

Article

Circulating Immune Mediators and Habitual Exercise Practice Among Older Adults: Beyond the Statistical Significance, Towards Clinical Significance

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Abstract

Physical exercise is considered an effective and relatively safe practice to reduce or control levels of pro-inflammatory mediators during aging. However, findings are often interpreted primarily through statistical significance, while the magnitude and potential clinical relevance of observed effects receive less attention. Therefore, the primary objective of this cross-sectional study was to investigate whether regular physical exercise was associated with differences in circulating levels of systemic inflammatory mediators (high-sensitivity C-reactive protein [hsCRP], TNF- α , IL-6, IL-8, IL-10, and IL-12) among community-dwelling older adults, emphasizing the magnitude and potential clinical relevance of these differences rather than an interpretation based exclusively on statistical significance. The results suggest that exercisers exhibited hsCRP levels 0.68 mg/L lower than those observed among non-exercisers (95% CI: -0.98 to -0.34 mg/L; $p = 0.001$). Although serum IL-6 levels did not differ statistically between groups ($p = 0.072$), the interval estimates remained compatible with potentially relevant reductions among exercisers. The estimated between-group difference indicated that exercisers presented median IL-6 concentrations 4.34 pg/mL lower than non-exercisers (95% CI: -9.41 to 0.24 pg/mL). No meaningful differences were observed for TNF- α , IL-8, IL-10, or IL-12. Taken together, these findings suggest that regular physical exercise is associated with a more favorable inflammatory profile in older adults, particularly through lower hsCRP concentrations. The findings for IL-6 remain inconclusive but support the need for future studies with more precise estimates of the magnitude and potential clinical relevance of this association.



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1. Introduction

Growing evidence suggests that cellular changes and dysregulated immune responses are prominent contributors to the development and progression of several chronic diseases during aging [1]. In this context, the terms immunosenescence and inflammaging are commonly used to describe, respectively, the age-related decline in adaptive immune function and the persistent activation of innate immune pathways that promote chronic low-grade inflammation [2,3]. Even moderately elevated levels of inflammatory markers, such as C-reactive protein (CRP), have been associated with an increased risk of pneumonia [4], diabetes [5], coronary artery disease [6], and mortality [7].

Although evidence from both cross-sectional and longitudinal studies has reinforced the role of physical exercise as an effective and safe strategy to mitigate the adverse effects of inflammaging, findings are frequently interpreted primarily through the lens of statistical significance, while the magnitude and potential clinical relevance of observed effects receive less attention. Therefore, the primary aim of this cross-sectional study was to investigate whether regular physical exercise is associated with differences in circulating inflammatory mediators among community-dwelling older adults, emphasizing the magnitude and potential clinical relevance of these effects rather than relying exclusively on statistical significance. Given the established association between elevated CRP levels and increased cardiovascular and inflammatory risk in older populations, we hypothesized that regular physical exercise would be associated with lower circulating CRP concentrations. Such a reduction could reflect a protective effect of exercise on systemic inflammatory processes, thereby contributing to healthier aging.

2. Materials and Methods

2.1. Study Design and Sample

Participants in this study were recruited from a study cohort known as the Prognosis and Therapeutics in Geriatrics (ProTeGer), established in 2008 with the aim of identifying cardiovascular risk factors in community-dwelling older adult volunteers with no evidence of myocardial infarction or peripheral vascular disease who were receiving primary prevention care. Additional exclusion criteria were the occurrence of autoimmune diseases, current or previous neoplastic disease, chronic obstructive pulmonary disorder, chronic or recurrent infections, liver disease, heart failure (left ventricular ejection fraction < 50%) and using steroid or non-steroid anti-inflammatory drugs in the last 30 days. We considered clinical and biochemical baseline records (medical history, blood biochemistry, use of therapeutic drugs), as well as data related to lifestyle (physical exercise) collected from a questionnaire. Blood samples were collected after 12 h of fasting for routine biochemical tests, and then stored at -80°C for later analysis.

