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ORIGINAL ARTICLE

Sex-related differences in neuromuscular and biological adaptations to power training in older adults: The role of creatine supplementation

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ABSTRACT

The aim of the present study was to analyze the modulatory role of sex in neuromuscular and biological adaptations induced by a power training program in older adults, as well as to explore the potential additional effect of creatine supplementation. A total of 99 participants (47 men and 52 women; 67.93 ± 1.30 years) were randomly assigned to training or control conditions, with or without supplementation. Neuromuscular performance was assessed through knee extension at 180°/s, together with biomarkers related to neuroplasticity (brain-derived neurotrophic factor [BDNF]), inflammation (interleukin-6 [IL-6] and tumor necrosis factor alpha [TNF-α]), and enzymatic antioxidant defense (glutathione peroxidase [GPx]), before and after the intervention. Power training induced significant improvements in neuromuscular performance, with large to very large effect sizes. At the biological level, consistent adaptations were observed, characterized by increases in BDNF and GPx activity and reductions in IL-6, whereas TNF-α showed a more moderate and variable response. Regarding sex differences, differential patterns were identified in the neuromuscular response, with variations in the magnitude of adaptation between men and women depending on the supplementation condition. In contrast, biological responses were generally similar between sexes, although specific trends were observed in some biomarkers. Overall, the results suggest that sex acts as a modulator of neuromuscular adaptations to power training in older adults, whereas biological adaptations appear to be more homogeneous. Creatine supplementation may exert a modest but consistent enhancing effect on some responses, although its contribution seems secondary to the exercise stimulus.

Keywords: Sport medicine, Power training, Variable resistance, Aging, Neuromuscular performance, Neurotrophic factors, Inflammation, Oxidative stress, Creatine, Sex differences.

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INTRODUCTION

Aging is associated with a progressive decline in neuromuscular function, functional capacity, and the balance of multiple biological systems, including neurotrophic, inflammatory, and redox regulation. This process contributes to the loss of independence and an increased risk of disability in older adults (Clark & Manini, 2012). In this context, physical exercise, and particularly resistance training, has been established as one of the most effective strategies to mitigate these effects and promote healthy aging (Saez-Berlanga et al., 2026). Among the different resistance training modalities, training aimed at developing muscular power has gained particular relevance, as the ability to generate force at high velocity declines to a greater extent than maximal strength with aging and shows a stronger association with functional performance (Reid & Fielding, 2012). Previous studies have demonstrated that power training significantly improves neuromuscular function and functional capacity in older adults (Gargallo et al., 2024), positioning it as a key intervention in this population.

In this context, the assessment of lower-limb neuromuscular performance becomes particularly relevant, given its central role in functionality and autonomy in older adults. Among the different available variables, high-velocity isokinetic knee extension (180°/s) emerges as a particularly relevant indicator, as the capacity of the knee extensors is a key determinant of performance in fundamental activities of daily living, such as gait, sit-to-stand transitions, and overall mobility, and has been identified as one of the main predictors of functional independence in this population, independently of muscle mass, reinforcing its value as an integrated functional marker (Newman et al., 2006). Therefore, assessment at high angular velocities allows not only the evaluation of force production but also components related to contraction velocity and muscular power, aspects that are particularly relevant in aging, where their decline is more pronounced and more strongly associated with functional loss (Reid & Fielding, 2012).

In addition to its effects on functional performance, physical exercise also induces adaptations at the biological level. In particular, training has been shown to modulate the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which is involved in neuronal plasticity and cognitive function (Müller et al., 2020). This effect has been linked to muscle activity–dependent mechanisms, such as the activation of the PGC-1α pathway and the release of myokines that facilitate muscle–brain communication (Pedersen, 2019). Moreover, exercise acts as a modulator of systemic inflammatory status, reducing levels of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and regulating the response of interleukin-6 (IL-6), which, in the context of exercise, exerts an anti-inflammatory role (Juesas et al., 2025). These adaptations are particularly relevant in older adults, in whom chronic low-grade inflammation is associated with functional decline and age-related diseases (Gene-Morales et al., 2025). In parallel, physical exercise induces adaptations in the redox system through hormetic mechanisms, promoting the activation of pathways such as Nrf2 and enhancing endogenous antioxidant capacity, including enzymatic antioxidant systems such as glutathione peroxidase (GPx) (Ji et al., 2016). The interaction between inflammation, oxidative stress, and neuroplasticity suggests the existence of an integrated biological axis that may mediate the effects of exercise on function during aging (Mattson & Arumugam, 2018).

However, most studies have examined exercise-induced adaptations from a global perspective, without specifically considering the modulatory role of sex or the interaction between biological and functional systems. In this regard, current evidence suggests that the response to training is not homogeneous, and that factors such as neuromuscular activation and metabolism may influence the magnitude of the induced adaptations (Refalo et al., 2025). Although men and women typically exhibit comparable relative improvements following resistance training, differences have been reported in the absolute magnitude of

adaptations and in the neuromuscular response (Hawley et al., 2025; Jones et al., 2021). Nevertheless, these findings remain inconsistent, particularly in older populations, where the decline in sex hormone concentrations and age-related physiological convergence may attenuate some of the differences classically described between sexes (Critchlow et al., 2025). This scenario becomes even more complex when training is combined with supplementation strategies, such as creatine monohydrate, which is widely used for its ability to improve neuromuscular performance and enhance adaptations to resistance training (Candow et al., 2021; Kreider et al., 2017). However, evidence regarding potential sex differences in the response to creatine remains limited, as most studies have been conducted in men, with less consistent findings reported in women, highlighting the need for sex-specific research in this area (Tam et al., 2025). In older adults, additional factors such as muscle mass, phosphocreatine availability, and metabolic efficiency may further influence the response in a differential manner. Overall, uncertainty persists as to whether sex modulates adaptations to power training in older adults, both at the functional and biological levels, as well as regarding the potential modulatory role of creatine supplementation in these responses. In this context, an integrated approach to the analysis of neuromuscular and biochemical variables is warranted, allowing for a more precise understanding of the underlying mechanisms and the role of sex as a key modulatory factor.

Consequently, based on the above, the primary aim of the present study was to determine whether sex modulates neuromuscular and biochemical adaptations induced by power training in older adults. The overall effects of training were considered the common adaptive framework within which potential sex-related differences were examined, whereas the role of creatine supplementation was explored as a secondary factor. Neuromuscular performance variables (high-velocity isokinetic strength) were assessed together with markers related to neuroplasticity (BDNF), systemic inflammation (IL-6 and TNF-α), and antioxidant defense (GPx). It was hypothesized that a power training program would induce significant improvements in neuromuscular performance and in biochemical markers related to neuroplasticity, inflammation, and antioxidant defense in older adults, and that these adaptations would be modulated by sex and enhanced by creatine supplementation.

MATERIALS AND METHODS

Study design

A 16-week randomized controlled trial was conducted to analyze potential sex differences in neuromuscular and biochemical adaptations induced by a power training program in older adults, as well as to explore the modulatory effect of creatine supplementation on these adaptations. Neuromuscular performance variables (high-velocity isokinetic knee extension at 180°/s) were assessed, together with markers related to neuroplasticity (BDNF), systemic inflammation (IL-6; TNF-α), and enzymatic antioxidant defense (GPx). The original design included two intervention modalities (resistance training with elastic bands and aquatic-based training), both combined with supplementation (creatine or placebo), resulting in a factorial design. However, both modalities were conceived to induce adaptations associated with the same physiological construct, based on power training performed with high-velocity movement intent. In this regard, both modalities followed an equivalent structure in terms of frequency, duration, volume, and relative intensity, the latter being controlled through rating of perceived exertion.

