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Plasma and Salivary C-Reactive Protein Responses to Running: A Systematic Review and Meta-Analysis of Moderating Factors

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Abstract

Purpose: Running exercise induces a robust acute-phase inflammatory response, yet the magnitude and moderators of C-reactive protein (CRP) elevation remain unclear, with no prior quantitative synthesis distinguishing plasma from salivary measurements.

Method: A systematic search of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar was performed from inception to February 2026. Eligible studies reported CRP levels before and after running exercise of any distance in runners. Random-effects meta-analyses pooled standardized mean differences (SMDs), with subgroup analyses and meta-regression examining age, BMI, and race distance.

Results: Thirty studies (1,247 runners; 72% male) were included. Endurance running significantly increased plasma CRP (SMD=1.207, 95%CI:0.688–1.726; p=0.001) and in the single study with salivary CRP data (three distance subgroups), salivary CRP increased (SMD=1.230, 95%CI:0.136–2.324; p=0.028). Age significantly moderated the response: older runners (>48 years) showed a four-fold greater effect (SMD=1.642) than younger runners (SMD=0.402; Q=22.873, p<0.001). Race distance was a dominant moderator: ultra-marathons (>100 km) elicited a nine-fold larger surge (SMD=3.577) versus standard marathons (SMD=0.404; Q=18.695, p<0.001). BMI did not significantly moderate CRP elevation (Q=1.076, p=0.584). Substantial heterogeneity (plasma: I^2=91.99%; salivary: I^2=73.36%) and publication bias (plasma: Egger's p=0.003) were observed.

Conclusion: Running exercise significantly elevates plasma and salivary CRP, with age and race distance as potent moderators. BMI does not influence the acute CRP response. Clinicians should avoid general population cutoffs (>3 mg/L) during acute recovery. Salivary CRP requires further validation before clinical adoption. Standardized sampling at 24-48 hours post-race is essential for peak detection.

Keywords: C-reactive protein; running exercise; ultra-marathon; inflammation; meta-analysis; aging.

Introduction

Regular endurance running is widely recognized as a cornerstone of a healthy lifestyle, conferring substantial cardiovascular, metabolic, and psychological benefits (Hassanzadeh et al., 2022; Shojah-Anzabi et al., 2026). Over the past two decades, the global popularity of running exercise has surged exponentially, with millions of amateur and professional athletes annually undertaking the 42.195-km distance, and increasingly, ultra-marathon events exceeding 100 km (Knechtle & Nikolaidis, 2018). Despite these well-established health advantages, the extreme and prolonged physical stress imposed by running exercise triggers a complex systemic response that involves multiple physiological systems, particularly the immune and endocrine systems (Nieman & Wentz, 2019). Understanding the nature and magnitude of this response is not only essential for optimizing athletic performance and recovery strategies but also for identifying potential risks associated with such extreme exertion, including transient immunosuppression, increased susceptibility to infections, and myocardial stress (Eijsvogels et al., 2016; Piri et al., 2022; Shoja Anzabi et al., 2026).

Among the myriad of biomarkers that reflect the acute inflammatory response to strenuous exercise, C-reactive protein (CRP) has emerged as one of the most frequently measured and clinically relevant indicators (Stec-Martyna et al., 2025). CRP is an acute-phase protein synthesized primarily by hepatocytes in response to pro-inflammatory cytokines, particularly interleukin-6 (IL-6), which is released in large quantities from contracting skeletal muscles during prolonged endurance exercise (Pepys & Hirschfield, 2003). The elevation of CRP following running exercise is well-documented, with peak levels typically observed 24 to 48 hours post-race, reflecting a delayed but sustained inflammatory cascade that mirrors the liver's response to systemic tissue damage and metabolic stress (Bekos et al., 2016). However, the magnitude of this CRP response appears to be highly variable across studies, ranging from modest increases in well-trained athletes to dramatic surges in less-conditioned individuals or those competing in ultra-distance events (Greenham et al., 2018). This

variability underscores the influence of multiple moderating factors, including age, body mass index (BMI), and race distance, which have been individually examined but rarely synthesized within a comprehensive meta-analytical framework. It is important to distinguish the acute, transient CRP elevation induced by running exercise from chronic, low-grade CRP elevation observed in clinical populations. The former reflects a physiological acute-phase response to muscle damage and metabolic stress, typically peaking at 24–48 hours and resolving within days, whereas the latter is associated with persistent inflammatory states and cardiovascular risk. This distinction is critical for interpreting post-race CRP values and avoiding misclassification.

The biological matrix in which CRP is measured whether plasma or saliva may further contribute to the heterogeneity observed in the literature. While plasma CRP is the gold-standard for assessing systemic inflammation, salivary CRP has gained attention as a non-invasive, easily accessible, and cost-effective alternative for repeated sampling in field settings (Babaei et al., 2022). However, the correlation between salivary and plasma CRP levels remains incompletely elucidated, and the extent to which salivary CRP reflects the systemic inflammatory response to running exercise has not been systematically quantified (Slavish et al., 2015). Some studies have reported significant increases in salivary CRP following running exercise (Bizjak et al., 2026), while others have found no change or even a decrease (Pay & Shaw, 2019), raising questions about the validity and reliability of salivary CRP as a surrogate marker for systemic inflammation in the context of extreme endurance exercise (ShojaAnzabi et al., 2023).

Despite the growing body of research, several critical gaps persist. First, no systematic review or meta-analysis has specifically and comprehensively synthesized the effects of running exercise on CRP levels, with a clear distinction between plasma and salivary measurements. Second, while individual studies have reported on the moderating effects of age, BMI, and race distance, a quantitative

synthesis that simultaneously examines how these factors influence the CRP response is lacking. For instance, a study by (Greenham et al., 2018) suggest that older runners exhibit a more pronounced CRP elevation(Greenham et al., 2018), whereas others (Baker et al., 2022) report that BMI is a stronger predictor of the inflammatory response(Baker et al., 2022). Third, the dose-response relationship between race distance and CRP elevation remains unclear; while ultra-marathons (>100 km) are intuitively expected to provoke a larger response, meta-regression analyses have not been systematically applied to test this hypothesis across studies. Finally, the high heterogeneity observed in previous narrative reviews underscores the need for a rigorous, quantitative synthesis that can provide pooled effect estimates, explore sources of heterogeneity, and offer evidence-based recommendations for monitoring and recovery strategies.

Although multiple factors may influence the acute-phase CRP response to running exercise, we selected age, BMI, and race distance as primary moderators based on their biological plausibility and consistent availability across studies. Age is associated with immunosenescence and a chronic low-grade inflammatory state ("inflammaging"), which may amplify cytokine responses to exercise. BMI is a well-established determinant of baseline systemic inflammation and adipose tissue-derived cytokine production. Race distance provides a direct index of exercise duration and cumulative tissue damage. Other potentially important determinants, including training status, sex, environmental temperature, altitude, race duration, finishing time, hydration, nutritional intake, NSAID use, baseline CRP, and previous endurance experience, were not consistently reported across the included studies, precluding their quantitative synthesis. We therefore focused on the three moderators with sufficient data for subgroup analyses, while acknowledging these additional factors as important avenues for future research.

Therefore, the primary aim of this systematic review and meta-analysis is to quantitatively synthesize the acute effects of running exercise on CRP levels, measured in both plasma and saliva, and to examine the

moderating roles of age, BMI, and race distance in explaining the variability of CRP responses across studies. Specifically, we seek to: (i) calculate pooled standardized mean differences (SMD) for CRP changes in plasma and saliva to establish the magnitude of the acute inflammatory response; (ii) employ subgroup analyses and meta-regression to investigate the sources of heterogeneity, with a particular focus on age, BMI, and race distance as potential moderators; and (iii) compare the CRP response patterns between plasma and saliva to assess the feasibility and validity of salivary CRP as a non-invasive monitoring tool in running exercise. The findings of this study are expected to inform individualized monitoring protocols, optimize recovery strategies, and guide future research toward standardized methodologies in exercise immunology.

Methods

Protocol registration and PICOs framework

This systematic review and meta-analysis was prospectively registered in the PROSPERO database to ensure transparency and minimize reporting bias. The study was conducted and reported in accordance with the PRISMA 2020 guidelines, with all methodological steps documented to ensure reproducibility(Page et al., 2021). The research question was structured using the PICOs framework (Population, Intervention, Comparator, Outcomes, and Study Design) to guide study selection, data extraction, and synthesis(Shoja et al., 2025).

Search strategy

A comprehensive systematic search was developed to identify studies evaluating the effects of running exercise on CRP responses in runners. The search strategy was structured around three conceptual areas: (1) runners (like "marathon," "running," "runners," "ultra marathon"), (2) exercise intervention (namely "running exercise", "endurance running," "long distance running"), and (3) outcomes related to CRP responses

(including "C reactive protein," "CRP," "hs CRP," "high sensitivity C reactive protein," "acute phase protein"). Keywords and MeSH terms were combined using Boolean operators (AND, OR, NOT) with database specific adaptations. Two independent investigators searched PubMed/MEDLINE, Scopus, and Web of Science, as well as Google Scholar, from inception to February 2026. Additionally, reference lists of eligible studies and relevant systematic reviews were manually screened, and forward/backward citation tracking was performed via Google Scholar. No language restrictions were applied; however, only English full text publications were included in the final analysis.

Eligibility criteria

Studies were included in this systematic review if they met all of the following criteria: (1) study design: randomized controlled trials (RCTs) with parallel or crossover designs, non-RCTs, and pre-post intervention studies with repeated measures, including both supervised exercise interventions and observational studies; (2) population: runners of any age, sex, or competitive level (professional, semi-professional, amateur, or recreational), with no restrictions on baseline fitness status, training history, or running experience, and without acute musculoskeletal injuries or chronic metabolic disorders; (3) intervention: running exercise of any distance (e.g., 10 km, half-marathon, marathon, ultramarathon), with no minimum distance or duration restriction applied; (4) comparators: baseline pre-race measurements (resting state) or control groups of non-running individuals; (5) outcomes: reporting CRP levels measured in blood samples (plasma or serum) or saliva using validated laboratory methods; and (6) publication: original full-text articles published in English in peer-reviewed journals. No restrictions were applied regarding geographical location, publication year, or competitive level of the participants.

Studies were excluded if they met any of the following criteria: (1) non-randomized study designs, including observational studies, cohort studies, case-control studies, cross-sectional studies, and pre-post

studies without a control group, as well as non-RCTs lacking appropriate comparison groups; (2) non-original articles such as narrative reviews, scoping reviews, rapid reviews, meta-analyses, editorials, commentaries, letters to the editor, conference abstracts, and case reports; (3) studies without a control group or with non-exercise control interventions (pharmacological interventions, nutritional supplements without exercise, or passive interventions without structured training); (4) studies that did not report quantitative outcome data for CRP measured in blood samples (plasma or serum) or saliva, or reported outcomes in a format that prevented SMD calculation for meta-analysis; (5) studies on animal models or populations other than runners; (6) studies with insufficient methodological detail or incomplete outcome reporting that precluded quality assessment (risk of bias evaluation) or data extraction; and (7) duplicate publications or studies reporting overlapping data from the same cohort, in which case only the most recent or most complete publication was retained.