Sample size was estimated a priori based on a two-sided Mann–Whitney test, assuming a significance level of 5%, statistical power of 80%, and an a priori between-group difference of 1 mg/L in CRP levels as the effect size of interest for sample-size planning, rather than as an established minimum clinically important difference. Based on the expected variability of CRP, this difference corresponded to an approximate standardized effect size of 0.64, resulting in a minimum required sample of 104 participants. The study was approved by the Research Ethics Committee of Faculty of Medicine of the University of Brasília, and all participants provided written informed consent before initial enrollment to the study and again whenever additional data collection procedures or biological sample collection were performed.

2.2. Clinical Evaluation

Clinical evaluation of patients was performed at an outpatient ward following a standardized protocol. Arterial blood pressure was measured according to recommendations of the 2020 Brazilian Guideline for Hypertension [8], with hypertension defined by systolic blood pressure (SBP) ≥ 130 mm Hg, diastolic blood pressure (DBP) ≥ 85 mm Hg, or antihypertensive use reported during clinical interview. Diagnosis of type 2 diabetes was determined by the presence of either glycated hemoglobin type-A1c (Hb1Ac) $\geq 6.5\%$ or fasting plasma glucose ≥ 126 mg/dL on routine laboratory tests, with the use of antidiabetic drug(s) [9]. Body mass index (BMI) for anthropometric analysis was determined by dividing weight (in kg) by the squared height (in m) with patients in light clothing.

2.3. Biochemical Analyses

After collection, blood was mixed with EDTA and centrifuged at 4500 rpm for 15 min at 5 °C for plasma separation, which was kept frozen at −80 °C until thawing for the assessments. Serum glucose, total cholesterol, triglycerides, TSH, VLDL and HDL-C measurements used reagents from Roche Diagnostics (Mannheim, Germany) and were processed on an AutoHumalyzer (Human GMBH, Wiesbaden, Germany) or nephelometer (DadeBehring, Marburg, Germany), according to the case. The Friedewald equation was used to produce LDL cholesterol estimates [10].

2.4. Inflammatory Analyses

Tests for high-sensitivity C-reactive protein (hsCRP) used products from DadeBehring (Marburg, Germany) and were read in an Immulite 2000 device from Siemens (Los Angeles, CA, USA). Cytokine concentrations were assessed by the multiplexed flow cytometry method using one set of bead-based immunoassays known as the Human Inflammatory Cytokine Cytometric Bead Array (CBA) Kit (BD Biosciences, San Diego, CA, USA) and applied according to the manufacturer to yield measurements of interleukins (IL-6, IL-8, IL-10, IL-12) and tumor necrosis factor- α (TNF α). Samples were processed using a BD FACSVerse flow cytometer, with a minimum of 300 events acquired for each cytokine bead used. Data were analyzed using the BD Biosciences' FCAP version 3.0 program (San Diego, CA, USA).

2.5. Exercise Practice

Exercise practice was self-reported during the clinical evaluation. Participants were asked about the frequency, duration, and intensity of their habitual physical activities, and were subsequently classified as physically active or not according to the 2020 World Health Organization guidelines on physical activity and sedentary behavior [11], according to which any adult would be physically active if undertaking a minimum of 150 min of exercise at a moderate intensity or at least 75 min of any vigorous-intensity physical activity on a weekly basis. Any combination of moderate-intensity and vigorous-intensity aerobic training would also satisfy the criteria. Exercise practice was self-reported by the interviewee as part of the clinical evaluation. Information regarding exercise modality and training history was not collected.