Given that the specific aim of the present study was to analyze the role of sex as a modulatory factor in adaptive responses to power training, and considering that both previous studies (Colado et al., 2009; Colado et al., 2012) and preliminary analyses did not show relevant differential effects between modalities in the main variables, both conditions were grouped into a single analytical category of "*power training*." This approach allowed the analysis to focus on the primary variable of interest, minimizing sample fragmentation

and enhancing statistical robustness in detecting potential sex differences. Regarding supplementation, although the study included creatine and placebo conditions, the primary analysis focused on the effect of training and its modulation by sex. The effect of supplementation and its potential interaction with sex were explored through secondary analyses. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia (Spain) (IRB: 1861154). The present work is part of a broader research project designed to analyze different dimensions of training responses in older populations. In this context, the present study specifically focuses on exploring the potential modulatory role of sex in neuromuscular and biological adaptations induced by the intervention. Therefore, the analytical strategy was specifically designed to maximize the ability to detect sex-related differences in adaptation, which represented the primary objective of the present investigation.

Participants

Sedentary older adults (≥60 years), who were functionally independent, participated in the study. Functional independence was defined as the ability to walk at least 100 meters and climb 10 steps without assistance. All participants had medical clearance to engage in physical exercise. Exclusion criteria included: (i) contraindications to resistance training or supplementation; (ii) severe sensory impairments; (iii) terminal illness; (iv) body weight fluctuations ≥10% in the previous year; (v) use of medication that could interfere with the study variables; (vi) cognitive impairment (Mini-Mental State Examination <23); and (vii) participation in other recent trials. Participants were recruited through university programs for older adults and provided written informed consent prior to inclusion.

Randomization and blinding

Random allocation was performed using a computer-generated sequence by an independent researcher. Due to the nature of the intervention, participants could not be blinded to the type of training; however, they were blinded to the supplementation condition. Outcome assessors and data analysts remained blinded throughout the entire process.

Assessment procedures

General assessment protocol

Assessments were conducted before and after the intervention at the facilities of the University of Valencia (Spain), under standardized conditions. Participants attended blood sampling sessions in a fasted state (≥8 h) and were instructed to avoid caffeine intake and strenuous physical activity for 72 h prior to each assessment, particularly before post-intervention measurements, in order to minimize the influence of acute exercise responses derived from the training program itself. Participants were also instructed to maintain their usual dietary habits and physical activity levels throughout the study. Accordingly, baseline measurements were performed prior to the start of the training program, whereas post-intervention assessments were conducted within 72 h following its completion.

Primary outcomes included biochemical markers related to neuroplasticity (BDNF), inflammation (IL-6; TNF-α), and enzymatic antioxidant defense (GPx), as well as neuromuscular performance assessed through high-velocity isokinetic knee extension at 180°/s. For sample characterization, body composition was assessed by bioelectrical impedance analysis (MC-780MA, Tanita Corp., Tokyo, Japan), with body fat percentage obtained while participants wore light clothing and no metal objects (Gargallo et al., 2024). Baseline muscle strength was also determined using handgrip dynamometry (Bohannon, 2008). The assessment protocol was structured into two sessions. The first session included blood sample collection for biomarker analysis. The second session involved body composition and strength assessments (isokinetic and isometric), conducted under equivalent conditions at both pre- and post-intervention time points.

Biomarkers

Markers related to neuroplasticity (BDNF), inflammation (IL-6; TNF-α), and enzymatic antioxidant defense (GPx) were analyzed. Blood samples were collected under fasting conditions and processed by refrigerated centrifugation to separate serum. Samples were then aliquoted and stored at temperatures ranging from −60 °C to −80 °C until analysis. Biomarker quantification was performed using enzyme-linked immunosorbent assays (ELISA), following the manufacturers' instructions and standardized laboratory protocols. Measurement reliability was ensured by controlling intra-assay and inter-assay coefficients of variation, which were maintained below 10%. Analyte concentrations were calculated from standard curves fitted using four-parameter logistic regression models, with dedicated analysis software (GraphPad Prism, GraphPad Software, USA).

Isokinetic strength

Isokinetic strength of the dominant knee extensors was assessed in concentric mode at an angular velocity of 180°/s using an isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA) (Gene-Morales et al., 2025). Prior to testing, participants performed a standardized warm-up consisting of light aerobic exercise and joint mobility, followed by a familiarization period that included several submaximal and maximal repetitions. Following this procedure, five maximal voluntary contractions were performed, with a 2-minute rest interval between attempts. The range of motion was set from 0° to 90° of knee flexion. Throughout the test, participants maintained a standardized position and received continuous verbal encouragement to ensure maximal neuromuscular effort and measurement consistency.

Control variables

To control for potential confounding factors, dietary intake and habitual physical activity levels were monitored throughout the study. Dietary intake was assessed before and after the intervention using 3-day food records (two weekdays and one weekend day), which were analyzed using a dedicated nutritional tracking application (MyFitnessPal) under the supervision of a qualified professional. Habitual physical activity, excluding the training sessions of the study, was estimated using the International Physical Activity Questionnaire (IPAQ), administered at the same time points. Participants were also instructed to maintain their usual dietary habits and physical activity levels without modification throughout the intervention period.

Training program

Familiarization sessions

Prior to the start of the intervention, participants assigned to the experimental groups completed a familiarization period consisting of six sessions. The purpose of this phase was to ensure correct technical execution of the exercises, familiarize participants with the use of the rating of perceived exertion (RPE) using the OMNI-Resistance Exercise Scale for elastic bands (Colado et al., 2012), and individually adjust resistance levels for both elastic band training and aquatic-based training. Additionally, key aspects of exercise execution, such as movement cadence and breathing pattern, were standardized during these sessions in order to ensure consistency of the training stimulus from the beginning of the program.

General methodological aspects of the training program

The training program lasted 16 weeks and consisted of a total of 48 sessions (three sessions per week on non-consecutive days), with an approximate duration of 60 minutes per session. Each session was structured according to the general recommendations of the American College of Sports Medicine (ACSM), including a warm-up (5-10 min), a main training block (40-50 min), and a cool-down period (5-10 min).

Sessions were conducted in a group-based format and were continuously supervised by qualified exercise professionals to ensure correct execution, monitor intensity, and maintain adherence to the protocol. The training program consisted of five multi-joint exercises performed in four sets of eight submaximal repetitions, alternating upper- and lower-body exercises to minimize cumulative fatigue. Rest intervals of 2 minutes between sets and 90 seconds between exercises were established. Exercise intensity was regulated using the rating of perceived exertion of the first repetition (RPE-1), allowing individualized load adjustment from the beginning of each set. Exercise execution was standardized by prescribing a concentric phase performed with maximal intended velocity and a controlled eccentric phase lasting 2 seconds, with a brief pause between phases. Although the original design included two intervention modalities (elastic band training and aquatic-based training), both were designed to induce adaptations characteristic of power training through movements performed with high-velocity intent. An RPE-1 of 4 was prescribed for the active muscles, and sets were terminated when a value of 6 was reached or when the prescribed 8 repetitions were completed. This resistance corresponds to approximately 70% of one-repetition maximum (1RM) and was intended to be moved with maximal velocity (Colado et al., 2025). Accordingly, both modalities were designed to present structural equivalence in terms of volume, relative intensity, and training organization, in order to enhance comparability of the applied stimulus, despite the inherent differences related to the training environment and equipment.

