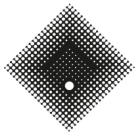
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The effects of running on systemic inflammatory markers in chronic low back pain: a secondary analysis of the ASTEROID randomised controlled trial

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The effects of running on systemic inflammatory markers in chronic low back pain: a secondary analysis of the ASTEROID randomised controlled trial

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ABSTRACT

Background: Exercise is a well-established treatment for chronic low back pain (LBP), yet its effects on inflammation remain unclear.
Objective: Examine the effects of running on inflammatory markers in chronic LBP and its associations with pain intensity, and mental health as an a priori secondary analysis.
Methods: An a priori secondary analysis of a 12-week, two-arm, parallel-group randomised controlled trial was conducted. Forty adults with chronic LBP were randomised to a run-walk program or waitlist control. The intervention was a digitally delivered, remotely supervised run-walk program, prescribed three times per week for 30 min. Outcomes assessed included systemic inflammatory markers (C-reactive protein [CRP], interleukin-8 [IL-8], and tumour necrosis factor alpha [TNF-α] as well as pain intensity (Visual Analogue Scale), and mental health (21-item Depression, Anxiety, and Stress Scale).
Results: No significant between-group differences were observed in CRP (β [95% CI] = 0.34 [-0.07, 0.74] (log-transformed scale), $p = 0.109$), TNF-α (−1.29 [-6.15, 3.58] pg/mL, $p = 0.595$), or IL-8 (−0.36 [-1.30, 0.58] (log-transformed scale), $p = 0.443$) over the 12 weeks. The associations between changes in inflammatory markers and pain intensity or mental health were not different between groups (all $p > 0.05$).
Conclusions: A 12-week run-walk training did not alter systemic CRP, TNF-α, or IL-8 in adults with chronic LBP. Improvements in pain intensity were not associated with changes in these inflammatory markers. Clinically, this intervention offers a low-cost and accessible approach that provides meaningful improvements in chronic LBP without observed changes in systemic CRP, IL-8, and TNF-α.

1. Introduction

Low back pain (LBP) progresses from acute to chronic (pain ≥12 weeks) in up to 32% of cases (Stevans et al., 2021), leading to considerable personal and societal burden (Ferreira et al., 2023). Systemic inflammation may drive this transition (Morris et al., 2020) by heightening sensitivity in both central (e.g., dorsal horn of the spinal cord) (Kawasaki et al., 2008) and peripheral (e.g., hyperexcitability of nociceptors) nociceptive pathways (Fang et al., 2023). Key inflammatory markers elevated in chronic LBP include C-reactive protein (CRP),

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tumour necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) (Morris et al., 2020; Puerto Valencia et al., 2024). IL-8 was selected because it is associated with pain persistence, highlighting its relevance as a potential therapeutic target in chronic LBP (Dhahri et al., 2025; Krock et al., 2019; Slouma et al., 2023). Although chronic LBP is defined by symptom duration, systemic markers of acute inflammation remain relevant, as they may capture low-grade immune activity influencing pain intensity, neuroimmune interactions, and responsiveness to exercise interventions (Alonso-Sal et al., 2024; Morris et al., 2020). Importantly, inflammatory processes can occur at both systemic and local levels (Li et al., 2021). Systemic inflammation reflects circulating immune activity measurable in whole blood. In contrast, local inflammation involves immune responses confined to a specific tissue (e.g., intervertebral disc) that may not be captured by systemic inflammatory biomarkers (Hiyama et al., 2022).

Elevated systemic inflammation often co-occurs with poor mental health in LBP (Beurel et al., 2020; Klyne et al., 2017; Wang et al., 2010), suggesting potential bi-directional interactions between the central nervous and immune systems. These interactions, referred to as neuroimmune mechanisms, have also been proposed as a potential driver of chronic pain development (Hore and Denk, 2019). Identifying interventions that reduce systemic inflammation may therefore be crucial for preventing or alleviating chronic LBP.

Exercise training is a first-line treatment for chronic LBP, effectively reducing pain intensity and enhancing mental health (Owen et al., 2020). Running, in particular, was associated with a low prevalence of LBP and may serve as a protective factor against the onset of LBP (Maselli et al., 2020, 2021). One proposed mechanism underlying these therapeutic effects is the modulation of systemic inflammation by reducing pro-inflammatory cytokines (Cheng et al., 2015; Ni et al., 2025; Zheng et al., 2019), decreasing central sensitisation (Chen et al., 2024), and improving regulation of pain and mood via neuroimmune interactions (Eyre and Baune, 2012; Hore and Denk, 2019). Despite these mechanistic hypotheses, few studies have directly examined exercise-induced changes in inflammation in chronic LBP. A recent systematic review found no randomised controlled trials (RCTs) meeting inclusion criteria that investigated the effects of exercise training on inflammatory markers in LBP, highlighting a critical area for future research (Alonso-Sal et al., 2024).