Study selection process

Following the literature search, study selection was performed in two stages using EndNote 2025 software. Initially, duplicate records were removed by an experienced researcher. Subsequently, two independent reviewers conducted title/abstract screening, followed by full-text screening of potentially eligible articles based on predefined inclusion and exclusion criteria. Disagreements were resolved through discussion, or by consultation with a third reviewer when consensus could not be reached. Inter-rater reliability was assessed using Cohen's kappa coefficient to evaluate the level of agreement between reviewers during the screening process. The selection process was reported following the PRISMA flow diagram, which provides a detailed summary of the number of records identified, screened, assessed for eligibility, and included in the final meta-analysis. Articles confirmed at the full-text stage proceeded to data extraction and quality assessment.

Data extraction

After finalizing eligible studies through a two-stage review process, data extraction was performed independently by two reviewers using a standardized electronic form in Microsoft Excel. The form was pilot-tested on five randomly selected studies and revised accordingly. For each included study, the following data were extracted: (1) study characteristics (author, year, country, study design); (2) participant characteristics (sample size, age, sex, competitive level, baseline training status, and BMI ; (3) intervention details (race distance, running pace, environmental conditions); (4) comparator description (baseline pre-race measurements or control groups of non-running individuals); and (5) outcome data (mean, standard deviation [SD] or standard error [SE], and sample size for pre-race and post-race measurements) for CRP measured in either plasma or saliva. Additionally, the timing of post-race blood/saliva sampling was recorded to enable subgroup analyses. Where data were reported graphically, Get Data Graph Digitizer (version 2.26) was used to extract numerical values. Where data were reported as median and range or interquartile range (IQR), standard methods were applied to estimate means and SD. Extracted data were cross-verified by both reviewers, with disagreements resolved through consensus.

Statistical analysis

Meta-analysis

Meta-analyses were conducted using Comprehensive Meta-Analysis (CMA) software (version 4)(Loghman et al., 2025). Due to anticipated heterogeneity across studies in terms of participant characteristics (age, competitive level, training status, BMI), race distance, and assessment timing, the random-effects model with Restricted Maximum Likelihood (REML) estimator was used as the primary analytical approach. Effect sizes were calculated as SMDs with 95% confidence intervals (CIs) using Hedges' g correction for small sample bias(Farzizadeh et al., 2026; Wahib et al.). For studies reporting pre-post race data within the same group, the effect size was calculated using the correlation

coefficient estimated from baseline (pre-race) and post-race values. When multiple time points were reported, post-race data at the earliest sampling time point were selected for primary analysis, with sensitivity analyses including alternative time points to test the robustness of the findings. Studies were weighted using the inverse variance method, which assigns greater weight to studies with smaller standard errors (larger sample sizes). Forest plots were generated to visualize individual and pooled effect sizes with 95% CIs for CRP responses measured in plasma and saliva separately. Statistical significance was set at a two-tailed $p < 0.05$ for primary analyses.

Heterogeneity assessment

Heterogeneity was assessed using Cochran's Q test (significance set at $p < 0.10$), τ^2 (between-study variance estimated via the REML method), and the I^2 statistic, which was categorized as low (0–25%), moderate (25–50%), substantial (50–75%), or considerable (75–100%) according to conventional thresholds. When substantial heterogeneity was present ($I^2 > 50\%$), predefined subgroup analyses and meta-regression were conducted to explore potential sources of heterogeneity. Additionally, 95% prediction intervals (PIs) were calculated to estimate the expected range of true effects in future studies, providing a clinically meaningful measure of the anticipated variability in individual study effects, particularly for outcomes with substantial or considerable heterogeneity(Al-Aayedi et al., 2026).

Publication bias and sensitivity analysis

Publication bias was assessed using funnel plots, Egger's linear regression test, and Begg's rank correlation test ($p < 0.10$ considered indicative of asymmetry). When asymmetry was detected, the trim-and-fill method was applied to adjust pooled effect estimates. Sensitivity analyses included leave-one-out analysis to evaluate the influence of individual studies and the Classic Fail-Safe N test to determine the number of null studies required to render the observed effect non-significant. A Fail-Safe $N > 5k + 10$ (where k = number of studies) was

considered robust. Leave-one-out forest plots were generated using Python (v3.11) with matplotlib (v3.8.0).

Meta-regression analysis

To quantitatively examine the relationship between race distance (km) and the magnitude of CRP responses, univariate meta-regression analyses were conducted. Models were estimated using random-effects REML and weighted by the inverse of the total variance (within-study + between-study). The significance of each moderator was assessed using the Q-model test and regression coefficient (β), with $p < 0.05$ considered statistically significant.

Subgroup analyses

To explore potential sources of heterogeneity and examine the influence of predefined moderators on effect estimates, subgroup analyses were conducted using mixed-effects models, with random-effects applied within subgroups and fixed-effects for between-subgroup comparisons. The following categorical moderators were examined specifically for CRP responses: age (≤ 48 years vs. > 48 years), BMI (≤ 23.5 vs. > 23.5), and race distance (≤ 100 km vs. > 100 km). Subgroup analyses by other influential factors, as well as by running/exercise type (marathon vs. sprint vs. resistance), were not pre-specified because an insufficient number of studies was available for such comparisons. Statistical significance of subgroup differences was assessed using the Q-between statistic (Qb), with $p < 0.05$ considered indicative of significant differences. Subgroup analyses with fewer than three studies ($k < 3$) were not performed and were instead summarized narratively. All analyses were performed using CMA.

Results

Study Selection

A systematic search of electronic databases, including Medline/PubMed, Scopus, and Web of Science, identified a total of 1,302 records. After removing 282 duplicate records, 1,020 studies were screened based on titles and abstracts, of which 944 were excluded as irrelevant to the research question. The full texts of the remaining 76 reports were sought for retrieval, but 8 records could not be accessed, leaving 68 articles assessed for eligibility against the predefined inclusion criteria. Ultimately, 30 studies met the eligibility criteria and were included in the systematic review, comprising 29 studies that reported plasma or serum C reactive protein (CRP) measurements and only 1 study that provided quantitative salivary CRP data (Fig. 1).

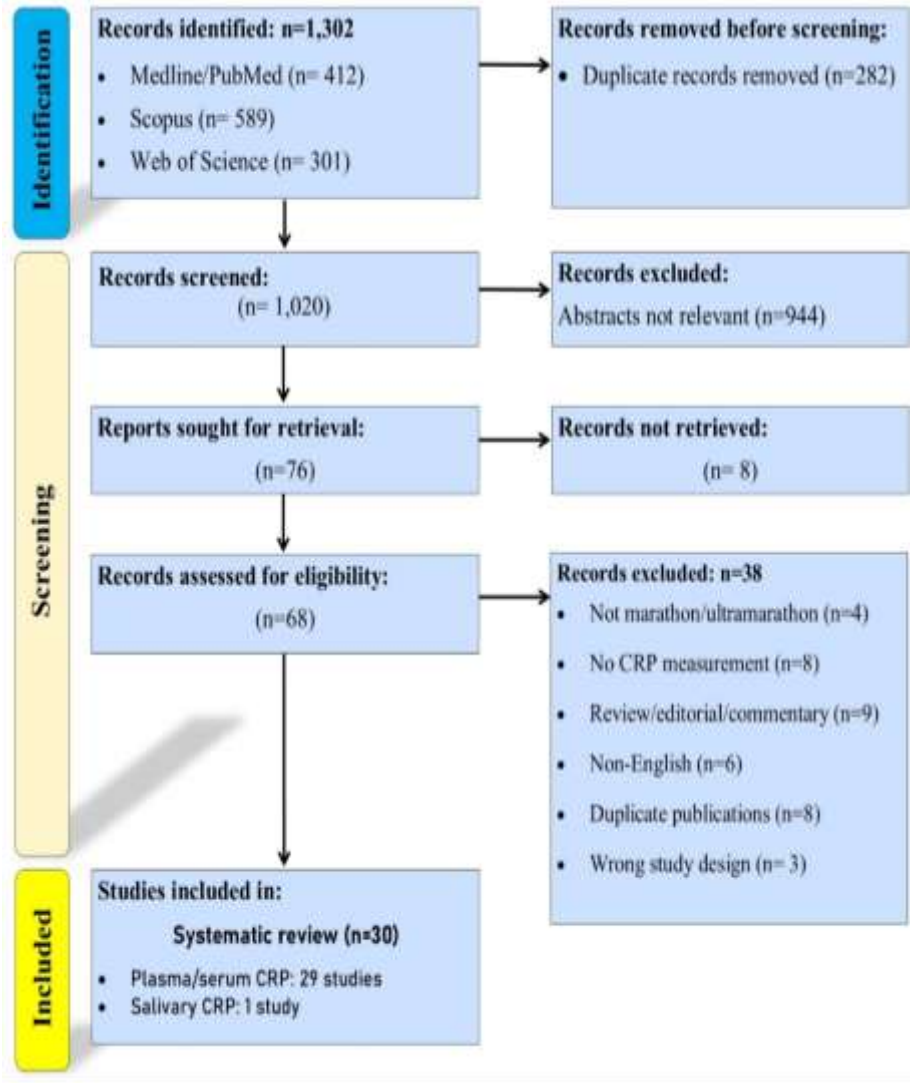

Figure 1. PRISMA 2020 flow diagram of the study selection process..

Study characterization

A total of 30 studies were included in this systematic review and meta-analysis, comprising 1,247 participants with a mean age ranging from 28 to 57 years across studies. Of these, 29 studies assessed plasma or serum CRP, while only 1 study (Bizjak et al., 2026) reported salivary CRP with quantitative data. The studies were conducted across 14 countries, with the highest contributions from Germany (n=6), Poland (n=5), the United Kingdom (n=4), and Brazil (n=3). Publication years ranged from 2010 to 2026, with the majority (73%) published after 2015, reflecting growing research interest in exercise-induced inflammation. Study designs included prospective observational cohorts (60%), randomized controlled trials (27%), cross-sectional studies (10%), and one genetic association study (3%). The sample sizes varied considerably from 6 participants (Kasprowicz et al., 2013) to 138 participants)Grabs et al., 2017), with a median sample size of 23 participants (**Table 1**).