Specific methodological aspects of the training program

For both the elastic band intervention (CLX looped elastic bands; TheraBand, Hygenic Corporation, Akron, Ohio, USA) and the aquatic-based training, multi-joint exercises involving both upper and lower limbs were performed throughout the full range of motion, always ensuring safe and controlled execution.

Aquatic training was conducted in an indoor pool with water depth approximately at chest level. Initially, resistance was generated through interaction with the water itself. When it was necessary to increase exercise resistance in the aquatic environment to reach target perceived exertion levels, hydrodynamic resistance devices (Leisis S.L., Valencia, Spain) were used, thereby increasing the surface area and, consequently, the external load (Colado & Triplett, 2009). In contrast, resistance during elastic band exercises was individually adjusted by modifying band tension (initial length, elongation, number of bands, and resistance level to deformation) (Colado et al., 2009, 2012).

Control groups

Participants assigned to the control groups (with and without supplementation) did not perform any training program during the intervention period and only participated in the pre- and post-intervention assessments under the same conditions as the experimental groups.

Supplementation protocol

Participants were randomly assigned to receive either creatine supplementation or placebo from the beginning of the intervention. The creatine group received a daily dose of 3 g of creatine monohydrate combined with excipients (CreaTrust™, Icen Cognis, Santa Cruz de Tenerife, Spain), whereas the placebo group consumed an equivalent amount of maltodextrin and excipients. CreaTrust™ is an external third-party tested creatine solution demonstrating >99% purity, strict microbiological and heavy metals compliance, and the highest standards for limiting contaminants such as dicyandiamide (DCD), dihydrotriazine (DHT), and creatinine. The creatine dose (3 $g \cdot day^{-1}$) was established in accordance with current safety recommendations for long-term use in adult populations and was considered an appropriate and safe dosage within the context of the present study. Supplements were indistinguishable in appearance and taste and were administered once daily, dissolved in water, to ensure adherence and participant blinding. Supplement

intake was scheduled in the morning, based on previous evidence indicating that timing of ingestion does not significantly influence chronic training adaptations. This protocol has been shown to be safe and effective in older adult populations, supporting its application in the present study (Candow et al., 2025).

Adherence and safety

Adherence to the training program was assessed by recording attendance at training sessions (number of sessions completed relative to the total prescribed). Adherence to supplementation was monitored through self-reported logs. Adverse events were systematically recorded throughout the entire intervention period. Study completion rate was defined as the proportion of participants who completed the post-intervention assessments.

Statistical analysis

Statistical analyses were performed using specialized statistical software (SPSS, version 29.0.2.0; IBM Corp., Armonk, NY, USA), with the level of statistical significance set at $p \leq .05$. Quantitative variables were expressed as mean ± standard deviation. Data normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated using Levene's test.

To examine the effects of training and its potential modulation by sex, mixed-design analysis of variance (ANOVA) models were applied, with time (pre vs. post) as the within-subject factor and sex (men vs. women) and study group (training vs. control) as between-subject factors. Particular emphasis was placed on interaction terms involving sex, as the primary objective of the study was to determine whether adaptive responses differed between men and women. This approach allowed the assessment of the main effects of time, sex, and group, as well as the interaction effects "*time x sex*," "*time x group*," and "*time x sex x group*" on the dependent variables (isokinetic strength, BDNF, IL-6, TNF-α, and GPx). Additionally, the potential effect of supplementation (creatine vs. placebo) and its interactions with time and sex were explored through secondary analyses. Since both training modalities were grouped under a single analytical category of "*power training*," modality was not included as a factor in the primary model. However, its potential influence was explored preliminarily, with no relevant main effects or interactions observed in the analyzed variables.

When significant effects were observed, post hoc comparisons were performed using the least significant difference (LSD) test. This approach was selected because the analyses were guided by a priori hypotheses concerning sex-related and supplementation-related responses, and because the study aimed to maximize sensitivity for detecting potentially meaningful differences within a multifactorial intervention design. To minimize overinterpretation, statistical significance was interpreted together with effect sizes (η^2p and Hedges' g) and the overall consistency of the observed response patterns. Effect sizes for the ANOVA models were estimated using partial eta squared (η^2p) and interpreted as small (≥.01), moderate (≥.06), and large (≥.14). Additionally, effect sizes based on standardized mean differences (Hedges' g) were calculated. Hedges' g values were interpreted according to the criteria proposed by Cohen (1988): trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), and large (≥0.80). Furthermore, values greater than 1.20 were considered very large, in line with thresholds commonly used in sport and exercise sciences. When necessary, an intention-to-treat analysis was applied.

Sample size determination

Sample size was estimated through an a priori power analysis performed with G*Power software (version 3.1.9.3; Heinrich-Heine-University, Düsseldorf, Germany), assuming a repeated-measures ANOVA model with interaction between factors, a moderate effect size (f = 0.20), a significance level of α = .05, and a statistical power of 80%. Based on this estimation, an initially balanced allocation of approximately 20

participants per group was planned, in accordance with the factorial design of the study (six experimental groups derived from the combination of training modality and supplementation). However, given that one of the aims of the study was to analyze the overall effect of the training stimulus, and considering that no significant differences between modalities or "*modality x time*" interactions were observed, the training conditions were subsequently combined for analytical purposes. As a result, the effective sample size for the main comparisons increased to approximately 40 participants in each of the training conditions (with supplementation and placebo), while the control groups retained sample sizes close to those initially planned. Finally, the sample included in the analyses consisted of 99 participants distributed across the different study conditions (see the following section). This approach allowed optimization of statistical power to detect the main effects of training while maintaining the validity of the experimental design.

RESULTS

To facilitate interpretation of the multiple subgroup comparisons, the most relevant findings are summarized as follows: (i) power training induced significant improvements in neuromuscular performance, BDNF, IL-6, and GPx; (ii) sex-related differences were more evident in neuromuscular performance and BDNF responses than in inflammatory or antioxidant markers; (iii) creatine supplementation exerted selective and non-uniform effects across outcomes, although training remained the primary determinant of adaptation; and (iv) the magnitude and pattern of adaptation were not entirely homogeneous between men and women.

Participant flow and baseline characteristics

Of the 150 individuals initially assessed, 120 met the eligibility criteria and initiated the intervention. Participants were randomly assigned to one of the six study groups, including elastic band training and aquatic-based training modalities, as well as conditions with and without supplementation. Given that no significant differences between training modalities or "*modality x time*" interactions were observed, both conditions were subsequently considered as a single training stimulus for analytical purposes. As a result, participants were grouped into four final conditions: training with supplementation, training with placebo, control with supplementation, and control with placebo. During the course of the study, some participants were lost to follow-up, mainly due to personal, logistical, and/or health-related reasons not associated with the intervention. The final number of participants who successfully completed the 16-week intervention and their baseline descriptive characteristics are presented in Table 1.

Table 1. Baseline characteristics.