2.6. Statistical Analyses

The Shapiro–Wilk Test and visual inspection were used to investigate the data distribution. Continuous variables with a distribution close to normal were expressed as mean $\pm$ SD, while variables with asymmetric distribution were expressed as median and interquartile range (Q₂₅–Q₇₅). Because most inflammatory mediators exhibited asymmetric distributions and occasional extreme values, non-parametric methods were preferred for between-group comparisons. Differences in circulating inflammatory mediators between exercise practitioners and non-practitioners were initially assessed using the non-parametric Mann–Whitney test. For hsCRP, two complementary analytical approaches were applied. First, differences in median hsCRP levels between groups were estimated using the Mann–Whitney test, together with bootstrap-based 95% confidence intervals. For the confidence intervals presented in Figure 1, a non-parametric bootstrap procedure with 1000 resamples was employed. The statistic of interest was the between-group difference in medians. At each iteration, participants were sampled with replacement from the original dataset, the median difference was recalculated, and the empirical bootstrap distribution was used to derive 95% confidence intervals. For hsCRP, values were subsequently log-transformed to better satisfy the assumptions of normality and homogeneity of variance, allowing adjusted

analysis through ANCOVA. This complementary analysis enabled adjustment for sex, age, and body mass index (BMI), thereby assessing whether the observed differences remained after accounting for potential confounding factors. Adjusted group means and their 95% confidence intervals on the log-transformed scale were subsequently back-transformed to obtain adjusted geometric means and their corresponding 95% confidence intervals on the original hsCRP scale. The between-group contrast was likewise back-transformed and expressed as a ratio of geometric means with its corresponding 95% confidence interval.

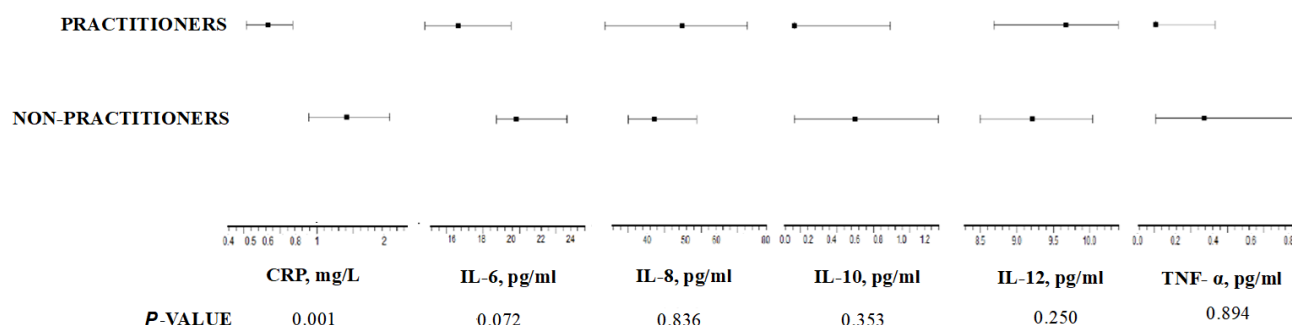


Figure 1. Bootstrap 95% confidence intervals ($n = 1000$ resamples). The line labeled “Clinical reference value” represents the absolute hsCRP threshold of 1.0 mg/L used for cardiovascular risk stratification. It is provided solely as clinical context for interpreting the observed effect sizes and should not be interpreted as a validated minimum clinically important between-group difference.

Different estimators and summary measures were used according to the objective of each analysis. Bootstrap-based confidence intervals were used to estimate the uncertainty around the between-group median differences displayed in Figure 1. Hodges–Lehmann estimators were used to summarize the location shift between independent groups. For the adjusted ANCOVA analyses, regression coefficients estimated on the log-transformed scale were back-transformed to the original hsCRP scale to facilitate clinical interpretation. The remaining inflammatory mediators were not subjected to adjusted parametric analyses because their distributions remained markedly asymmetric and highly influenced by extreme values, even after exploratory transformations. Chi-squared tests were used, when applicable, to investigate associations between hsCRP levels and potential covariates. Spearman’s rank correlation test (r_s) was employed to assess the relationship between inflammatory markers and age. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