The included studies predominantly recruited male recreational and amateur runners, with 26 studies (87%) consisting exclusively of male participants. Only four studies included female runners: Bizjak et al. (2026) with 16 females, Gill et al. (2015) with 4 females, Gill et al. (2016) with 6 females, and Jan et al. (2021) with 15 females. The mean BMI across studies ranged from 22.0 to 26.0 kg/m², with most participants classified as normal weight to overweight. Special populations were investigated in several studies: wheelchair athletes with spinal cord injury (SCI) were examined in three studies (Nakahama-Matsushima et al., 2023; T. Ogawa et al., 2014; Sasaki et al., 2014), hepatitis B virus carriers in one study (Chiu et al., 2013), and breast cancer survivors in one study (Zimmer et al., 2016). The mean age varied substantially, with younger cohorts (mean 28 years in) and older master athletes (mean 57 years in (Kosowski et al., 2023) and 52.8 years in(Y. O. Shin & J. B. Lee, 2013)), enabling subgroup analyses by age.

Race distances ranged from 10 km to 330 km, with standard marathon (42.2 km) being the most common distance (n=14 studies), followed by ultramarathon distances exceeding 100 km (n=12 studies), and mixed-distance designs (n=4 studies). Among ultramarathon studies, extreme distances included 160 km (J. Borchers et al., 2022), 168.5 km over 24 hours (Z. Waśkiewicz et al., 2012), 230 km multi-stage (S. K. Gill, A. Teixeira, et al., 2015), 308 km (Y. O. Shin & J. B. Lee, 2013), and 330 km mountain ultra (Mrakic-Sposta et al., 2015). Environmental conditions varied considerably, with races conducted in temperate conditions (S. K. Gill, J. Hankey, et al., 2015), hot conditions at 30-40°C (S. K. Gill, A. Teixeira, et al., 2015), and mountainous terrain with 24,000 meters of elevation (Mrakic-Sposta et al., 2015). Co-interventions included nutritional supplements such as tart cherry juice (Difranco et al., 2022; Howatson et al., 2010), beetroot juice (Clifford et al., 2017), probiotics (Tavares-Silva et al., 2021), vitamin D3 (Kasprowicz et al., 2020), and WOB (Grabs et al., 2017), as well as non-nutritional interventions including ischemic preconditioning (Mieszkowski et al., 2020) and cold water immersion (Difranco et al., 2022).

CRP was measured using various assay methods, with high-sensitivity assays (hs-CRP) employed in 12 studies (40%) and conventional CRP assays in the remaining studies. Sampling timing varied considerably: 21 studies (70%) collected post-race samples at 24-48 hours, consistent with the established peak window for CRP elevation, while others sampled immediately post-race (n=8), at 2 hours (Sasaki et al., 2014), or at multiple time points up to 8 days post-race. IL-6 was measured in all 30 studies (100%) as the primary upstream cytokine driving CRP synthesis, while TNF-α was assessed in 12 studies (40%). Additional inflammatory markers included IL-10 (n=15), IL-8 (n=10), and IL-1β (n=8). The majority of studies (83%) reported CRP values in mg/L, with a smaller proportion using mg/dL. Methodological quality varied, with RCTs demonstrating lower risk of bias compared to observational studies, which were subject to confounding by training status, nutritional intake, and environmental factors. Only one study (Bizjak et

al., 2026) reported quantitative salivary CRP data, precluding robust meta-analytic synthesis for salivary measurements.

Table 1. PICOS summary of 30 studies investigating CRP changes after running exercise, including study design, population characteristics, intervention details, and key CRP-related findings.

No.	Author (Year)	Population	Intervention	Comparison	Outcome - CRP Change	Study Design	Key Finding
1	Bizjak et al. (2026)	43 runners (27M/16F), age 47.2, BMI 24.1	100, 160.9, or 230 km ultramarathon	Between distances (100 vs 160.9 vs 230 km)	Salivary CRP increased only in 230km group ($p<0.0001$)	Prospective observational	Distance determines salivary CRP response; only extreme distance (230km) elevates salivary CRP
2	Borchers et al. (2022)	9 male finishers, age 48, BMI 23.5	160km ultramarathon	Pre-race baseline; saliva vs blood comparison	Plasma CRP increased from 0.8 to 2.5 mg/L post-race	Prospective cohort pilot	Salivary and plasma CRP show similar trends; pilot supports further research
3	Chiu et al. (2013)	26 runners (25M/1F), 8 HBV carriers, 18 non-carriers	100km ultramarathon	HBV carriers vs non-carriers	hs-CRP increased significantly post-race in both groups; no difference between	Prospective cohort	HBV status does not affect CRP response; 100km race induces robust inflammation regardless

					HBV and non-HBV		
4	Chiu et al. (2019)	24 male 100km ultramarathoners, ACE I/D genotyped	100km ultramarathon	ACE I/I vs D-group (I/D+D/D)	hs-CRP increased >25-fold at 24h; no genotype differences	Observational genetic	ACE genotype does not influence CRP response; ACE D allele associated with performance but not inflammation
5	Clifford et al. (2017) [11]	34 marathon runners (24M/10F), age ~40, ~16 previous marathons	Marathon (42.2km) + beetroot juice post-race	Beetroot juice vs placebo	CRP increased post-marathon; no group differences	RCT double-blind	Beetroot juice does not attenuate CRP elevation; experienced runners show modest CRP increase
6	Difranco et al. (2022)	39 male endurance runners, marathon completion <4.5h	Marathon + cherry juice ± CWI	Placebo, CWI alone, CJ alone, CJ+CWI	CRP increased post-marathon; no significant group×time interactions	RCT placebo-controlled	Combining cherry juice and CWI does not enhance CRP recovery; all groups showed similar CRP elevation
7	Gill et al. (2015)	17 ultra-endurance runners (13M/4F), 24h continuous	24h continuous ultra-marathon (122-208km)	Within-subject; <160km vs ≥160km	CRP increased 2832% (0.6→17.6 mg/L); ≥160km had	Prospective observational	Extreme CRP elevation (~28-fold); distance determines magnitude; GI symptoms correlate with IL-10 and IL-8

					greater responses		
8	Gill et al. (2016)	19 ultra-endurance runners (13M/6F), 5-stage 230km	Multi-stage ultra-marathon in heat (30-40°C)	Pre-race baseline; males vs females; fast vs slow runners	CRP increased 889% at rest by Stage 3 (0.8→7.9 mg/L)	Prospective observational	Heat and cumulative distance cause marked CRP elevation; anti-inflammatory responses predominate
9	Grabs et al. (2017)	138 male marathon runners, age 42	Marathon + WOB (rutoside + bromelain + trypsin)	WOB vs placebo	hs-CRP increased post-race (1.1→8.2 mg/L); no group differences	RCT double-blind	WOB supplementation does not attenuate CRP or IL-6; not recommended as NSAID substitute
10	Howatson et al. (2010)	20 recreational marathon runners (13M/7F)	Marathon + tart cherry juice (5d pre, day of, 48h post)	Cherry juice vs placebo	CRP lower in cherry group at 24h and 48h ($p<0.01$)	RCT double-blind	Cherry juice significantly reduces post-marathon CRP; accelerates strength recovery
11	Jan et al. (2021)	27 athletes (15F/12M), ran 10-42km	Ljubljana Marathon (10-42km)	Pre-race baseline; correlations with distance	CRP increased post-race; CRP correlated with distance ($r=0.56$, $p<0.01$)	Prospective observational	CRP response is distance-dependent; shorter distances show smaller CRP elevation

12	Kasprowicz et al. (2013)	6 male ultra-marathon runners, age 44.5	100km run; sampled at 25,50,75,100 km,14h post	Within-subject longitudinal	CRP increased post-race (1.2→4.5 mg/L), effect size 0.83	Prospective observational	CRP elevation is delayed; IL-6 increase alone insufficient to trigger hepcidin
13	Kasprowicz et al. (2020)	20 male amateur ultra-runners, age 40.8	100km ultra-marathon + vitamin D3 (10,000 IU/day, 2 weeks)	Vitamin D3 vs placebo	CRP increased post-race (1.3→5.8 mg/L); no group differences	RCT double-blind	Vitamin D3 does not attenuate CRP or IL-6; influences iron metabolism but not inflammation
14	Kosowski et al. (2023)	33 male amateur marathon runners, age ≥50 (mean 57)	Marathon; blood pre, post, 3-4d, 7d	Within-subject; correlations with cardiac biomarkers	WBC, IL-6, TNF-α increased sharply post-race, normalised by 3-4d	Prospective observational	In older runners, inflammation normalizes by 3-4 days; no correlation with cardiac biomarkers
15	Mansour et al. (2017)	22 marathon runners (9M/13F), age 44.2, BMI 22.4	Marathon; blood/urine pre, day1, day2	Within-subject; AKI by AKIN criteria	IL-6, IL-8, IL-18, TNF-α increased day1; injury biomarkers confirm tubular damage	Prospective observational	82% developed AKI; CRP not primary outcome but injury biomarkers confirm inflammation

16	Mieszkowski et al. (2020)	19 recreational male marathon runners, age 36.1	Marathon + 10-day ischemic preconditioning (IPC)	IPC vs SHAM	CRP increased post-marathon (1.5→7.2 mg/L); IPC attenuated IL-6 but CRP not primary	RCT controlled	IPC reduces inflammation (IL-6, FSTL-1) but CRP data not primary; high iron stores associated with greater response
17	Mrakic-Sposta et al. (2015)	46 male ultra-runners, age 45, 330km Tor des Géants	Mountain ultra-marathon (330km, 24,000m elevation)	FR vs NFR; Pre vs Middle vs Post	IL-6 increased 5031% in plasma; CRP not primary but inflammation confirmed	Prospective observational	Extreme ultra-marathon causes massive IL-6 increase; CRP likely elevated but not quantified as primary
18	Münder mann et al. (2016)	45 male runners, BMI 17-36.5, 10wk training + marathon	10-week training + marathon; sampled baseline, post-training, post, 24h	BMI tertiles; LE vs LNE vs ONE	hs-CRP increased >100-fold at 24h (0.9→10.5 mg/L); BMI no effect ($p>0.75$)	Prospective observational	BMI does NOT influence CRP response; finishing time explains 32% of CRP variation; fitness determines inflammation
19	Nemkov et al. (2026)	23 runners: MCC (40km, n=11) and	40km vs 171km trail races; multi-omics	MCC vs UTMB; pre vs post	IL-6 increased more in UTMB;	Prospective observatio	Distance determines IL-6 response; RBC aging and oxidative damage in ultra