The only two RCTs we identified (Nambi et al., 2020; Oghumu et al., 2023) compared strength training interventions but lacked a true control group. Nambi et al. (2020) observed that isokinetic trunk training led to greater reductions in CRP, TNF-α, IL-2, IL-4, and IL-6 compared to core stabilisation training. However, the results were inconsistently reported across the article and were therefore evaluated as not reliable by Puerto Valencia et al. (2024). In contrast, Oghumu et al. (2023) reported no changes in IL-1α, IL-18 receptor 1, IL-18 receptor accessory protein, and cyclooxygenase-2, while IL-6 increased. No study has yet examined aerobic exercise training effects on inflammatory markers in chronic LBP. Existing research has instead focused on acute LBP (Al-Obaidi and Mahmoud, 2014; Cheng et al., 2015; Kim et al., 2008) or on other clinical (e.g., cardiovascular diseases, type 2 diabetes) and healthy populations (Fedewa et al., 2017). While these studies suggest that exercise training may exert anti-inflammatory effects, it remains unclear whether such effects also occur in chronic LBP and whether changes in inflammatory markers correlate with pain intensity and mental health, as proposed by neuroimmune models (Eyre and Baune, 2012; Hore and Denk, 2019). Clarifying whether exercise training elicits inflammatory responses in chronic LBP may help elucidate underlying mechanisms, inform the development of more targeted exercise interventions, and provide practitioners with reassurance regarding the safety and effectiveness of exercise prescription.

Therefore, our aim was to examine the effects of a 12-week run-walk interval program compared to a waitlist control on CRP, TNFα, and IL-8 in adults with non-specific chronic LBP. We hypothesised that the run-walk interval program would reduce levels of these inflammatory markers relative to the control group. The secondary aim was to determine whether the intervention modified the associations between changes in inflammatory markers and changes in pain intensity or mental health, with the hypothesis that reductions in inflammatory markers would be associated with improvements in pain intensity and mental health outcomes.

2. Methods

2.1. Trial design

A pre-planned secondary analysis of a 12-week two-arm parallel individual randomised (1:1) controlled trial examining the effects of a running (progressive run-walk interval exercise training) intervention compared to waitlist control on CRP, TNF-α, and IL-8 in adults with non-specific chronic LBP was conducted. The primary outcomes of the original trial were pain intensity, disability, and intervertebral disc health (Tagliaferri et al., 2023), while systemic inflammatory markers were a priori secondary outcomes. As a secondary analysis, the study was not specifically powered to detect changes in inflammatory markers, which warrants consideration when interpreting the findings. The trial was pre-registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001276741). The full study protocol has been published (Tagliaferri et al., 2023), along with the primary outcomes of pain intensity and disability (Neason et al., 2025). Data were collected at pathology collection centres (Melbourne Pathology, Melbourne, Australia) and using REDCap electronic data capture tools (Harris et al., 2009, 2019). Assessments were conducted at baseline and at 12-week follow-up. Ethical approval was obtained from the primary institution sponsoring the trial, and all participants provided written informed consent prior to enrolment. The trial adhered to the Consolidated Standards of Reporting Trials Statement (Supplementary File 1) (Schulz et al., 2010).

2.2. Participants

Web-based advertisements were used to recruit participants from the Melbourne metropolitan area. Individuals aged between 18 and 45 years with non-specific chronic LBP (≥12 weeks; experienced on most days in an average week; with or without leg pain) were eligible. All interested participants who registered via the study website underwent a structured telephone screening with a member of the research team to assess eligibility and rule out potential red flags or serious clinical conditions. Exclusion criteria relevant to the current study were: (a) history of spinal surgery, spine trauma (e.g., fracture or motor vehicle accident), cauda equina symptoms, known structural scoliosis requiring surgical consultation, symptomatic radiculopathy (diagnosed via medical professional or leg pain greater than back pain), inflammatory spondyloarthropathies, or non-musculoskeletal causes of LBP (e.g., infection and visceral pain), (b) inability to communicate in English, (c) pregnancy, lactating or <1 year postpartum (d) current or prior elite athletes i.e. member of Australian Institute of Sport, State Institutes or Academies of Sport or the national squad of any sport) (Gulliver et al., 2015), (e) participation in running or sport that involves running in the last three months (>1 session per month), (f) having experienced a lower limb injury in the last six weeks, (g) any absolute contraindications for exercise training or deemed higher risk of adverse event due to physical activity per the Adult Pre-Exercise Screening System (Norton and Norton, 2011), and (h) unable to access and use a smartphone with a cellular internet connection.