The original database included 348 participants who met the predefined eligibility criteria and were initially considered for the present analysis. Six participants were subsequently excluded because they exhibited hsCRP concentrations > 10 mg/L, which may reflect acute inflammatory processes rather than the chronic low-grade inflammation characteristic of inflammaging [12]. Therefore, the final analytical sample comprised 342 participants, whose demographic and laboratory characteristics are shown in Table 1 according to regular physical exercise practice. Compared with non-exercisers, older adults classified as regular exercisers exhibited lower hsCRP levels (Table 2), with an estimated median reduction of -0.68 mg/L [95% CI, -0.98 to -0.34 mg/L, $p = 0.001$]. To account for potential confounding factors, hsCRP values were additionally analyzed using ANCOVA after logarithmic transformation. After adjustment for sex ($p = 0.01$), age ($p < 0.01$) and BMI ($p = 0.02$), the results remained consistent with the non-parametric analysis, showing significantly lower log-transformed hsCRP levels among exercisers compared with non-exercisers (adjusted mean difference = -0.128 ; 95% CI: -0.23 to -0.03 ; $p = 0.017$).

In this complementary ANCOVA adjusted for sex, age, and BMI, the adjusted geometric mean hsCRP concentrations after back-transformation were 2.28 mg/L among exercisers and 3.03 mg/L among non-exercisers. The corresponding geometric mean ratio was 0.75 (95% CI, 0.62–0.92; $p = 0.001$), indicating an approximately 25% lower adjusted geometric mean hsCRP concentration among exercisers.

Table 1. Clinical and laboratory characteristics according to the classification of older adults who practice or do not practice physical activity.

	Practitioners ($n = 135$)	Non-Practitioners ($n = 207$)
Age	77.6 (8.8)	80.6 (8.5)
Female, %	57.0	79.7
WC, cm	92.6 (10.5)	97.7 (11.9)
BMI	25.7 (3.9)	27.6 (5.4)
SBP, mmHg	140.7 (20.6)	141.6 (20.7)
DM2, %	20.7	25.1
DBP, mmHg	77.3 (10.4)	78.2 (11.9)
HbA1c, %	5.9 (0.7)	6.1 (1.1)
Glucose, mg/dL	99.6 (21.2)	104.7 (37.8)
TSH, mU/L	2.7 (2.0)	2.8 (2.3)
Total cholesterol, mg/dL	201.5 (97.0)	197.8 (40.7)
Triglycerides, mg/dL	128.1 (54.5)	136.8 (63.4)
HDL, mg/dL	53.3 (13.5)	51.4 (12.7)
LDL, mg/dL	109.9 (34.1)	116.6 (36.0)
VLDL, mg/dL	29.3 (14.6)	30.1 (13.2)

Data expressed as mean (standard deviation) or proportion within the group. BMI = body mass index; DBP = diastolic blood pressure; DM = diabetes mellitus; HDL = high-density lipoprotein; HbA1c = glycated hemoglobin A1c; LDL = low-density lipoprotein; SBP = systolic blood pressure; TSH = thyroid stimulating hormone; VLDL = very-low-density lipoprotein; WC = waist circumference.

Table 2. Inflammatory profile among older adults who practice and do not practice any form of physical exercise.

	Practitioners	Non-Practitioners	Median Difference (95% CI)
hsCRP, mg/L	1.0 [0.7–2.0] ($n = 135$)	1.9 [1.0–3.7] ($n = 207$)	−0.68 [−0.98 to −0.34]
IL-6, pg/mL	17.9 [10.5–28.3] ($n = 52$)	21.7 [15.8–32.3] ($n = 87$)	−4.34 [−9.41 to 0.24]
IL-8, pg/mL	51.7 [24.7–142.4] ($n = 47$)	43.1 [30.3–91.9] ($n = 91$)	−1.15 [−17.16 to 9.21]
IL-10, pg/mL	2.2 [0.84–3.81] ($n = 132$)	2.4 [1.3–3.7] ($n = 197$)	−0.23 [−0.26 to 0.75]
IL-12, pg/mL	9.5 [7.3–12.3] ($n = 132$)	8.8 [6.8–10.9] ($n = 197$)	−0.65 [−1.89 to 0.43]
TNF- α , pg/mL	2.3 [0.96–8.1] ($n = 132$)	2.6 [0.61–11.9] ($n = 197$)	0.12 [−1.64 to 1.06]