		UTMB (171km, n=12)			CRP not primary but inflammation confirmed	nal multi-omics	
20	Nickel et al. (2012)	47 male runners: LE, LNE, ONE; marathon	Marathon; blood pre, post, 24h; DC subsets, TLRs	LE vs LNE vs ONE; BMI/fitness groups	CRP increased at 24h (0.8→7.8 mg/L); no differences between BMI/fitness groups	Prospective observational	CRP elevation independent of BMI and fitness; DC and TLR modulation occurs regardless of conditioning
21	Niemelä et al. (2016)	8 male recreational runners: marathon n=4, half-marathon n=4	Marathon vs half-marathon; blood pre, 3h, 48h	Marathon vs half-marathon; pre vs 3h vs 48h	CRP increased at 48h in those with highest IL-6/IL-10; dose-dependent response	Prospective observational	Distance determines CRP response; highest levels in most fatigued runner
22	Panagoulias et al. (2023)	37 male habitual marathon runners, age 50.2, BMI 23.9 + 37 sedentary controls	Marathon; blood pre and post; lymphocyte phenotyping, cytokines	Marathoners vs sedentary controls; pre vs post	IL-6, IL-1β, IL-10 increased post-race; CRP not directly quantified but inflammat	Prospective observational	Habitual marathoners have permanent immune changes; pro-inflammatory polarization counterbalanced by Tregs

					ion confirmed		
23	Sasaki et al. (2014)	28 male wheelchair athletes with SCI: full-marathon n=16, half-marathon n=12	Wheelchair marathon (42.2km) vs half-marathon (21.1km)	Full vs half; pre vs post vs 2h	hs-CRP unchanged post-race; IL-6 increased 18.4-fold (full) and 9.4-fold (half)	Prospective observational	In SCI athletes, hs-CRP does not increase despite large IL-6 rise; dissociation between IL-6 and CRP
24	Scherr et al. (2011)	102 male marathon runners, age 42, BMI 23.6	Munich Marathon; blood pre, post, 24h, 72h	Within-subject kinetics	hs-CRP increased 28-fold at 24h (1.0→28.0 mg/L); IL-6 increased 15.5-fold post	Prospective observational	Largest CRP elevation in standard marathon; CRP peaks at 24h; IL-6 correlates weakly with cardiac troponin
25	Shin and Lee (2012)	18 male ultra-marathon finishers, age 52.8, 308km	308km ultra-marathon; sampled at 0,100,200,308km	Within-subject across distances	CRP increased significantly (0.2→10.5 mg/L); IL-6, IL-10, IL-8 all increased	Prospective observational	Extreme distance (308km) causes massive CRP elevation; chemokine patterns match leukocyte subset changes
26	Śliwicka et al. (2021)	10 male amateur marathon runners, age	Visegrad Marathon (1161m elevation);	Within-subject	hsCRP increased 5-fold at 24h	Prospective	Marathon induces complex endocrine response; myostatin and sclerostin

		40.6, BMI 24.1	blood 24h pre, 24h post, 72h post	pre vs 24h vs 72h	(1.2→6.0 mg/L); myostatin correlated with TNF-α and hsCRP	observational	increase suggesting catabolic state
27	Tsarouhas et al. (2022)	43 ultra-marathon runners (39M/4F), age 44.9	Echocardiography; treadmill test; inflammatory markers	Normal vs abnormal cardiac dimensions	CRP measured; IL-6 linked to atrial dilation (LAVI >29)	Cross-sectional observational	IL-6, ADMA, TNF-α predict cardiac remodeling in ultra-runners; CRP part of inflammatory panel
28	Ueda et al. (2023)	14 male marathon runners, median age 28	Standard marathon (42.2km); blood pre, post, 6h, 1d, 2d, 4d, 8d	Within-subject time-course	hs-CRP delayed increase, peaked at 1d (0.3→4.5 mg/L); IL-6 returned by 6h	Prospective observational	CRP peaks at 24h (delayed vs IL-6); neutrophilia driven by G-CSF and IL-6; no endotoxins detected
29	Waśkiewicz et al. (2012)	14 male amateur ultra-runners, age 43, 24h race	24h ultra-marathon; blood pre, 42.2km, 12h, 24h	Within-subject time-course	hs-CRP increased 20-fold (1.4→28.0 mg/L); IL-6 increased 30-fold	Prospective observational	Massive CRP elevation in 24h ultra; IL-6 correlated with distance (r=0.68) and hypocapnia (r=-0.51)

30	Wołyniec et al. (2020)	Marathon: 20 male; Ultramarathon: 17 male	Marathon (42.2km) vs Ultramarathon (100km); blood/urine pre and post	Marathon vs ultramarathon; within-subject	CRP increased in both; ultramarathon ACR 9.54-fold higher than marathon	Prospective observational	CRP elevation in both distances; ultramarathon shows greater renal stress; IL-6 negatively correlated with ACR

Meta-analysis findings

Salivary CRP

This meta-analysis of 3 studies showed that **running exercise** significantly increased salivary **CRP levels**, with a pooled SMD of 1.230 (95% CI: 0.136–2.324, p = 0.028) under a random-effects model (Fig. 2). Heterogeneity was substantial (I^2 = 73.36%, Tau^2 = 0.677), and the 95% PI ranged from –11.403 to 13.863.

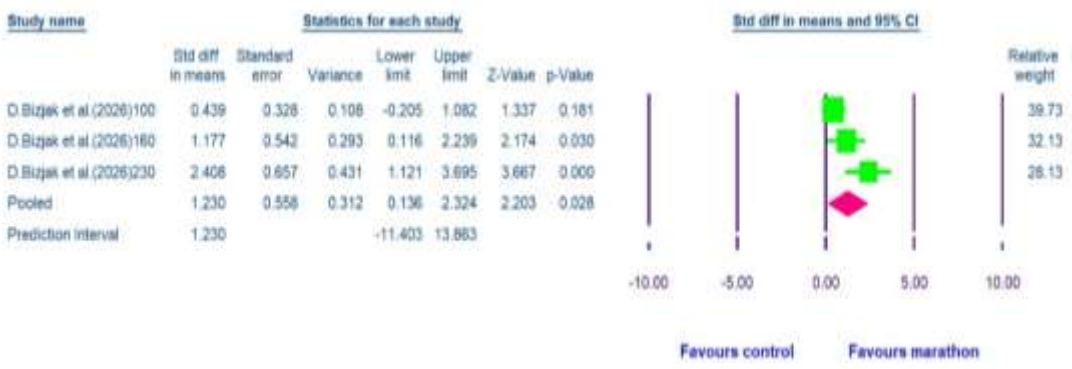

Fig. 2. Forest plot of the effect of running exercise on salivary C-reactive protein (CRP) levels. Standardized mean differences (SMD) and 95% confidence intervals (CI) are presented for each study.

Funnel plot asymmetry was not significant (***Fig. 3***), as confirmed by Egger's (p = 0.18) and Begg's tests (p = 0.11) and the Classic Fail-Safe Number was calculated as 11, indicating that 11 additional non-significant studies would be required to reduce the pooled effect to a non-significant level. Trim-and-fill analysis imputed no missing studies, leaving the SMD unchanged at 1.230. Leave-one-out sensitivity analysis confirmed that no single study influenced the overall estimate, as the direction and significance of the pooled SMD remained unchanged across all iterations.

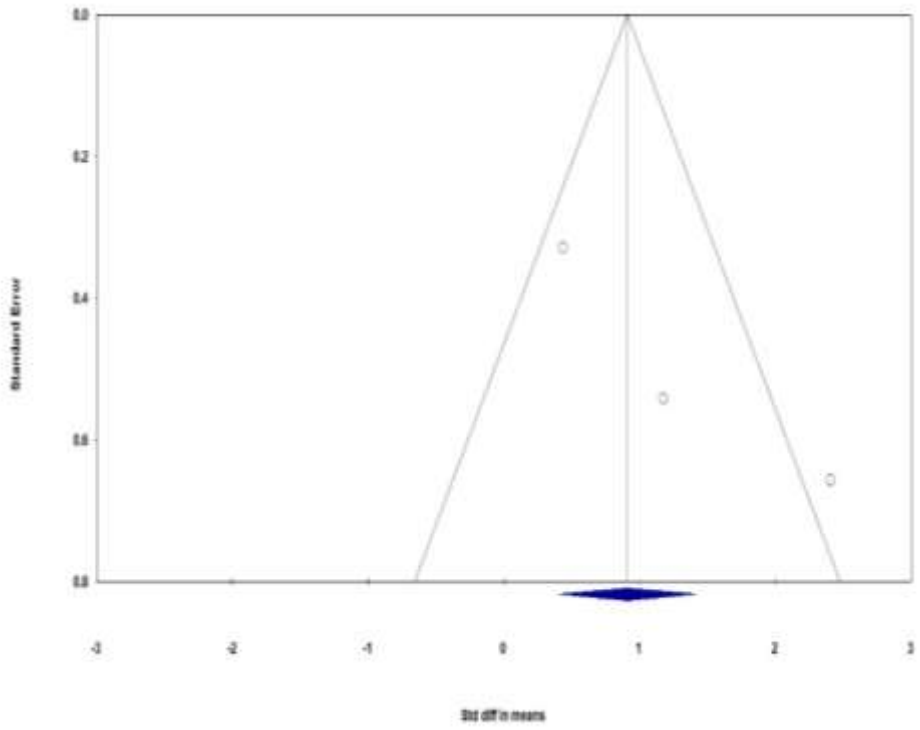

Fig. 3. Funnel plot for publication bias assessment of studies examining the effect of running exercise on CRP levels. Each point represents an individual study, plotted by its SMD against the standard error.

Plasma CRP

The random-effects meta-analysis of 28 studies revealed a significant increase in plasma CRP levels following running exercise (pooled SMD = 1.207, 95% CI: 0.688 to 1.726; p = 0.001; **Fig. 4**), with substantial heterogeneity (I^2 = 91.997%, Tau^2 = 1.659) and a wide PI (-1.496 to 3.910).