2.3. Interventions

2.3.1. Run-walk intervals

A full description of the run-walk interval program was published elsewhere (Tagliaferri et al., 2023). In short, three 30-min run-walk

interval sessions per week were prescribed over a 12-week period. Running intervals were interspersed with walking (active rest periods) and participants had the option to increase their running intervals each week. The intervals started with 15 s of running and 120 s of walking in stage 1 and progressed to 180 s of running and 15 s of walking in stage 13. The training sessions were prescribed and remotely supervised by an accredited exercise physiologist from the research group via weekly (weeks 1-4) and fortnightly (weeks 6-12) 10-15 min video consultations (Zoom Video Communications, California, United States of America). Participants completed the training sessions, which included an optional 5-min mobility warm-up, independently in the local communities. During the running intervals, participants were instructed to run at a slow to moderate pace (maximum of 10 km/h). Exercise intensity was prescribed using subjective pace and progressive interval durations but was not objectively monitored using heart rate or other physiological measures. In addition to the intervention, participants were permitted to manage their LBP as usual (e.g., general practitioner care or over-the-counter medication) and to engage in other physical activities as desired.

2.3.2. Waitlist control

Participants randomised to waitlist control were instructed to continue managing their LBP as usual, such as following the general practitioner advice and/or over-the-counter analgesic pharmacotherapy, and to not to commence a running program. No further restrictions on physical activity were applied. After completion of the study, control participants were offered the same run-walk interval program, and one-on-one consultations provided to the intervention group.

2.4. Outcomes

2.4.1. Inflammatory markers

Fasted morning (08:00-10:00) venous blood samples were collected at Melbourne Pathology within seven days prior to baseline assessments and between three to seven days after the final run-walk session. Blood samples were centrifuged at 3000 rpm for 10 min at 4 °C to separate serum and plasma. Serum high-sensitivity CRP was analysed by Melbourne Pathology using the Cardiac CRP (Latex) High Sensitive assay (Roche Diagnostics, Mannheim, Germany) on Roche/Hitachi cobas c analysers, following the instructions of the manufacturer. The remaining serum was initially stored at −70 °C and later transported to Deakin University, where it was stored at −80 °C until analysis. Bio-Plex Pro Human Cytokine Assays (Bio-Rad, Hercules, CA, United States of America) were used to measure TNF-α and IL-8, as per recommendations by the manufacturer. Samples were analysed in duplicate in a single batch. Analyses recorded an intra-assay % coefficient of variation (%CV) of <10% and inter-assay %CV of <34%. Values below the detection threshold were imputed using the detection limit divided by two method (Handelsman and Ly, 2019).

2.4.2. Pain intensity

LBP intensity was assessed using a visual analogue scale (VAS) ranging from 0 to 100 points (0 representing “no pain” and 100 representing “worst pain imaginable”). The test-retest reliability of the VAS is reported as excellent (intraclass correlation coefficient [ICC] = 0.90) in individuals with LBP (Chiarotto et al., 2019).

2.4.3. Mental health

Symptoms of depression, anxiety, and stress over the past week were measured using the Depression Anxiety and Stress Scale 21 (DASS-21) (Lovibond and Lovibond, 1995). This self-report questionnaire comprises 21 items, with seven items allocated to each subscale of depression, anxiety, and stress. Items are rated on a 4-point Likert scale ranging from 0 (never) to 3 (almost always), with higher scores indicating greater severity of depression, anxiety and stress. Subscale scores were summed separately and then multiplied by two to obtain final scores for each domain. The reliability (internal consistency) of the DASS-21 was found to be excellent (α = 0.93) in a non-clinical adult population (Henry and Crawford, 2005).

2.5. Sample size

A total of 40 participants (20 per group) were recruited. The sample size was determined using the G*Power program (V.3.1.9.7)(Faul et al., 2007) based on calculations designed to detect the smallest effect size of interest for between-group differences in the primary study outcomes of pain intensity, disability, and intervertebral disc T2, as reported previously (Tagliaferri et al., 2023).

2.6. Randomisation

Participants were randomly allocated in a 1:1 ratio to either the run-walk interval group or waitlist control group using block randomisation with random block lengths (ranging from 2 to 6) and stratification by sex. The randomisation sequence was generated using the ‘blockrand’ package in R (V.4.1.2; The R Foundation, Vienna, Austria) (Snow, 2022). An author with no contact with participants (SDT) implemented the allocation process using sequentially numbered, opaque, sealed envelopes to ensure allocation concealment.

2.7. Blinding

Due to the nature of the intervention, blinding of participants and group members administering the intervention was not feasible. To minimise bias in outcome assessment, however, blood samples for inflammatory markers were collected by a phlebotomist blinded to group allocation. Likewise, the biomedical researcher responsible for analysing the samples remained blinded to group allocation.