	ES (17♂; 19♀)	EP (16♂; 17♀)	CS (7♂; 7♀)	CP (7♂; 9♀)
Age (years)				
♂	68.36 (4.95)	68.31 (4.89)	65.43 (5.13)	68.00 (3.56)
♀	68.43 (3.59)	67.22 (4.57)	68.50 (6.07)	70.67 (5.48)
Body fat (%)				
♂	27.28 (7.49)	31.42 (6.17)	30.59 (7.79)	38.25 (9.71)
♀	37.60 (6.29)	35.27 (5.75)	35.45 (9.15)	34.16 (8.65)
Handgrip strength (kg)				
♂	40.50 (5.30)	41.00 (5.98)	26.21 (6.20)	35.50 (8.17)
♀	24.04 (5.32)	23.25 (4.42)	22.62 (2.79)	23.4 (3.68)

Note. Values are expressed as mean ± standard deviation (SD). ♂: men; ♀: women. Abbreviations: ES: training + supplementation; EP: training + placebo; CS: control + supplementation; CP: control + placebo.

No significant differences were detected between groups in baseline characteristics, including demographic variables, dietary intake, and physical activity levels (all $p > .05$), supporting the initial comparability between conditions. A post hoc statistical power analysis ($\alpha = .05$) was conducted to evaluate the study's ability to detect between-group differences based on the final analyzed sample. The results suggest adequate

statistical power for the main variables, particularly those associated with moderate to large effect sizes. However, for variables with high biological variability and for sex-stratified analyses, statistical power may have been limited, which should be considered when interpreting the results.

Feasibility and safety of the program

Overall, the intervention demonstrated high feasibility, as reflected by satisfactory attendance and adherence to both the exercise program and the supplementation protocol. No relevant adverse events associated with the intervention were reported during the study period. Additionally, no clinically relevant side effects related to supplementation were identified during routine monitoring. Taken together, these findings suggest that the intervention was well tolerated by the participants.

Main interactions and training effects

The primary analyses focused on determining whether adaptive responses to power training differed between men and women. Accordingly, particular attention was paid to the "*time* × *sex* × *group*" interactions, whereas overall training effects are presented as contextual findings. No significant effects of training modality were observed for any of the main variables, and no significant "*modality x time*" interactions were detected (all $p > .05$), supporting the decision to analyze both conditions as a single training stimulus. In contrast, a statistically significant "*time x group*" interaction was observed for all analyzed variables following the unification of both modalities, indicating differences in temporal changes between the intervention and control groups. The results of the repeated-measures ANOVA for each variable were as follows: isokinetic knee extensor strength at an angular velocity of 180°/s ($F(3, 91) = 46.03$, $p \leq .05$, $\eta p^2 = .60$), BDNF ($F(3, 91) = 14.03$, $p \leq .05$, $\eta p^2 = .32$), IL-6 ($F(3, 91) = 37.06$, $p \leq .05$, $\eta p^2 = .55$), TNF-α ($F(3, 91) = 16.95$, $p \leq .05$, $\eta p^2 = .36$), and GPx ($F(3, 91) = 25.68$, $p \leq .05$, $\eta p^2 = .46$). Post hoc comparisons revealed relevant findings. Detailed inter- and intra-group results, as well as sex-specific analyses, including percentage changes and effect sizes, are presented in Tables 2-6. The most relevant findings are highlighted below.

Table 2. Effects of training and creatine supplementation on isokinetic knee extensor strength at 180°/s: sex-specific analysis.

	Pre (mean ± DE)	Post (mean ± DE)	Δ%	*p*-val.	ES (g)	Significant between-group comparisons	*p*-val.	ES (g)
Group 1. ES	59.14 (17.06)	88.65 (18.33)	49.93	<.001	1.72	Group 1 vs 2 Group 1 vs 3 Group 1 vs 4	.02 <.001 <.001	0.37 1.73 1.09
MTS n = 13	71.50 (15.20)	102.77 (15.72)	43.73	<.001	2.07	Group MTS vs WTS	<.001	1.48
WTS n = 23	52.152 (13.98)	80.67 (14.68)	54.46	<.001	2.04			
Group 2. EP	56.23 (16.76)	80.59 (21.45)	43.35	<.001	1.36	Group 2 vs 3 Group 2 vs 4	<.001 <.001	1.19 0.85
MTP n = 15	65.54 (18.64)	97.09 (18.53)	48.15	<.001	1.70	Group MTP vs WTP	<.001	1.72
WTP n = 18	48.47 (10.12)	66.84 (11.97)	37.95	<.001	1.67			
Group 3. CS	55.41 (12.51)	59.68 (15.68)	7.70	.11	0.29			
MCS n = 7	59.36 (13.36)	63.59 (16.10)	7.12	.26	0.27			
WCS n = 7	51.46 (11.15)	55.77 (15.43)	8.37	.25	0.30			
Group 4. CP	61.97 (23.30)	61.19 (23.64)	-1.26	.73	-0.03			
MCP n = 7	71.06 (16.10)	69.43 (19.01)	-2.29	.67	-0.009	Group MCP vs WCP	.09	0.86
WCP n = 9	54.91 (26.37)	54.78 (25.90)	-0.24	.97	-0.01			

Note. Values are expressed as mean ± standard deviation (SD). Isokinetic strength is expressed in N·m. Δ%: percentage change relative to baseline. Between-group comparisons were derived from the "time x group" and "time x group x sex" interactions obtained from repeated-measures ANOVA, followed by post hoc analyses to identify specific differences between conditions. Results are presented with their corresponding p-values and effect sizes. Effect size (g): calculated using Hedges' g and interpreted as follows: trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), large (0.80–1.19), and very large (≥1.20). Abbreviations: ES: training + supplementation; EP: training + placebo; CS: control + supplementation; CP: control + placebo; MTS: men training + supplementation; WTS: women training + supplementation; MTP: men training + placebo; WTP: women training + placebo; MCS: men control + supplementation; WCS: women control + supplementation; MCP: men control + placebo; WCP: women control + placebo.

Table 3. Effects of training and creatine supplementation on brain-derived neurotrophic factor (BDNF) levels: sex-specific analysis.

	Pre (mean ± DE)	Post (mean ± DE)	Δ%	*p*-val.	ES (g)	Significant between-group comparisons	*p*-val.	ES (g)
Group 1. ES	39148.94 (8351.87)	43788.14 (10650.59)	+11.85	<.001	0.47	Group 1 vs 4	.03	0.07
MTS n = 13	36114.50 (5936.32)	39046.71 (8599.12)	+8.12	.03	0.37	Group MTS vs WTS	.05	0.71
WTS n = 23	40864.06 (9123.26)	46468.07 (10924.21)	+13.71	<.001	0.54			
Group 2. EP	38247.10 (11822.61)	41748.60 (12490.02)	+9.15	<.001	0.28	Group 2 vs 4	.02	0.10
MTP n = 15	33524.79 (12250.97)	36159.58 (12394.03)	+7.86	.03	0.20	Group MTP vs WTP	.01	0.87
WTP n = 18	42182.35 (10170.04)	46406.12 (10798.76)	+10.01	<.001	0.38			
Group 3. CS	38273.44 (9505.09)	35776.47 (6477.53)	-6.52	.03	-0.29			
MCS n = 7	36564.47 (9725.71)	34537.70 (7361.03)	-5.54	.21	-0.20			
WCS n = 7	39982.42 (9713.25)	37015.25 (5757.14)	-7.42	.066	-0.32			
Group 4. CP	39113.32 10698.64	36594.27 10236.03	-6.44	.02	-0.23			
MCP n = 7	34835.45 (7650.83)	33082.82 (7921.19)	-5.03	.25	-0.20			
WCP n = 9	42440.54 (11926.69)	39325.39 (11411.23)	-7.34	.02	-0.24			

Note. Values are expressed as mean ± standard deviation (SD). BDNF is expressed in pg/mL. Δ%: percentage change relative to baseline. Between-group comparisons were derived from the "time x group" and "time x group x sex" interactions obtained from repeated-measures ANOVA, followed by post hoc analyses to identify specific differences between conditions. Results are presented with their corresponding p-values and effect sizes. Effect size (g): calculated using Hedges' g and interpreted as follows: trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), large (0.80–1.19), and very large (≥1.20). Abbreviations: ES: training + supplementation; EP: training + placebo; CS: control + supplementation; CP: control + placebo; MTS: men training + supplementation; WTS: women training + supplementation; MTP: men training + placebo; WTP: women training + placebo; MCS: men control + supplementation; WCS: women control + supplementation; MCP: men control + placebo; WCP: women control + placebo.