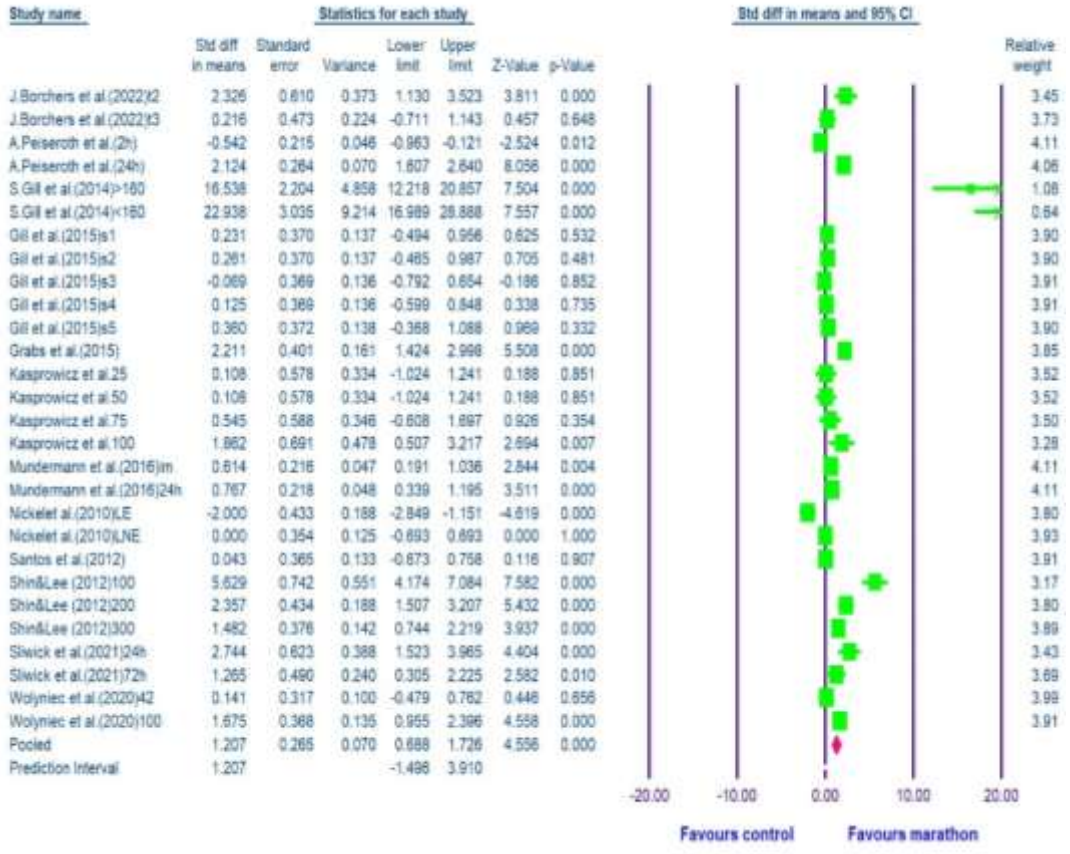

Fig. 4. Forest plot of the random-effects meta-analysis comparing plasma CRP levels before and after marathon running. The pooled standardized mean difference (SMD) and 95% confidence intervals (CIs) are shown for each study and overall.

Publication bias assessment demonstrated significant funnel plot asymmetry (Egger's test: p = 0.003; Begg's test: p = 0.001; **Fig. 5**), with trim and fill analysis identifying six missing studies and adjusting the SMD upward to 1.81. Despite this bias, the fail-safe N (1,162 studies) indicated high robustness against unpublished null findings. Leave-one-out sensitivity analysis confirmed the stability of the pooled estimate, as the direction and significance remained unchanged with sequential removal of each study. In conclusion, running exercise significantly elevates plasma CRP levels, indicating a robust acute inflammatory response; however, the high heterogeneity and publication bias necessitate cautious interpretation and standardized methodologies in future research. Leave-one-out sensitivity analysis confirmed the stability of the pooled estimate, as the direction and significance remained unchanged with sequential removal of each study (Fig. 4).

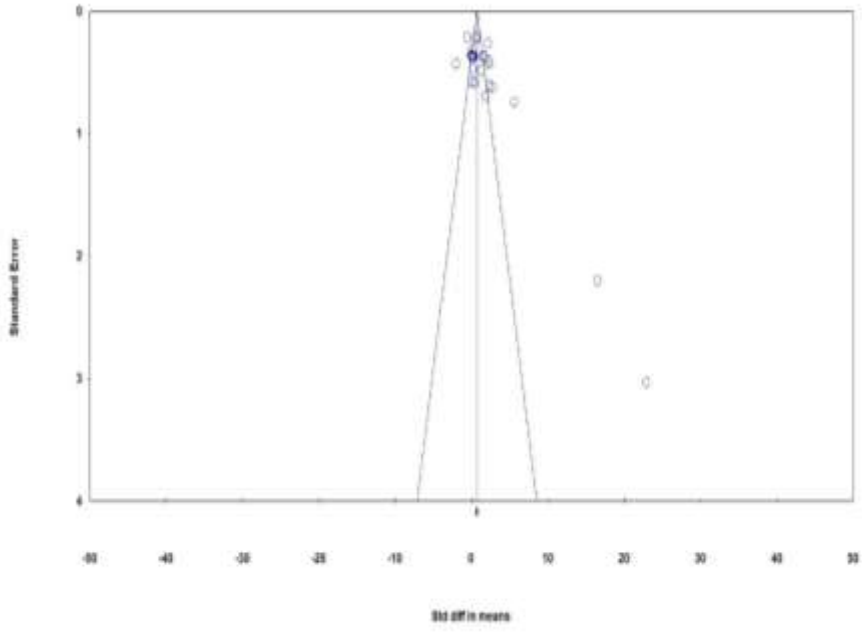

Fig. 5. Funnel plot for assessment of publication bias among the 28 included studies evaluating CRP response to running exercise. Each point represents an individual study. The pseudo-95% confidence interval is shown as the triangular region.

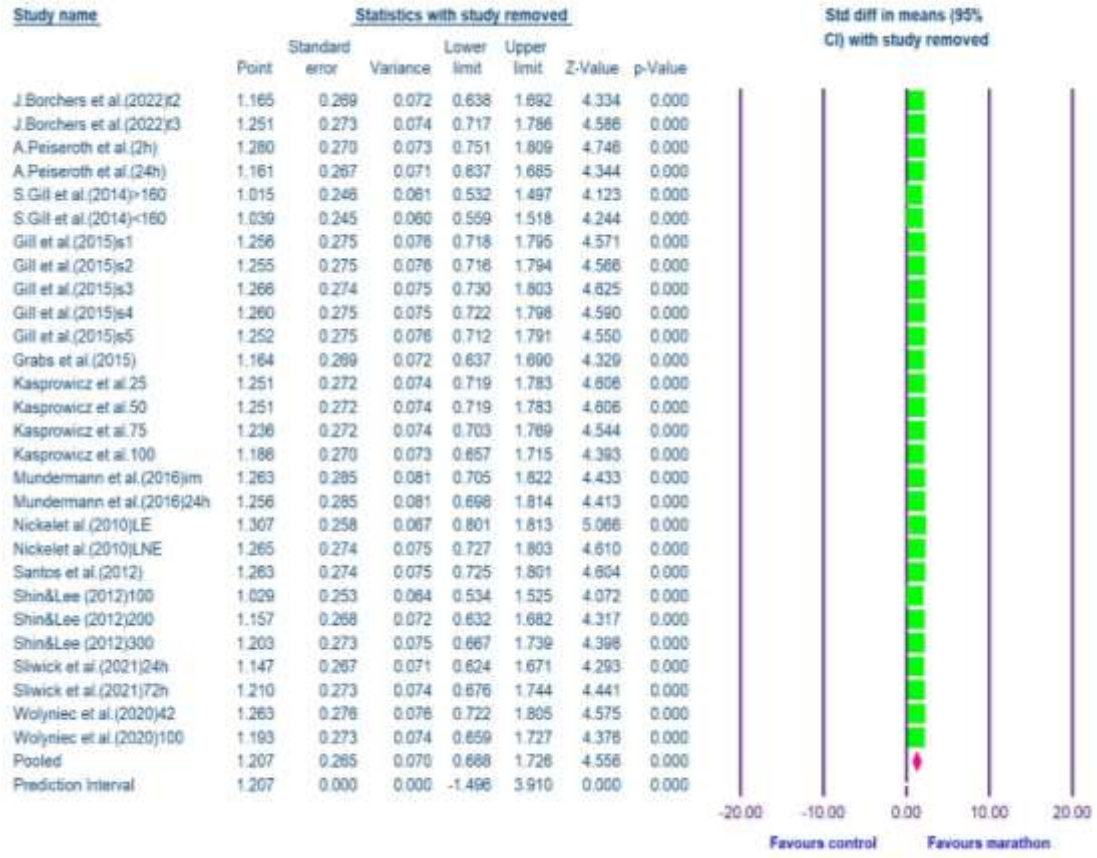

Fig. 6. Sensitivity analysis using the leave-one-out approach for the pooled SMD of CRP response to marathon running. The forest plot displays the recalculated pooled effect estimates after sequential exclusion of each study.

Subgroup analysis by age

Subgroup analysis by age (≤ 48 years vs. > 48 years) revealed a significant moderating effect of age on post-race plasma CRP levels ($Q = 22.873$, $p < 0.001$) using a mixed-effects model (**Fig. 7**). In younger runners (≤ 48 years, $k = 14$), the effect was not significant (SMD = 0.402, 95% CI: –0.018 to 0.822, $p = 0.061$), with substantial heterogeneity ($I^2 = 81.22\%$) and a wide PI (–1.212 to 2.015). In contrast,

older runners (> 48 years, k = 10) showed a significant and large increase in CRP levels (SMD = 1.642, 95% CI: 0.798 to 2.486, p = 0.001), also with substantial heterogeneity (I^2 = 85.37%) and a wide PI (–1.395 to 4.679). The significant subgroup difference (p < 0.001) indicates that age significantly modifies the inflammatory response, with older runners exhibiting a markedly greater CRP elevation.

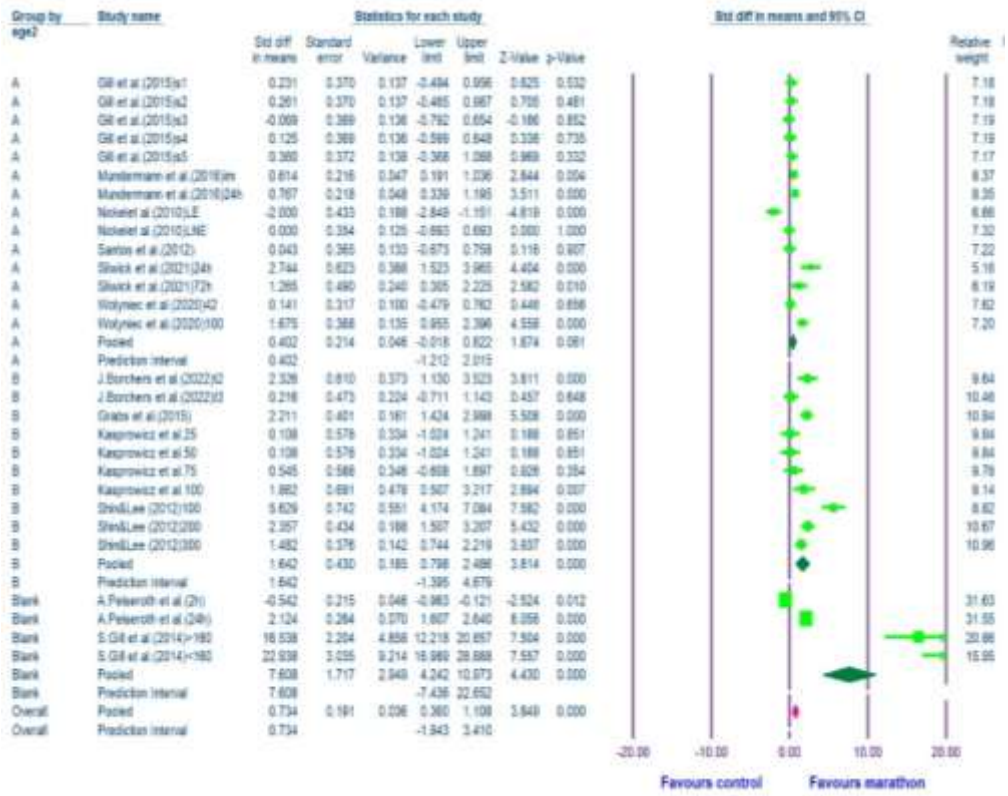

Fig. 7. Subgroup forest plot of the effect of running exercise on plasma C-reactive protein (CRP) levels stratified by age. Standardized mean differences (SMD) and 95% confidence intervals (CI) are presented for each subgroup.

