Body fat (%)	17.0 ± 4.4	29. ± 6.2	***	**– 2.28**
Basal level of biological variables				
Basal CK activity (U/l)	186 ± 86	107 ± 48	***	**1.12**
Basal Mb (µg/l)	37 ± 13	27 ± 14	***	**0.74**
Training load and sport activity characteristics				
Weekly sport activity sessions (n)	5.0 ± 3.1	4.8 ± 2.1	0.64	0.07
Weekly training time (h)	7.0 ± 4.4	8.5 ± 4.9	0.23	– 0.32
Strength-based activity (n, % per sex)	7 (25.9)	10 (37.0)	0.23	Na
Endurance-based activity (n, % per sex)	10 (37.0)	4 (14.8)		
Mixed activity (n, % per sex)	6 (22.2)	11 (40.7)		
Other activity (n, % per sex)	4 (14.8)	2 (7.4)		
IEE characteristics				
AR (N)	977 ± 115	984 ± 127	0.85	– 0.05
AR normalized to eMM (N/kg)	96 ± 13	122 ± 18	***	**– 1.61**
RPE (score)	6.9 ± 1.5	5.6 ± 1.9	**0.04**	**0.75**
Max_ΔCK (U/l)	202 ± 178	110 ± 92	0.07	0.63
Max_ΔCK normalized to eMM (U/l/kg)	19.9 ± 18.4	13.7 ± 11.7	0.29	0.40

AR, applied resistance during the IEE; *CK*, creatine kinase; *eMM*, estimated muscle mass of the dominant lower limb; *IEE*, intense eccentric exercise; *max_ΔCK*, peak blood – basal CK activity; *Mb*, myoglobin; *Na*, not applicable; *RPE*, rate of perceived exertion from 0 to 10, based on the Foster method [39]. *p*-values

were adjusted with the Benjamini-Hochberg procedure: ***, *p*-adjusted < 0.001. Hedges' |*g*|, with $g < 0.2$, $g < 0.5$, $g < 0.8$, and $g \geq 0.8$, representing a negligible, small, medium, and large effect, respectively. For $g > 0$, men paired > women paired, and for $g < 0$, women paired > men paired. Descriptive data are presented as mean ± SD.

Table 6 CK activity fold change from baseline in men and women paired for AR.

	Measure	Fold-change [95% CI]	*p*-value adjusted *vs.* Pre
Women paired (n = 27)	Pre (baseline)	1.00 [0.90, 1.12]	Na
	Post	1.16 [1.04, 1.30]	**0.02**
	+ 24 h	1.90 [1.70, 2.12]	***
	+ 48 h	1.45 [1.29, 1.62]	***
	+ 72 h	1.29 [1.15, 1.44]	***
Men paired (n = 27)	Pre (baseline)	1.00 [0.90, 1.12]	Na
	Post	1.16 [1.04, 1.30]	**0.02**
	+ 24 h	1.98 [1.77, 2.21]	***
	+ 48 h	1.43 [1.28, 1.60]	***
	+ 72 h	1.13 [1.01, 1.27]	**0.06**

AR, applied resistance during the IEE*; Na*, not applicable. *p*-values were adjusted with the Holm correction: ***, *p*-adjusted < 0.001.