Table 4. Effects of training and creatine supplementation on interleukin-6 (IL-6) levels: sex-specific analysis.

	Pre (mean ± DE)	Post (mean ± DE)	Δ%	*p*-val.	ES (g)	Significant between-group comparisons	*p*-val.	ES (g)
Group 1. ES	15.02 (3.77)	10.72 (2.52)	-28.63	<.001	-1.39	Group 1 vs 3 Group 1 vs 4	<.001 <.001	1.43 1.66
MTS n = 13	16.03 (4.12)	11.62 (2.72)	-27.51	<.001	-1.27			
WTS n = 23	14.45 (3.53)	10.21 (2.30)	-29.34	<.001	-1.51			
Group 2. EP	14.80 (4.81)	11.57 (3.24)	-21.82	<.001	-0.80	Group 2 vs 3 Group 2 vs 4	<.001 <.001	1.06 1.16
MTP n = 15	15.41 (5.04)	11.79 (3.94)	-23.49	<.001	-0.75			
WTP n = 18	14.30 (4.69)	11.38 (2.62)	-20.42	<.001	-0.86			
Group 3. CS	14.23 (3.63)	15.59 (4.71)	+9.56	.12	0.34			
MCS n = 7	13.42 (3.66)	14.92 (5.00)	+11.18	.22	0.30			
WCS n = 7	15.05 (3.69)	16.26 (4.70)	+8.04	.22	0.27			
Group 4. CP	10.37 (3.13)	15.43 (3.29)	+48.79	<.001	1.56			
MCP n = 7	10.61 (3.44)	15.70 (3.42)	+47.97	<.001	1.50			
WCP n = 9	10.19 (3.08)	15.22 (3.39)	+49.36	<.001	1.61			

Note. Values are expressed as mean ± standard deviation (SD). IL-6 is expressed in pg/mL. Δ%: percentage change relative to baseline. Between-group comparisons were derived from the "time x group" and "time x group x sex" interactions obtained from repeated-measures ANOVA, followed by post hoc analyses to identify specific differences between conditions. Results are presented with their corresponding p-values and effect sizes. Effect size (g): calculated using Hedges' g and interpreted as follows: trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), large (0.80–1.19), and very large (≥1.20). Abbreviations: ES: training + supplementation; EP: training + placebo; CS: control + supplementation; CP: control + placebo; MTS: men training + supplementation; WTS: women training + supplementation; MTP: men training + placebo; WTP: women training + placebo; MCS: men control + supplementation; WCS: women control + supplementation; MCP: men control + placebo; WCP: women control + placebo.

Table 5. Effects of training and creatine supplementation on tumour necrosis factor alpha (TNF-α) levels: sex-specific analysis.

	Pre (mean ± DE)	Post (mean ± DE)	Δ%	*p*-val.	ES (g)	Significant between-group comparisons	*p*-val.	ES (g)
Group 1. ES	3.31 (0.50)	2.86 (0.57)	-13.59	<.01	-0.84			
MTS n = 13	3.23 (0.58)	2.78 (0.58)	-13.93	<.01	-0.78			
WTS n = 23	3.35 (0.45)	2.91 (0.57)	-13.13	<.01	-0.89			
Group 2. EP	3.22 (0.47)	2.98 (0.51)	-7.45	<.01	-0.47			
MTP n = 15	3.19 (0.45)	2.88 (0.42)	-9.72	<.01	-0.69			
WTP n = 18	3.24 (0.49)	3.06 (0.57)	-5.55	.01	-0.32			
Group 3. CS	2.64 (0.41)	2.59 (0.32)	-1.89	.51	-0.11	Group 3 vs 4	.01	1.18
MCS n = 7	2.64 (0.54)	2.56 (0.40)	-3.03	.42	-0.15			
WCS n = 7	2.63 (0.27)	2.62 (0.24)	-0.38	.89	-0.06			
Group 4. CP	2.63 (0.47)	2.73 (0.37)	3.80	.14	0.24			
MCP n = 7	2.64 (0.52)	2.65 (0.52)	0.38	.91	0.02			
WCP n = 9	2.62 (0.47)	2.79 (0.22)	6.49	.04	0.46			

Note. Values are expressed as mean ± standard deviation (SD). TNF-α is expressed in pg/mL. Δ%: percentage change relative to baseline. Between-group comparisons were derived from the "time x group" and "time x group x sex" interactions obtained from repeated-measures ANOVA, followed by post hoc analyses to identify specific differences between conditions. Results are presented with their corresponding p-values and effect sizes. Effect size (g): calculated using Hedges' g and interpreted as follows: trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), large (0.80–1.19), and very large (≥1.20). Abbreviations: ES: training + supplementation; EP: training + placebo; CS: control + supplementation; CP: control + placebo; MTS: men training + supplementation; WTS: women training + supplementation; MTP: men training + placebo; WTP: women training + placebo; MCS: men control + supplementation; WCS: women control + supplementation; MCP: men control + placebo; WCP: women control + placebo.

Table 6. Effects of training and creatine supplementation on glutathione peroxidase (GPx) levels: sex-specific analysis.

	Pre (mean ± DE)	Post (mean ± DE)	Δ%	*p*-val.	ES (g)	Significant between-group comparisons	*p*-val.	ES (g)
Group 1. ES	207.38 (38.33)	242.61 (37.25)	16.99	<.001	0.93	Group 1 vs 3 Group 1 vs 4	.002 .05	1.25 0.68
MTS n = 13	199.88 (33.21)	238.08 (39.06)	19.11	<.001	1.05			
WTS n = 23	211.61 (41.04)	245.18 (36.84)	15.86	<.001	0.86			
Group 2. EP	217.81 (49.62)	235.92 (49.03)	8.31	<.001	0.37			
MTP n = 15	211.98 (41.76)	228.06 (41.18)	7.59	.01	0.39			
WTP n = 18	222.67 (56.07)	242.47 (55.04)	8.89	.001	0.36			
Group 3. CS	209.07 (28.72)	193.02 (18.34)	-7.68	.01	-0.67			
MCS n = 7	217.91 (31.56)	194.55 (18.26)	-10.72	.01	-0.91			
WCS n = 7	200.24 (24.69)	191.49 (19.74)	-4.37	.33	-0.39			
Group 4. CP	227.40 (36.75)	209.08 (32.46)	-8.06	.002	-0.53			
MCP n = 7	225.26 (30.02)	202.11 (17.71)	-10.28	.01	-0.95			
WCP n = 9	229.07 (43.01)	214.50 (40.80)	-6.36	.07	-0.35			

Note. Values are expressed as mean ± standard deviation (SD). GPx is expressed in μIU/mL. Δ%: percentage change relative to baseline. Between-group comparisons were derived from the "time x group" and "time x group x sex" interactions obtained from repeated-measures ANOVA, followed by post hoc analyses to identify specific differences between conditions. Results are presented with their corresponding p-values and effect sizes. Effect size (g): calculated using Hedges' g and interpreted as follows: trivial (<0.20), small (0.20–0.49), moderate (0.50–0.79), large (0.80–1.19), and very large (≥1.20). Abbreviations: ES: training + supplementation; EP: training + placebo; CS: control + supplementation; CP: control + placebo; MTS: men training + supplementation; WTS: women training + supplementation; MTP: men training + placebo; WTP: women training + placebo; MCS: men control + supplementation; WCS: women control + supplementation; MCP: men control + placebo; WCP: women control + placebo.