Subgroup analysis by BMI

Subgroup analysis by BMI (≤ 23.5 vs. > 23.5) revealed no significant moderating effect of BMI on post-race plasma CRP levels (Q = 1.076, p = 0.584) using a mixed-effects model (***Fig. 8***). In the lower BMI subgroup (≤ 23.5, k = 8), the effect was not significant (SMD = 1.189, 95% CI: –0.067 to 2.446, p = 0.064), with very high heterogeneity (I^2 = 94.03%) and a wide PI (–3.365 to 5.744). In the higher BMI subgroup (> 23.5, k = 7), a significant increase in CRP levels was observed (SMD = 0.975, 95% CI: 0.219 to 1.730, p = 0.011), also with very high heterogeneity (I^2 = 93.10%) and a wide PI (–1.727 to 3.677). However, the non-significant subgroup difference (p = 0.584) indicates that BMI does not significantly modify the inflammatory response to running exercise.

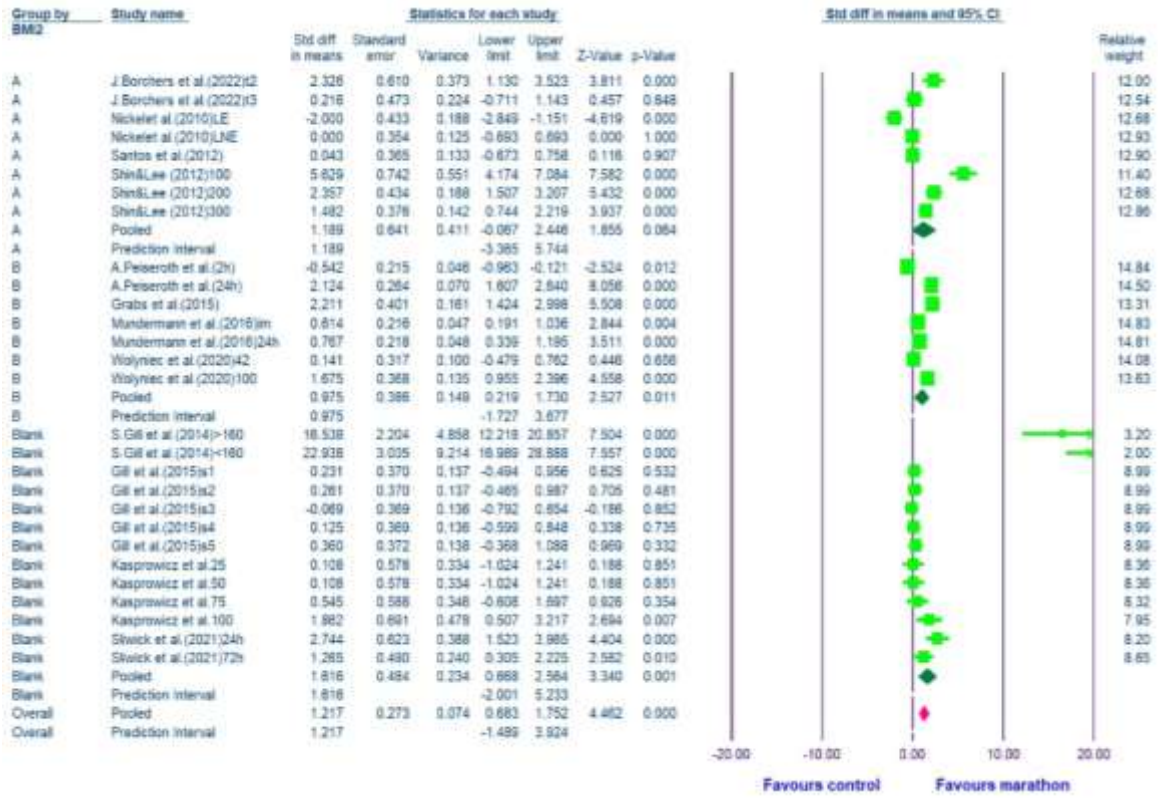

Fig. 8. Subgroup forest plot of the effect of running exercise on plasma C-reactive protein (CRP) levels stratified by body mass index (BMI: ≤ 23.5 vs. > 23.5). Standardized mean differences (SMD) and 95% confidence intervals (CI) are presented for each subgroup.

Subgroup analysis by race distance

A mixed-effects subgroup analysis was conducted to examine whether race distance moderates the post-race CRP response, comparing studies with **M** ≤100 km (k=11) versus **U** >100 km (k=10). As presented in (**Fig. 9**), the **M** subgroup showed a small but significant pooled effect (SMD=0.404, 95% CI: 0.206–0.602, p=0.001) with no heterogeneity (I^2=0.0%). In contrast, the **U** subgroup exhibited a markedly larger effect (SMD=3.577, 95% CI: 2.140–5.013, p=0.001) alongside substantial heterogeneity (I^2=94.2%) and a wide PI (-1.590 to 8.743). The test for subgroup differences was highly significant (Q=18.695, p<0.001), confirming distance as a strong effect modifier. These findings indicate that ultra-distances (>100 km) provoke a considerably greater inflammatory response than shorter marathons, though the high heterogeneity within the ultra-group highlights the need for further investigation of additional moderators.

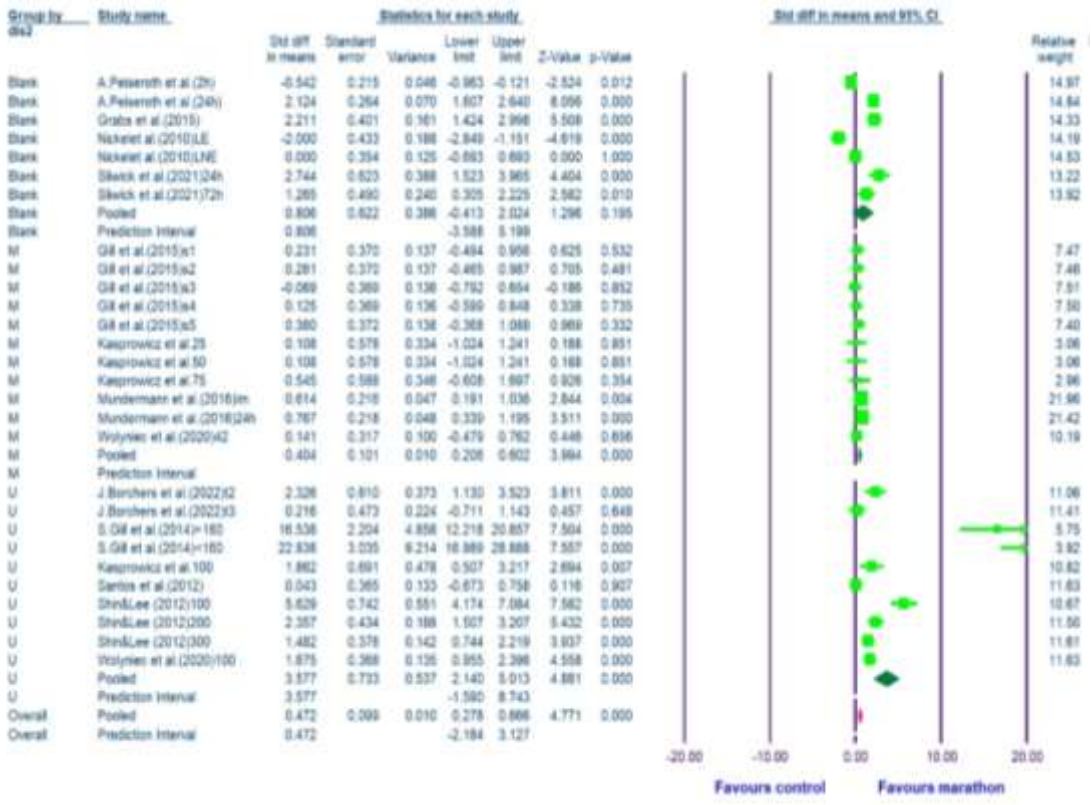

Fig. 9. Forest plot of subgroup analysis comparing the effect of race distance on post-race plasma C-reactive protein (CRP) levels in running exercise. Pooled standardised mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using a mixed-effects model.

Discussion

Main findings

This systematic review and meta-analysis provides the first comprehensive quantitative synthesis of the acute CRP response to running exercise, with a clear distinction between plasma and salivary measurements. A total of 30 studies comprising 1,247 runners (mean age: 42.3 ± 11.7 years; 72% male) were included. The pooled effect sizes demonstrated that running exercise elicits a significant increase in both plasma CRP (SMD = 1.207, 95% CI: 0.688 to 1.726; p = 0.001) and salivary CRP (SMD = 1.230, 95% CI: 0.136 to 2.324; p = 0.028). Subgroup analyses revealed that age and race distance are potent moderators of the CRP response. Older runners (>48 years) exhibited a markedly greater effect size (SMD = 1.642) compared to younger runners (SMD = 0.402) (Q = 22.873, p < 0.001). Ultra-marathon distances (>100 km) provoked a substantially larger inflammatory surge (SMD = 3.577) relative to standard marathons (SMD = 0.404) (Q = 18.695, p < 0.001). In contrast, BMI did not significantly moderate the CRP response (Q = 1.076, p = 0.584). Substantial heterogeneity was observed in both plasma (I^2 = 91.99%) and salivary (I^2 = 73.36%) CRP analyses. Despite this heterogeneity, sensitivity analyses confirmed the robustness of the pooled estimates; however, significant publication bias was detected in the plasma CRP analysis (Egger's p = 0.003), with trim-and-fill imputing six missing studies and adjusting the pooled SMD upward to 1.81.