Figures

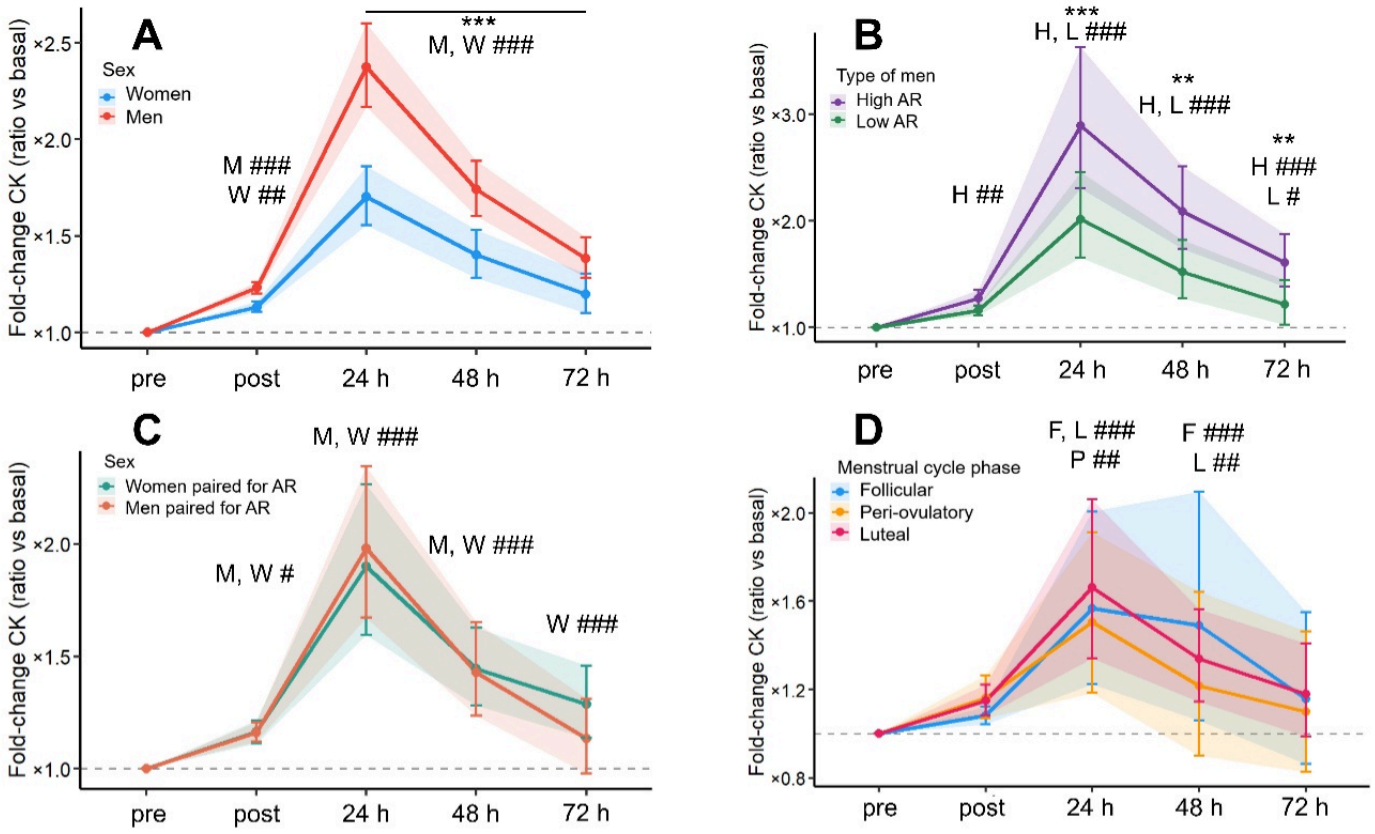


Figure 1

Comparisons of kinetics of CK activity fold change from baseline between: all included men (n = 127) *vs*. all included women (n = 73, A), men with a high-AR *vs*. men with a low-AR (n = 30 per group, B), men *vs*. women paired for AR (n = 27 per group, C), and women without hormonal contraception according to the menstrual cycle phase in which they performed the intense eccentric exercise (D): follicular group (n = 13), peri-ovulatory group (n = 8), and luteal group (n = 14). *AR*, applied resistance during the intense eccentric exercise; *CK*, creatine kinase; *F*, follicular; *H*, high-AR; *L*, low-AR for (B) or luteal for (D); *M*, men; *P*, peri-ovulatory; *W*, women. Data are presented as mean ± 95% CI: ###, $p < 0.001$ *vs*. pre; ##, $p < 0.01$ *vs*. pre; #, $p < 0.05$ *vs*. pre; ***, $p < 0.001$ between groups at the measurement time; **, $p < 0.01$ between groups at the measurement time.

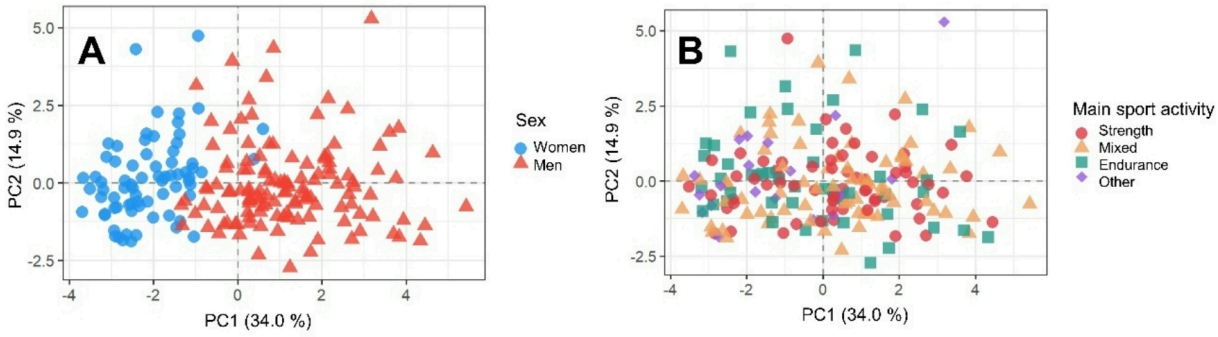


Figure 2

PC1-PC2 representation of the participants by sex (A) or by the type of the main sport activity (B). *AR*, applied resistance; *eMM*, estimated muscle mass of the dominant limb; *PC*, principal component.

Supplementary Files

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- 20260907SupplementaryInformation.docx