Data are expressed as medians (interquartile range, Q_{25} – Q_{75}). The values presented in the last column correspond to Hodges–Lehmann estimates of the median difference between groups and their respective 95% CI. hsCRP = high-sensitivity C-reactive protein; IL = interleukin; TNF = tumor necrosis factor; CI = confidence interval. Sample sizes: hsCRP, $n = 342$; IL-6, $n = 139$; IL-8, $n = 138$; IL-10, $n = 329$; IL-12, $n = 329$; TNF- α , $n = 329$.

Figure 1 illustrates the magnitude and uncertainty of the estimated effects through bootstrap-based 95% confidence intervals. While the interval estimates for most inflammatory markers included the null effect, the estimates for hsCRP consistently favored exercisers and were compatible with between-group differences approaching 1.0 mg/L. It is important to emphasize, however, that the 1.0 mg/L value represents an absolute threshold used for cardiovascular risk stratification rather than a validated minimum clinically important between-group difference. Therefore, these estimates should be interpreted as reflecting the magnitude and uncertainty of the observed association, rather than evidence of an effect whose clinical relevance has been established. No statistically significant differences were observed for the remaining inflammatory mediators. Given the strong influence

of age on systemic inflammation, exploratory analyses were conducted to examine the relationship between age and the immune markers investigated herein among exercisers and non-exercisers. Spearman's correlation analysis revealed a significant positive association between hsCRP levels and age ($r_s = 0.27$, $p = 0.001$), whereas no significant association was observed between IL-6 and age ($r_s = 0.05$, $p = 0.588$). As indicated in Figure 2, the IL-6 analysis was based on a smaller subset of participants because cytokine measurements were not available for the entire study sample.

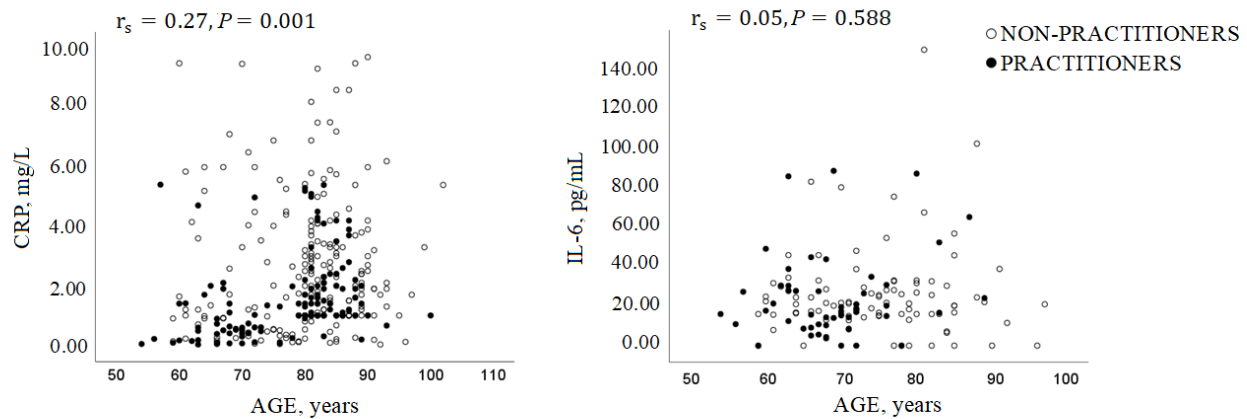


Figure 2. Association between hsCRP ($n = 342$) and IL-6 ($n = 139$) inflammatory markers and age of those who practice and do not practice physical exercise; r_s —Spearman's correlation.