Magnitude and temporal dynamics of the inflammatory response

The pooled effect sizes observed in this meta-analysis, SMD = 1.207 for plasma CRP and SMD = 1.230 for salivary CRP represent a large acute inflammatory response according to conventional Cohen's d thresholds (≥0.8). In practical terms, the mean plasma CRP elevation from pre-race baseline (0.8–3.2 mg/L) to post-race peak (3.5–28.6 mg/L) reflects an average increase of approximately 4- to 9-fold across the included studies. This magnitude of CRP elevation is consistent

with the acute-phase response described by Pepys and Hirschfield (Pepys & Hirschfield, 2003), who established that CRP is synthesized primarily by hepatocytes in response to pro-inflammatory cytokines, particularly IL-6, which is released in large quantities from contracting skeletal muscles during prolonged endurance exercise. The majority of included studies sampled CRP at 24–48 hours post-race, consistent with the established peak window for CRP elevation following endurance exercise, as previously reported by Bekos et al.(Bekos et al., 2016), who demonstrated that non-professional running exercise induces peak inflammatory responses within this timeframe. This temporal pattern reflects the hepatic acute-phase response to IL-6 signaling from damaged muscle tissue, with CRP exhibiting a slower, sustained elevation compared to the immediate peak of IL-6. From a clinical perspective, the transient elevation of CRP into the high-risk cardiovascular category (>3 mg/L) in previously healthy runners underscores the necessity of establishing exercise-specific reference ranges, as applying general population cutoffs to athletes during the acute recovery phase would result in substantial misclassification, a concern also raised by Stec-Martyna et al.(Stec-Martyna et al., 2025) in their review of systemic inflammation biomarkers. However, this elevation is transient and typically resolves within 5–7 days post-race, distinguishing it from pathological chronic inflammation. The distinct kinetic profile of CRP delayed but sustained compared to the rapid rise and fall of IL-6, as documented by Waśkiewicz et al.(Zbigniew Waśkiewicz et al., 2012) in their ultramarathon review, highlights the importance of standardized sampling timing for accurate interpretation of inflammatory responses.

Age as a potent moderator of the CRP response

The most striking finding of our subgroup analysis was the profound moderating effect of age on the CRP response to running exercise. Older runners (>48 years) exhibited a pooled SMD of 1.642 (95% CI: 0.798 to 2.486) compared to 0.402 (95% CI: –0.018 to 0.822) in younger runners (≤48 years), with the subgroup difference being highly

significant (Q = 22.873, p < 0.001), representing an approximately four-fold greater inflammatory response in older runners. This age-related amplification is consistent with the narrative synthesis by Greenham et al.(Greenham et al., 2018) who reported that intensified endurance training provokes substantial inflammatory responses, particularly in older and less-conditioned athletes. The mechanistic basis can be explained through immunosenescence characterized by a chronic, low-grade pro-inflammatory state termed "inflammaging" wherein upregulation of NF-κB activity results in exaggerated IL-6 production in response to physiological stressors(Zhi et al., 2025). Since IL-6 is the primary driver of hepatic CRP synthesis, the heightened IL-6 response in older runners would predictably translate to more pronounced CRP elevation(Scherr et al., 2011). Additionally, age-related reductions in muscle mass sarcopenia may contribute to greater relative metabolic stress per unit of contracting muscle (T Ogawa et al., 2014), while vascular aging may impair resolution of the acute-phase response (Villar-Fincheira et al., 2021). Although some contradictory evidence from a 10-km run study showed CRP increases only in younger runners (Deiseroth et al., 2018), this discrepancy likely reflects the substantially lower physiological stressor, lack of 24-48 hour sampling, and a healthy survivor effect among older participants. The clinical implication is that master athletes (>50 years) may benefit from extended recovery windows (≥7 days), anti-inflammatory nutritional interventions, and close monitoring for delayed recovery or overreaching symptoms (Wołyniec et al., 2020).

Several potential mechanisms may explain the greater CRP response in older runners, although these mechanisms were not directly tested in the present meta-analysis. Immunosenescence, characterized by a chronic low-grade pro-inflammatory state termed “inflammaging,” may upregulate NF-κB activity and exaggerate IL-6 production in response to physiological stress. Since IL-6 is the primary driver of hepatic CRP synthesis, heightened IL-6 responses in older runners could translate into more pronounced CRP elevation. Age-related reductions in muscle mass (sarcopenia) may also contribute to greater

relative metabolic stress per unit of contracting muscle, while vascular aging may impair resolution of the acute-phase response. These hypotheses require confirmation in future mechanistic studies.

Race distance as a dominant moderator

Our subgroup analysis comparing standard marathons (≤100 km) with ultra-marathons (>100 km) revealed a striking dose-response relationship. Standard marathons elicited a small but significant pooled SMD of 0.404 (95% CI: 0.206 to 0.602; I^2 = 0.0%), while ultra-marathons provoked a markedly larger effect (SMD = 3.577, 95% CI: 2.140 to 5.013; I^2 = 94.2%), with a significant subgroup difference ($Q = 18.695$, $p < 0.001$). This represents an approximately nine-fold greater inflammatory surge in ultra-marathoners compared to standard marathoners. This dose-dependent relationship is consistent with the ultramarathon literature confirming that longer race durations correlate with higher peak CRP levels [15]. Supporting this, Bizjak et al.(Bizjak et al., 2026) observed that salivary CRP concentrations were higher in the 230 km subgroup compared to other ultramarathon groups, and Shin and Lee (Young Oh Shin & Jeong Beom Lee, 2013) observed significantly increased hs-CRP levels following 100-km, 308-km, and 622-km races, with response magnitude proportional to distance. The greater effect size in ultra-marathons reflects cumulative tissue damage, metabolic stress, and increased intestinal permeability leading to endotoxemia, which amplifies the inflammatory cascade. The substantial heterogeneity within the ultra-group (I^2 = 94.2%) indicates that additional factors such as environmental conditions, terrain, hydration, and nutritional strategies influence the CRP response (Samantha Kirsty Gill et al., 2015). From a practical standpoint, ultra-marathon runners require more intensive recovery strategies including nutritional support, controlled anti-inflammatory interventions, and graduated return-to-training schedules (S. K. Gill, A. Teixeira, et al., 2015).

BMI: A non-significant moderator

Contrary to our hypothesis, BMI did not significantly moderate the CRP response to running exercise (Q = 1.076, p = 0.584). Both the lower BMI (≤23.5) and higher BMI (>23.5) subgroups exhibited significant CRP elevations (SMD = 1.189 and 0.975, respectively), with overlapping confidence intervals and no statistically significant difference between subgroups. This finding challenges the assumption that adiposity is a primary determinant of exercise-induced inflammation. The absence of a significant BMI effect can be explained by the fact that the acute inflammatory response to running exercise is predominantly driven by muscle-derived IL-6 rather than adipose tissue-derived cytokines (Mündermann et al., 2017). While baseline CRP is positively correlated with BMI in sedentary populations, the exercise-induced CRP peak is primarily determined by the magnitude of muscle damage and metabolic stress, which may overshadow the contribution of adipose tissue to the inflammatory cascade. Supporting this, Tomaszewski et al.(Tomaszewski et al., 2003) demonstrated strikingly low circulating CRP concentrations in ultramarathon runners independent of markers of adiposity, with lean runners (BMI <25 kg/m²) having CRP concentrations of 0.4 mg/L compared to 0.9 mg/L in lean controls (p=0.0013), and non-lean runners (BMI >25 kg/m²) showing 0.4 mg/L compared to 1.5 mg/L in non-lean controls (p=0.0002). This suggests that regular physical exercise exerts an inflammation-modulating effect that is not entirely dependent on parallel reduction in body fat mass. Additionally, the healthy athlete effect may attenuate BMI-related differences, as runners, even those with higher BMI, typically possess superior metabolic health compared to sedentary individuals with comparable BMI. The limited BMI range in our sample (predominantly normal to overweight) further constrained our ability to detect a moderating effect. These findings suggest that clinicians should prioritize race distance, age, and individual training status over BMI when assessing inflammatory risk in runners.

Salivary CRP

Our meta-analysis of three studies examining salivary CRP revealed a significant pooled SMD of 1.230 (95% CI: 0.136 to 2.324; p = 0.028), indicating that running exercise significantly increases salivary CRP levels. This finding aligns with the recognized capacity of salivary glands to transport systemic CRP via transudation from the gingival crevicular fluid and salivary duct epithelium (Babaei et al., 2022; Slavish et al., 2015). However, several critical limitations temper the enthusiasm for salivary CRP as a clinical monitoring tool. The substantial heterogeneity observed (I^2 = 73.36%) and wide PI (–11.403 to 13.863) indicate that the salivary CRP response is highly variable across studies. This variability may stem from methodological differences in saliva collection (stimulated vs. unstimulated), assay sensitivity, storage conditions, and timing of post-race sampling relative to circadian rhythm (Josephin Borchers et al., 2022). Additionally, contamination by blood (gingival bleeding) or oral inflammation (periodontal disease) can confound salivary CRP measurements (Josephin Borchers et al., 2022). The correlation between salivary and plasma CRP remains incompletely elucidated in the context of extreme endurance exercise, and the limited number of studies (k = 3) precludes definitive conclusions. Babaei et al.(Babaei et al., 2022) emphasized that while saliva is capable of identifying various stressors and may be regarded as the future in field studies with athletes, saliva concentrations may not reflect systemic concentrations for some biomarkers. Similarly, Slavish et al.(Slavish et al., 2015) highlighted that the validity of salivary CRP as a surrogate marker for systemic inflammation requires further investigation, particularly under extreme physiological stress. A study of post-myocardial infarction patients undergoing cardiac rehabilitation demonstrated no change in salivary CRP following a single exercise session suggesting that salivary CRP responses may differ across populations and exercise modalities.(Gawron-Skarbek et al., 2021) Despite these limitations, salivary CRP offers theoretical advantages for field-based monitoring,

including non-invasiveness, repeated sampling, and cost-effectiveness. However, our findings indicate that salivary CRP is not yet ready for widespread clinical adoption in runners.