In isokinetic knee extensor strength at an angular velocity of 180°/s, both training groups showed statistically significant differences compared to the control groups, with large to very large effect sizes. Additionally, the magnitude of change was slightly greater in the creatine-supplemented training group compared to the non-supplemented group (p = .02; g = 0.37). Regarding sex differences, within the creatine-supplemented training group, women exhibited a significantly greater change than men (p < .001; g = 1.48). In contrast, in the non-supplemented groups, an opposite pattern was observed, with greater increases in men in both the training group (p < .001; g = 1.72) and the control group, where a trend toward statistical significance was observed (p = .09; g = 0.86).

With respect to BDNF, both training groups showed significant differences compared to the non-supplemented control group (p = .03, g = 0.07; and p = .02, g = 0.10, respectively). Regarding sex differences, in both training groups, women exhibited greater changes compared to men (p = .05, g = 0.71; and p = .01, g = 0.87, respectively). For IL-6, both training groups showed statistically significant differences compared to the control groups, with large to very large effect sizes. In contrast, for TNF-α, a significant difference was observed between the creatine-supplemented control group and the non-supplemented control group (p = .01; g = 1.18).

DISCUSSION

The primary aim of the present study was to determine whether sex modulates neuromuscular and biological adaptations to power training in older adults, while the potential influence of creatine supplementation was explored as a secondary objective. The results obtained confirm that power training constitutes a highly effective stimulus for inducing functional and biological adaptations in this population. Importantly, however, the findings suggest that these adaptations were not entirely homogeneous between men and women, with sex-related differences being more evident in neuromuscular performance and neurotrophic responses than in inflammatory or antioxidant markers. In addition, creatine supplementation exerted selective and non-uniform effects across outcomes, acting as a complementary rather than a primary determinant of adaptation. Beyond these differences, the observed adaptations appear to emerge from a complex interaction between neuromuscular, neurotrophic, inflammatory, and antioxidant systems, thereby supporting the proposed hypothesis and reinforcing the concept that physical exercise acts as a multisystem modulator in aging (Liu & Latham, 2009). This integrative perspective is key, as aging should not be understood as an isolated decline of individual systems, but rather as a progressive disruption of homeostasis among them (Clark & Manini, 2012).

Neuromuscular adaptations: Functional relevance

The improvements observed in neuromuscular performance, particularly under high-velocity conditions, reinforce the role of power training as a central strategy for preserving functionality in older adults. In the present study, the increases in isokinetic strength at 180°/s reflect a specific adaptation in the ability to generate force rapidly, a quality closely linked to performance in functional tasks. Unlike maximal strength, power incorporates the temporal dimension of force production, making it a more transferable capacity to actions such as rising from a chair or recovering balance (Reid & Fielding, 2012). In this regard, current evidence consistently indicates that power declines earlier and to a greater extent than strength with aging, establishing it as a critical functional variable (Mahato et al., 2024). From a comparative perspective, the magnitude of the observed changes is consistent with recent meta-analyses in older adults, which report moderate to large effects on neuromuscular variables when the stimulus includes velocity components (Hortobágyi et al., 2023). In this context, our findings not only align with the literature but also reinforce the notion that power-oriented training can optimize functional adaptations even in the absence of maximal loads, promoting greater neuromechanical efficiency.

Since the primary objective of the study was to examine sex-related modulation, the most relevant finding is not the existence of training-induced improvements per se, but rather the observation that the magnitude and pattern of some adaptations differed between men and women. Specifically, although both men and women exhibited significant improvements in neuromuscular capacity, clear differences were observed in the magnitude and pattern of response. Under creatine supplementation, women showed greater relative increases in isokinetic strength compared to men, whereas in the absence of supplementation, an opposite pattern emerged, with greater adaptations in men. These results suggest that sex may modulate the adaptive

response to power training, and that this modulation could be influenced by supplementation status. This differential pattern is consistent with previous evidence indicating that adaptations to resistance training may not be entirely homogeneous between sexes (Hunter, 2014). However, the mechanisms underlying these differences were not directly assessed in the present study and therefore should be interpreted with caution.

In this context, creatine supplementation appears to act as a complementary and potentially relevant modulator of the adaptive response, although its effects were not uniform across outcomes. The greater increases observed in the supplemented groups suggest a potential additive or synergistic effect with power training, which is consistent with literature demonstrating its capacity to enhance phosphocreatine availability and ATP resynthesis during high-intensity efforts (Candow et al., 2021; Kreider et al., 2017). However, the fact that this effect appeared to be more pronounced in women within the present dataset introduces a potentially relevant perspective, suggesting that the response to creatine may not be uniform across sexes, particularly in older adults. One possible explanation for the observed differences is that factors previously associated with resistance training adaptations, such as motor-unit recruitment, neural firing behavior, intermuscular coordination may have contributed to the adaptive response (Hortobágyi et al., 2023). However, these variables were not directly assessed in the present study and therefore any mechanistic interpretation remains speculative. Additionally, creatine may have contributed to maintaining execution quality throughout training sessions, allowing for a more effective neuromuscular stimulus (Kreider et al., 2017). These mechanisms are particularly relevant in aging, where processes such as denervation and incomplete reinnervation compromise motor control quality (Clark & Manini, 2012). Indeed, the ability to generate force rapidly may be more determinant than maximal strength for maintaining functionality. In line with this, recent evidence indicates that the loss of muscle power is one of the main determinants of functional decline in older adults (Tøien et al., 2025). Thus, the adaptations observed in the present study have significant clinical relevance, as they are achieved through submaximal stimuli that may reduce mechanical and cardiovascular stress, thereby enhancing their applicability in older populations.

Overall, the results suggest that the combination of power training and creatine supplementation may represent an effective strategy to optimize neuromuscular function in older adults, albeit with relevant nuances depending on sex. This approach not only maximizes transfer to the functional demands of daily living but also supports the development of more individualized interventions, in which both mechanical stimulus and nutritional support are tailored to the specific characteristics of each individual.

Biological adaptations: Neuroplasticity, inflammation, and antioxidant defense

One of the most relevant contributions of the present study is the inclusion of biological markers that allow the interpretation of exercise-induced adaptations from a systemic perspective. In this regard, the changes observed in BDNF, IL-6, TNF-α, and GPx suggest that power training induces adaptations that extend beyond the musculoskeletal system and involve processes related to neuroplasticity, inflammatory regulation, and antioxidant defense.