4. Discussion

The present study investigated whether regular physical exercise was associated with differences in circulating inflammatory mediators among community-dwelling older adults, with particular emphasis on the magnitude and potential clinical relevance of these differences. Exercisers exhibited median hsCRP concentrations 0.68 mg/L lower than those observed among non-exercisers, with 95% bootstrap confidence intervals consistently favoring exercisers. The observed between-group difference should nevertheless be interpreted cautiously, as its clinical relevance remains uncertain. The established hsCRP value of 1.0 mg/L represents an absolute threshold used for cardiovascular risk stratification rather than a validated minimum clinically important between-group difference. In this prognostic context, hsCRP concentrations above 1.0 mg/L have been consistently associated with increased risks of cardiovascular mortality, acute myocardial infarction, and stroke, even after adjustment for baseline characteristics and ongoing therapies [13]. Even so, our findings are consistent with an association between regular physical exercise and chronically lower hsCRP concentrations, a pattern that may be relevant to cardiovascular risk among community-dwelling older adults.

The use of the Mann–Whitney test was motivated by the asymmetric distributions observed for most inflammatory mediators, as demonstrated by the Shapiro–Wilk test and visual inspection of the data. In addition, inflammatory biomarkers commonly exhibit extreme values that may unduly influence parametric analyses. Although logarithmic transformation can facilitate compliance with the assumptions of parametric procedures, it often complicates the direct clinical interpretation of results. For this reason, we prioritized effect estimates expressed in the original measurement scale whenever possible. For hsCRP, ANCOVA of log-transformed values was used as a complementary adjusted analysis, with adjusted group estimates subsequently back-transformed to geometric means on the original hsCRP scale and the between-group contrast expressed as a ratio of geometric means.

CRP levels in older adult populations with healthy aging and no evidence of cardiovascular disease (CVD) increase in an age-dependent manner. The results of one study suggest

that high CRP levels after adjusting for age, gender, BMI, lipid levels, and smoking status were associated with shorter survival and worse physical and cognitive performance [14]. Consistent with these observations, our findings suggest that although age was positively associated with hsCRP levels in both exercisers and non-exercisers (Figure 2), older adults who engaged in regular exercise consistently exhibited lower hsCRP concentrations. This pattern indicates that regular exercise practice is associated with lower hsCRP concentrations even in the context of the age-related increase in systemic inflammation. The potential clinical relevance of this finding is reinforced by evidence from a systematic review showing that CRP concentrations ≥ 1.78 mg/L (95% CI, 1.12–2.85 mg/L) are associated with an increased risk of frailty [15]. Taken together, these observations suggest that the lower hsCRP concentrations observed among regular exercisers may characterize a more favorable inflammatory profile in relation to cardiovascular health, functional reserve and resilience during aging.

In addition to this important acute phase protein, other inflammatory mediators can act as risk factors for the health of the older adults. For example, IL-6 and TNF- α are cytokines which stimulate the release of CRP by hepatocytes, being associated with a greater risk for chronic conditions, including cardiovascular diseases, diabetes, cancer and frailty [3]. IL-6 is particularly implicated in activating pathways that degrade muscle proteins and impede myogenesis, contributing to progressive muscle atrophy [16]. Although our results did not show statistically significant differences when comparing IL-6 levels between groups, it is important to note that the interval estimates were compatible with differences of up to 9 pg/mL favoring older adult exercisers. Therefore, although this finding is not conclusive ($p > 0.05$), the available data do not support ruling out potentially clinically relevant differences between groups. The biological plausibility of an association between physical exercise and lower IL-6 levels is supported by previous intervention studies in older adults, in which both functional and traditional exercise training were associated with reductions in circulating IL-6 and TNF- α concentrations [17]. Further studies with larger sample sizes are warranted to provide more precise estimates of the association between physical exercise and IL-6 levels. We are not aware of established thresholds of clinical relevance for the outcomes considered above, which limits both the definition of clinically important effect sizes for sample size estimation and the interpretation of the clinical significance of the observed effects.