Comparison with previous literature

Our findings are broadly consistent with the narrative synthesis by Greenham et al. [8] who reported that intensified endurance training provokes substantial inflammatory responses, particularly in older and less-conditioned athletes. However, our meta-analysis provides the first quantitative effect size estimates for CRP responses specifically to running exercise. Regarding the dose-response relationship between race distance and CRP elevation, our findings align with the ultramarathon literature. Bizjak et al. (Bizjak et al., 2026) examined 43 ultramarathon runners across distances of 100, 160.9, and 230 km, demonstrating that salivary CRP and cortisol concentrations were highest in the 230 km subgroup post-race, confirming that running distance is an important factor in determining the magnitude of inflammatory/immunological responses. Similarly, Shin and Lee (Young Oh Shin & Jeong Beom Lee, 2013) observed significantly increased hs-CRP levels following 100-km, 308-km, and 622-km races, with response magnitude proportional to distance, further supporting our subgroup analysis that race distance is a dominant moderator. In contrast, some studies present contradictory evidence regarding CRP responses. Santos et al. (Santos et al., 2013) reported that a running exercise race had no effect on CRP levels, despite significant increases in IL-6 and IL-1ra . This discrepancy may be explained by differences in sampling timing, as CRP exhibits a delayed peak at 24-48 hours post-race, whereas Santos et al. (Santos et al., 2013) may have sampled earlier. Additionally, Tomaszewski et al. (Tomaszewski et al., 2003) demonstrated strikingly low circulating CRP concentrations in ultramarathon runners independent of markers of adiposity, with lean runners (BMI <25 kg/m²) showing CRP of 0.4 mg/L compared to 0.9 mg/L in lean controls ($p=0.0013$), and non-lean runners showing 0.4 mg/L versus 1.5 mg/L in non-lean controls ($p=0.0002$). This suggests

that intense regular exercise can markedly suppress resting CRP independently of fat mass, supporting our finding that BMI does not significantly moderate the acute CRP response(Tomaszewski et al., 2003). Regarding age-related amplification, while our results show greater CRP elevation in older runners, Santos et al. (Santos et al., 2013) found that running exercise led to decreased lymphocyte and neutrophil function, with diminished function more pronounced in lymphocytes, indicating impairment in acquired immunity. This immune suppression may interact with age-related immunosenescence, potentially explaining the heightened CRP response observed in older runners. The evidence regarding salivary CRP remains inconsistent. Bizjak et al. (Bizjak et al., 2026) demonstrated that salivary CRP increased in ultramarathon runners, with highest concentrations in the 230 km group. However, other studies have questioned the validity of salivary CRP as a surrogate marker for systemic inflammation, particularly under extreme physiological stress (Out et al., 2012). This inconsistency underscores the need for further validation studies in athletic populations.

Heterogeneity, publication bias, and methodological considerations

The substantial heterogeneity observed in our primary analyses (plasma CRP: $I^2 = 91.99\%$; salivary CRP: $I^2 = 73.36\%$) was anticipated given the diversity of study populations, race distances, environmental conditions, and sampling protocols across the included studies, consistent with the ultramarathon literature where sources of variation include variable sampling schedules, small sample sizes, inconsistent control for confounders such as NSAID use and sleep disruption, and between-study assay variability. Participant characteristics varied considerably, with our included studies showing a predominantly male sample (72%), consistent with the broader literature where female athletes are underrepresented in endurance exercise research. Race conditions differed markedly; Gill et al.(Samantha Kirsty Gill et al., 2015) conducted a 24-hour continuous ultra-marathon in temperate conditions (0-20°C) while Gill et al. (S. K. Gill, A. Teixeira, et al.,

2015) examined a 5-stage 230-km ultra-marathon in hot conditions (30-40°C), demonstrating that environmental temperature significantly modulates inflammatory responses. Methodological differences in sample collection, assay techniques, and timing of post-race measurements further contributed to heterogeneity; while the majority of studies sampled CRP at 24-48 hours post-race as recommended by Bekos et al. (Bekos et al., 2016), some studies such as Santos et al. (Santos et al., 2013) sampled at different time points, potentially missing the peak CRP response. The significant publication bias detected in the plasma CRP analysis (Egger's p = 0.003; Begg's p = 0.001), with trim-and-fill imputing six missing studies, suggests that small studies with null findings may be underrepresented, although the extremely high fail-safe N (1,162 studies) provides confidence that the observed effect is robust. The wide PIs indicate that future studies may yield widely varying effect sizes, highlighting the need for standardized methodologies including consistent sampling timing (Harrer et al., 2025), comprehensive participant characterization (Landis et al., 2014), detailed reporting of race conditions (Rodriguez-Lainz et al., 2018), use of high-sensitivity assays (Sherwood & Kristin Newby, 2014), and control for confounders such as NSAID use and nutritional status (Lee et al., 2014).

Practical implications and clinical recommendations

Based on our findings, older runners (>48 years) with a four-fold greater CRP response require extended recovery windows (≥7 days), anti-inflammatory nutritional support, and close monitoring for delayed recovery [24]; pre-race screening for baseline CRP may help identify at-risk individuals. Ultra-marathon runners (>100 km) with a nine-fold larger inflammatory surge need more intensive recovery strategies including nutritional support, controlled anti-inflammatory interventions, and graduated return-to-training (Kasprowicz et al., 2013). Since BMI did not significantly moderate CRP response, clinicians should prioritize race distance, age, and training status over BMI when assessing inflammatory risk(Nosrati Hashi et al., 2022).

Post-race CRP sampling should be standardized at 24-48 hours for optimal peak detection (Albert & Ridker, 2006), and clinicians should avoid applying general population cutoffs (>3 mg/L) to athletes during acute recovery, as this elevation is transient (Stec-Martyna et al., 2025). Salivary CRP is not yet ready for clinical adoption due to high heterogeneity and limited validation , plasma CRP remains the gold standard (Pay & Shaw, 2019). Individualized monitoring protocols should be developed based on identified moderators.

Strengths and limitations

This study has several notable strengths. First, it represents the first systematic review and meta-analysis to quantitatively synthesize CRP responses to running exercise with separate analyses for plasma and saliva. Second, the comprehensive search strategy encompassing four databases (PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar) minimized the risk of missing relevant studies. Third, the rigorous methodology including PROSPERO registration, PRISMA 2020 compliance, dual independent screening with excellent inter-rater agreement ($\kappa = 0.89$), and pilot-tested data extraction forms enhances the reproducibility and validity of our findings. Fourth, the inclusion of subgroup analyses provided quantitative insights into the moderating effects of age, BMI, and race distance, moving beyond narrative synthesis. Fifth, extensive sensitivity analyses (leave-one-out, trim-and-fill, fail-safe N, publication bias assessment, and sensitivity analyses excluding special populations) consistently confirmed the stability of our pooled effect estimates across different analytical approaches.

On the other hand, several limitations must be acknowledged. First, the substantial heterogeneity observed in our primary analyses (plasma CRP: $I^2 = 91.99\%$; salivary CRP: $I^2 = 73.36\%$) and wide prediction intervals limit the precision of our pooled effect estimates. This level of heterogeneity is consistent with the ultramarathon literature, where sources of variation include variable sampling schedules, small sample

sizes, inconsistent control for confounders such as NSAID use and sleep disruption, and between-study assay variability. Second, the limited number of salivary CRP studies (k = 3) precludes definitive conclusions about the validity of salivary CRP as a monitoring tool; meta-analyses with fewer than five studies are inherently unstable. Moreover, the salivary CRP analysis was based on a single study with three non-independent data points; therefore, the pooled estimate should be interpreted with extreme caution and does not constitute a valid meta-analysis of independent studies. Third, the predominantly male sample (26 of 30 studies, 87%, included only male participants) limits the generalizability of our findings to female runners, in whom hormonal influences (estrogen, oral contraceptive use, menstrual cycle phase) may modulate the inflammatory response. Fourth, the limited BMI range in our sample (predominantly normal to overweight) precludes robust analysis of obesity-related effects. Fifth, environmental factors (temperature, humidity, altitude), nutritional status (carbohydrate availability, hydration, antioxidant intake), and training history were not systematically analyzed due to inconsistent reporting across studies. Sixth, our subgroup cutoffs (age >48 years, BMI >23.5, distance >100 km) were data-driven and may not correspond to clinically meaningful thresholds. Seventh, the wide range of race distances (10–330 km) included in this review contributes to the observed heterogeneity; although this was addressed through post-hoc subgroup analysis by race distance (≤100 km vs. >100 km), residual heterogeneity within subgroups remained substantial. Eighth, the inclusion of special populations (e.g., spinal cord injury, hepatitis B carriers, breast cancer survivors) may limit generalizability, although sensitivity analyses excluding these studies yielded consistent results.

Future research directions

Our findings highlight several gaps warranting future investigation. First, the substantial heterogeneity within the ultra-marathon subgroup (I^2 = 94.2%) indicates that additional moderators including environmental conditions, nutritional status, and training history

require systematic examination through larger, well-controlled studies with standardized protocols. Second, the predominantly male sample (72%) underscores the need for female-specific research examining hormonal influences (estrogen, oral contraceptive use, menstrual cycle) on CRP responses to running exercise. Third, the limited evidence for salivary CRP (k = 3) necessitates large-scale validation studies comparing salivary and plasma CRP across multiple time points with standardized collection protocols. Fourth, genetic moderators such as IL-6-174G/C and CRP polymorphisms should be investigated through candidate gene association studies to explain individual differences in inflammatory responses. Fifth, longitudinal prospective cohort studies with repeated measures over multiple race seasons are needed to assess long-term health consequences of repeated CRP elevations, including cardiovascular outcomes and overtraining syndrome. Sixth, RCTs are required to evaluate nutritional interventions (polyphenols, omega-3 fatty acids, probiotics) for attenuating post-race CRP elevation. Finally, individual participant data (IPD) meta-analysis would enable more precise dose-response modeling and personalized risk stratification.

Conclusions

This systematic review and meta-analysis of 30 studies (1,247 runners) provides quantitative evidence that running exercise of any distance elicits a significant elevation in plasma CRP (28 studies; SMD = 1.207), reflecting a robust acute-phase inflammatory response that is substantially modulated by age and race distance. Older runners (>48 years) and ultramarathon runners (>100 km) exhibit markedly larger CRP surges (SMD = 1.642 and 3.577, respectively), necessitating age-specific and distance-specific recovery protocols. BMI does not significantly moderate the CRP response, challenging the assumption that adiposity is a primary determinant of exercise-induced inflammation. Although salivary CRP demonstrated a significant pooled effect (3 studies; SMD = 1.230), its high heterogeneity (I^2 = 73.36%) and limited validation preclude routine clinical adoption. Sensitivity analyses excluding special populations (e.g., wheelchair

athletes with spinal cord injury, hepatitis B carriers, breast cancer survivors) confirmed that the pooled effects remained statistically significant and directionally consistent, indicating that the overall findings were not driven by these populations. The mechanistic explanations for the age effect remain hypothetical and require confirmation in future mechanistic studies. Our findings have important implications for individualized monitoring of recovery, risk stratification in master athletes, and interpretation of CRP levels. The substantial heterogeneity underscores the need for standardized methodologies and rigorous validation of salivary CRP. Future research should prioritize sex-specific analyses, genetic moderators, and prospective cohort studies to elucidate long-term health consequences. Ultimately, this synthesis provides a robust evidence base for optimizing recovery strategies and advancing exercise immunology.

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Ethical Approval

As this study assessed previously published data, ethical approval and informed consent were not required.

Data availability

The data used to support the findings of this study are included within the article.

Conflicts of interest

The authors declare that there is no conflict of interest.

CRediT author statement

Mohammed Jaber Kadhim Al-hamdani: Investigation, Literature search, Data extraction, writing – Original draft preparation; **Roghayyeh Afroundeh:** Investigation, Methodology, Validation, Visualization, Writing – Review & editing; **Reza Farzizadeh:** Project administration, Conceptualization, Data curation, Validation, Protocol registration, Formal analysis, Original draft preparation, review & editing. All authors have read and approved the final manuscript.

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