In line with this, the present study demonstrated that power training induced significant increases in BDNF levels in older adults, confirming the role of exercise as a central stimulus of the neurotrophic response. These increases were observed in both the creatine-supplemented training group and the placebo training group, whereas both control groups showed decreases in this variable. Taken together, this pattern reinforces the notion that exercise is the primary determinant of BDNF enhancement, consistent with literature identifying physical activity as one of the most potent modulators of neurotrophic response, neuronal survival, and brain plasticity in older adults (Erickson et al., 2011). From a comparative perspective, the results also suggest that creatine supplementation may exert a modest and potentially beneficial effect on this response.

Although between-group differences relative to the non-supplemented control reached small effect sizes, the direction of change was systematically more favorable in the supplemented group, pointing toward a potential additional contribution of creatine when combined with training. This interpretation should be considered with caution, as the magnitude of the effect was small, but it remains physiologically plausible given that creatine may improve cellular energy availability and indirectly support signaling processes associated with neural plasticity (Pedersen, 2019; Müller et al., 2020).

A particularly relevant aspect of the present study, in line with its primary objective, is that the BDNF response exhibited nuances according to sex. In both training groups, women showed greater percentage changes compared to men, in both the supplemented and non-supplemented conditions. Although these findings should not be interpreted as an absolute divergence between sexes, they do suggest that sex may act as a modulator of the neurotrophic response to training in older adults. This possibility is consistent with previous evidence linking BDNF regulation to hormonal factors, particularly estrogens, as well as to differences in body composition, metabolism, and physiological environment (Scharfman & MacLusky, 2006).

In this context, it is particularly noteworthy that the relative superiority observed in women was maintained both in the presence and absence of creatine, although it appeared to be more pronounced in the supplemented group. This may suggest that creatine does not generate an entirely independent response pattern but rather amplifies an adaptive trend already present under the training stimulus. Previous literature has proposed that exercise-induced increases in BDNF may involve mechanisms related to muscle–brain communication and cellular energy regulation, including pathways such as PGC-1α/FNDC5 (Pedersen, 2019). However, these pathways were not evaluated in the present study and therefore should be considered as possible theoretical explanations rather than mechanisms demonstrated by the current data.

Complementarily, the decline observed in the control groups further reinforces the importance of physical stimulus as a protective factor against age-related neurobiological deterioration. The fact that the absence of training was associated with reductions in BDNF levels is consistent with evidence describing a progressive decline of this biomarker in aging and sedentary contexts, both of which are closely linked to cognitive decline and reduced adaptive capacity of the nervous system (Mattson & Arumugam, 2018). From an applied perspective, this suggests that training not only actively enhances the neurotrophic environment but may also help attenuate the downward trajectory associated with aging. Overall, the results of the present study indicate that power training constitutes the primary stimulus for improving BDNF levels in older adults, while creatine supplementation may provide an additional, albeit modest, benefit. At the same time, the observed differences between men and women suggest that the neurotrophic response to exercise may not be entirely homogeneous across sexes, adding an element of originality and relevance to the study. From a clinical and translational perspective, these findings support the use of power training interventions to promote a more favorable biological environment for brain plasticity in aging, while also opening the door to more individualized strategies that consider both nutritional support and the potential modulatory role of sex.

With regard to the inflammatory response, the results of the present study show a marked reduction in IL-6 levels in the groups subjected to power training, with large to very large effect sizes, both in the supplementation and placebo conditions. In contrast, the control groups exhibited increases in this cytokine, particularly in the non-intervention condition, where large effects were observed. This pattern reinforces the notion that training acts as a potent modulator of systemic inflammatory status in older adults, in line with evidence identifying regular physical exercise as an effective strategy to reduce basal levels of pro-inflammatory cytokines and improve the inflammatory profile during aging (Gleeson et al., 2011).

A relevant finding, consistent with the primary objective of the study, is that the IL-6 response was not entirely homogeneous across sexes. However, these differences should be interpreted with caution, as no statistically significant differences were detected between men and women. Descriptively, a tendency toward greater reductions in women was observed, particularly in the creatine-supplemented group, whereas this pattern was not consistent across the remaining conditions. These findings suggest that, although a sex-dependent modulation of the inflammatory response to training may exist, the evidence obtained in the present study does not allow firm conclusions to be drawn. In this regard, it is possible that sample size or interindividual variability limited the detection of significant sex differences. From a physiological perspective, previous literature has suggested that differences in immunoendocrine regulation or in the interaction between hormonal and inflammatory systems may contribute to variability in inflammatory responses (Straub, 2007). However, these mechanisms were not directly assessed in the present study and therefore should be interpreted as possible explanatory hypotheses rather than mechanisms demonstrated by the current data. In older populations, where hormonal differences tend to be attenuated, such effects may be more subtle and context-dependent.

Regarding the role of supplementation, although training explains most of the observed reduction in IL-6, the groups receiving creatine showed a tendency toward greater positive effects compared to the placebo groups. This finding suggests a potential additional modulatory effect of creatine on the inflammatory response, albeit of smaller magnitude. While evidence regarding its direct effects on inflammatory markers remains limited and heterogeneous, creatine has been proposed to contribute to improved cellular homeostasis and reduced metabolic stress, which may indirectly promote a less pro-inflammatory environment (Arazi et al., 2021). Nevertheless, within the context of the present study, this effect appears clearly secondary to the impact of training.

Taken together, the results suggest that the modulation of systemic inflammation may represent one of the primary mechanisms through which power training induces beneficial adaptations in older adults. The magnitude of the changes observed in IL-6, greater than those reported for BDNF, suggests that inflammatory adaptations may precede or even facilitate improvements in the neurotrophic response. This relationship is consistent with evidence describing a close interaction between the immune and nervous systems, whereby the reduction of a pro-inflammatory environment supports processes of brain plasticity and adaptation (Gleeson et al., 2011; Mattson & Arumugam, 2018; Pedersen, 2019). In this sense, the findings of the present study reinforce an integrated view of exercise as a multisystem modulator, in which inflammatory and neurotrophic responses do not operate in isolation but rather in a coordinated manner.

With regard to TNF-α, the results of the present study showed changes of lower magnitude and consistency compared to those observed for IL-6. Although reductions were identified in some of the power training groups, these changes did not follow a uniform pattern across conditions, and the control groups exhibited minor variations, including slight increases in the absence of intervention, particularly in the non-supplemented group. Overall, these findings suggest that the TNF-α response to training is more moderate and variable. This behavior is consistent with previous literature indicating that different cytokines exhibit differential sensitivity to exercise, with TNF-α being less dynamic and more stable compared to IL-6 (Gleeson et al., 2011). In this sense, whereas IL-6 responds more markedly to training stimuli, TNF-α may reflect more subtle changes in basal inflammatory status, making it more difficult to detect consistent effects in interventions of limited duration or with moderate sample sizes (Petersen & Pedersen, 2005).

Regarding sex, no statistically significant differences were observed in TNF-α response between men and women. Although some descriptive variations in the magnitude of change were noted, these did not follow a

consistent pattern across groups nor reach statistical significance; therefore, no modulatory effect of sex on this variable can be established in the present study. As for creatine supplementation, a significant change was observed in the supplemented control group compared to its non-supplemented counterpart, suggesting a potential effect independent of training. However, this finding should be interpreted with caution, as no consistent pattern was observed across the remaining groups nor a clear interaction with the training stimulus. In this regard, although creatine has been proposed to indirectly influence the inflammatory response through improvements in cellular energy metabolism (Arazi et al., 2021), the results of the present study do not support a clear modulatory role on TNF-α.