On the other hand, the literature has shown great variability in results regarding TNF- α , IL-8, IL-10 and IL-12 levels, which makes it difficult to both interpret the consistency of the findings and to establish future values as a clinical reference. This variability can be attributed to several factors, such as differences between the clinical profile of the populations investigated, the diversity of collection and analysis methods, as well as the course of the disease stages. For IL-8, median levels were numerically higher among exercisers than among non-exercisers. Although the interval estimates were compatible with this direction of effect, the finding was not statistically conclusive and should therefore be interpreted with caution, as it may reflect biological variability, sampling variability, or limited statistical precision. Further studies with larger sample sizes will be necessary to clarify the direction, magnitude, and consistency of this association. A systematic review on inflammatory markers and frailty [3] identified that only 4 of 13 studies showed relevant changes in TNF- α levels. In line, our results also did not show clear between-group differences for TNF- α , regardless of the statistical approach adopted. However, it is important to note that this cytokine is secreted in greater quantities from adipose tissue [18]. From this perspective, it is plausible to infer that obese individuals must have higher levels of TNF- α in relation to eutrophic individuals. Because the estimated difference in BMI between groups was relatively small, this factor may have contributed, at least partially,

to the modest estimated difference of 0.12 pg/mL observed for TNF- α levels between the groups. Another possible explanation is the complex regulatory interaction between IL-6 and TNF- α , whereby IL-6 may exert suppressive effects on TNF- α production under certain physiological conditions [19]. This hypothesis highlights the importance of analyzing the inflammatory milieu rather than interpreting individual cytokines in isolation.

It is important to emphasize that the potential effects of practicing physical activities/exercises on systemic inflammatory mediators can be influenced by both the modalities practiced and the protocol (duration, frequency and intensity) of the exercises performed [20], which represents an important limitation of the present study. In fact, as observed elsewhere [21], CRP is the most responsive independent marker to the physiological effects of physical exercise, while IL-6, IL-10, and TNF- α seem to be more sensitive to differences in exercise modality and training protocols. Furthermore, given the cross-sectional design of the study, causal relationships cannot be established. Individuals with lower baseline levels of systemic inflammation may be more likely to engage in regular physical exercise, rather than exercise itself being responsible for the lower hsCRP concentrations observed. Another limitation is that medications with potential immunomodulatory effects, such as statins, metformin and ACE inhibitors, were not included in the adjusted analyses. Finally, physical activity was assessed by self-report, without the use of objective measures such as accelerometry or step counts, which may have introduced information bias and reduced the precision of the estimates. Future studies should incorporate objective measures of physical activity to improve the robustness and reliability of the findings.

5. Conclusions

Regular physical exercise was associated with lower circulating hsCRP concentrations among community-dwelling older adults, whereas no statistically conclusive differences were observed for the remaining inflammatory mediators. Although the estimated reduction in hsCRP was compatible with an effect magnitude that may be clinically relevant, its interpretation should be made cautiously. The well-established cardiovascular risk threshold of 1.0 mg/L for hsCRP represents an absolute prognostic reference rather than a validated minimum clinically important between-group difference. Although the findings for IL-6 were not statistically conclusive, the corresponding confidence interval remained compatible with potentially relevant effects, supporting the need for future studies with larger sample sizes and greater precision. Overall, these findings highlight the importance of interpreting associations between physical exercise and inflammatory markers by integrating statistical significance, effect magnitude, estimation uncertainty, and their potential clinical relevance.

Author Contributions: C.C. and O.T.N.: designed the study, analyzed and interpreted the results, prepared the original manuscript. G.S.M.-J.: assessed immune mediators and assisted other laboratory evaluations. C.C. executed the statistical analyses. C.F.M., E.F.C. and L.L.L.: executed the medical assessments. L.L.L. and O.T.N.: managed the grant obtained. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine of the University of Brasília, Brazil (approval number: 95222125.8.0000.5558; last amendment issued on 20 March 2025). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and registered at the National

System for Management of Genetic Heritage and Traditional Knowledge (SisGen, Brazil), under access # A407626).

Informed Consent Statement: Written informed consent was obtained from all participants before clinical enrollment and biological sample collection procedures were performed.

Data Availability Statement: Data can be made available upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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