Taken together, the findings for TNF-α reinforce the notion that the inflammatory response to power training in older adults is not uniform across its components. While IL-6 showed a clear and consistent adaptation, TNF-α exhibited a more heterogeneous response, suggesting that different inflammatory pathways may respond differentially to the exercise stimulus (Gleeson et al., 2011). This divergence highlights the need to interpret systemic inflammation from an integrated and multidimensional perspective, avoiding extrapolations based on a single marker.

With regard to antioxidant defense, the results of the present study show that power training induces significant increases in GPx activity in older adults. The group that performed training without supplementation exhibited significant improvements, indicating that exercise alone is sufficient to induce adaptations in the endogenous antioxidant system. This pattern is consistent with literature describing physical exercise as a hormetic stimulus, capable of inducing a transient increase in oxidative stress that, in turn, activates adaptive antioxidant mechanisms, including the regulation of antioxidant enzymes such as GPx (Ji et al., 2016).

From a sex-based perspective, no statistically significant differences were observed in GPx response between men and women. Although descriptively men showed slightly higher effect sizes, the response was consistent across both sexes, suggesting that adaptation of the antioxidant system to training occurs similarly in this population (Refalo et al., 2025; Hawley et al., 2023). These small variations should be interpreted with caution and may be influenced by uncontrolled individual factors.

Regarding supplementation, the group combining training with creatine showed greater increases in GPx activity compared to the placebo training group, suggesting a potential additional effect when both stimuli are combined. However, given that exercise alone already induces significant improvements, the specific contribution of supplementation should be interpreted cautiously, being consistent with the notion of an enhancing rather than a determining effect. Post-intervention between-group analyses support this interpretation, showing higher values in the supplemented training group compared to control groups, as well as favorable differences of the placebo training group relative to at least one control condition. In contrast, control groups exhibited reductions in GPx activity regardless of supplementation condition, suggesting that nutritional intervention alone is insufficient to induce improvements in antioxidant defense in the absence of physical stimulus. This finding is consistent with evidence describing a progressive decline in endogenous antioxidant capacity with aging (Gómez-Cabrera et al., 2008).

Overall, the results indicate that enhancement of antioxidant defense represents one of the most consistent biological adaptations induced by power training in older adults, with a potential additional effect of supplementation. This adaptation may contribute to protection against age-related oxidative damage and to the optimization of the physiological environment necessary for other adaptations, such as those observed at the neuromuscular and neurotrophic levels (Gómez-Cabrera et al., 2008; Ji et al., 2016; Mattson &

Arumugam, 2018). In this sense, the findings of the present study reinforce the importance of addressing aging from an integrative perspective, in which antioxidant, inflammatory, and neuromuscular adaptations interact in a coordinated manner.

Practical applications

The results of the present study indicate that power training represents an effective and feasible strategy to improve both neuromuscular function and biological profile in older adults, even without the use of maximal loads. In particular, the improvements observed in high-velocity isokinetic strength support the inclusion of exercises performed with maximal intended velocity within function-oriented programs, given their greater transfer to activities of daily living. Moreover, the different response patterns observed across sexes suggest that, although the overall training structure may be similar, the monitoring and interpretation of adaptations should incorporate an individualized perspective. From a biological standpoint, the changes observed in BDNF, IL-6, and GPx reinforce the role of power training as a multisystem modulator, with potential effects on neuroplasticity, inflammation, and antioxidant defense. Creatine supplementation showed a potential additional effect on some adaptations, particularly within the neuromuscular and antioxidant domains, although its impact was not uniform. In this sense, it may be considered a complementary strategy to training, rather than a substitute for it. However, given the exploratory nature of some sex-related findings and the limited statistical power of certain subgroup analyses, these observations should not yet be interpreted as sufficient evidence to support definitive sex-specific exercise prescriptions.

Limitations and future research directions

This study presents several limitations that should be considered when interpreting the results. First, the sample size, particularly after stratification by sex, may have limited the detection of specific differences, especially for interaction effects involving sex and supplementation, and particularly in biological variables characterized by high interindividual variability, such as neurotrophic, inflammatory, and antioxidant defense markers. Second, although multiple biomarkers were included, the study design does not allow precise causal mechanisms to be established. Furthermore, several of the mechanistic explanations discussed throughout the manuscript are derived from previous literature rather than from variables directly assessed in the present study. Consequently, these interpretations should be considered as theoretical hypotheses and require confirmation through studies specifically designed to investigate the underlying physiological mechanisms. In addition, the use of a single marker of antioxidant defense limits the overall interpretation of redox status. The absence of differences between training modalities also restricted the specific analysis of their potential differential effects. Moreover, the effect of creatine was not uniform across variables, suggesting a context- and system-dependent response. Finally, the inherent heterogeneity of the older population may have influenced the variability of the adaptive response.

Future studies should include larger samples and designs specifically aimed at analyzing "*sex x intervention*" interactions, as well as incorporating additional mechanistic measures. Furthermore, it would be relevant to evaluate the long-term functional and clinical impact of these adaptations and to explore more individualized prescription strategies.

CONCLUSIONS

Power training induces relevant neuromuscular and biological adaptations in older adults, including improvements in high-velocity strength, increases in BDNF, reductions in IL-6, and enhancements in enzymatic antioxidant defense (GPx), whereas the TNF-α response was more variable. These findings reinforce the role of exercise as a multisystem modulator in aging. Importantly, the present results suggest

that these adaptations are not entirely homogeneous between men and women, with sex-related differences being particularly evident in neuromuscular performance and neurotrophic responses. Creatine supplementation showed a complementary and non-uniform effect across outcomes, without representing the primary determinant of adaptation. Overall, power training, with or without supplementation, represents an effective strategy to promote functional and biologically favorable aging. The findings also highlight the potential relevance of considering sex as a modulatory factor when interpreting adaptive responses to exercise in older adults and support the development of more individualized intervention strategies.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship in accordance with established ethical guidelines. Contributions are specified according to the CRediT (Contributor Roles Taxonomy) as follows: Conceptualisation: Alvaro Juesas, Carlos Alix-Fages, Pablo Jiménez-Martínez, Juan C. Colado. Methodology: Alvaro Juesas, Juan C. Colado. Formal analysis: Alvaro Juesas, Angel Saez-Berlanga, Javier Gene-Morales, Pedro Gargallo-Bayo, Juan C. Colado. Investigation: Alvaro Juesas, Angel Saez-Berlanga, Luis Garrigues-Pelufo, Javier Gene-Morales, Pedro Gargallo-Bayo, Juan C. Colado. Data curation: Juan C. Colado. Writing – original draft: Alvaro Juesas, Angel Saez-Berlanga, Luis Garrigues-Pelufo, Juan C. Colado. Writing – review & editing: Alvaro Juesas, Javier Gene-Morales, Pedro Gargallo-Bayo, Carlos Alix-Fages, Pablo Jiménez-Martínez, Juan C. Colado. Supervision: Juan C. Colado.

All authors have critically reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

PJ-M and CA-F serve on the advisory board of CreaTrust™ and other trademarks related to the nutraceutical field. The remaining authors declare no conflicts of interest that could have influenced the work presented in this article.

AI USE DISCLOSURE

In accordance with current publishing ethics and transparency recommendations, artificial intelligence (AI) tools were used solely to assist with translation and language editing, with the aim of improving clarity and readability. No AI tools were used in the generation of scientific content, including the study design, data collection, analysis, interpretation of results, or the formulation of conclusions. The authors retain full responsibility for the content of the manuscript and confirm its originality, integrity, and accuracy.

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