2.8. Statistical methods

Statistical analyses were conducted using RStudio (version 2025.5.1.513) (Posit team, 2025). Linear mixed-effects models were used to evaluate changes in CRP, TNF-α, and IL-8 over time and between groups, accounting for repeated measurements within individuals by including a random intercept for participant ID. Model residuals were assessed for normality using Q-Q plots and the Shapiro-Wilk test. Due to violations of normality assumptions, CRP and IL-8 were log-transformed prior to analysis. Results from transformed models were back-transformed to the original scale for interpretability. All analyses were conducted according to the intention-to-treat principle, and linear mixed-effects models were estimated using restricted maximum likelihood (Horton and Kleinman, 2007).

To examine whether the intervention influenced the relationships between inflammatory markers, pain intensity, and mental health, we calculated change scores (Δ) for each participant by subtracting baseline values from 12-week values for inflammatory markers (CRP, IL-8, TNF-α) and outcome measures (pain intensity; depression, anxiety, and stress subscores of the DASS-21). Pearson correlations were computed separately for the intervention and control groups to quantify the association between Δinflammatory markers and Δoutcomes. Between-group differences in correlations were tested using Fisher's r-to-z transformation for independent samples. Correlation coefficients were interpreted as weak (0.10–0.39), moderate (0.40–0.69), strong (0.70–0.89), and very strong (0.90–1.0) (Schober et al., 2018).

3. Results

3.1. Participants

A total of 155 individuals were screened for eligibility (Fig. 1).

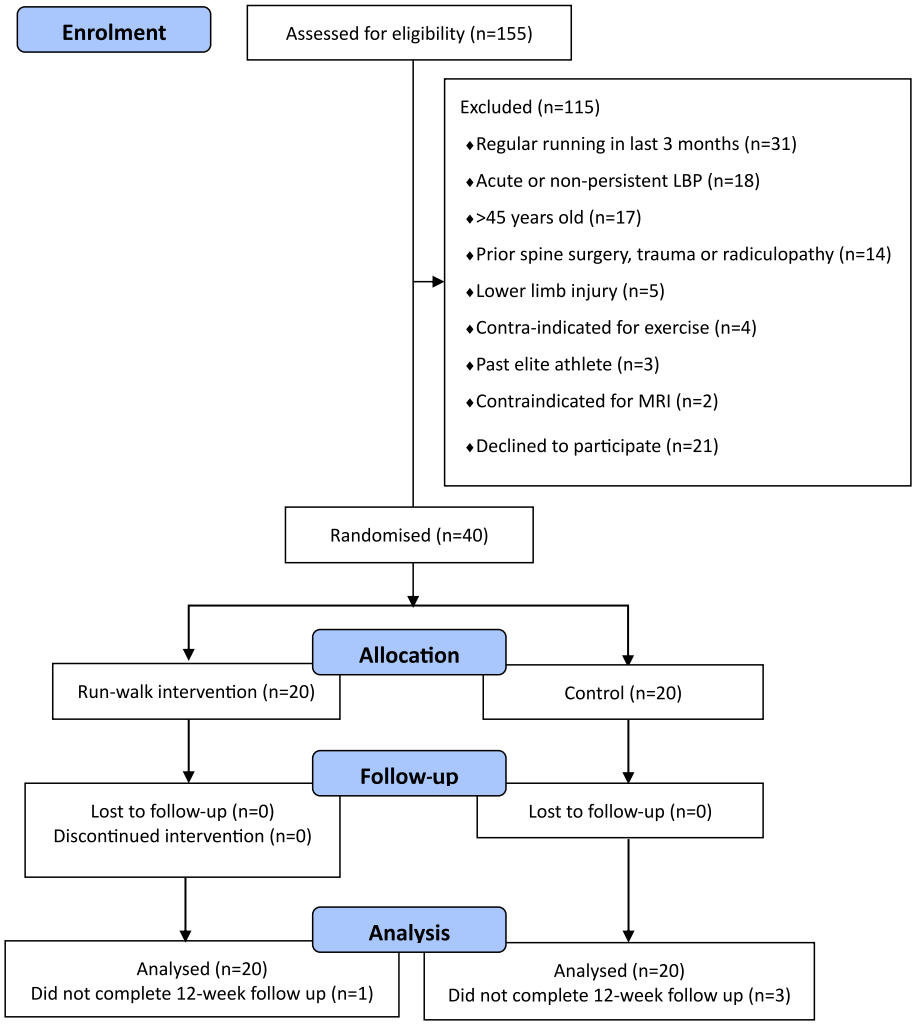

Fig. 1. Participant flow diagram. LBP, Low back pain.

Following randomisation, 20 participants were allocated to the run-walk intervention and 20 participants to the control group. No participants dropped out of the study, and all participants were analysed per the intention-to-treat approach. Blood samples from three control participants and one intervention participant were missing at week 12. The trial was conducted from December 2022 to May 2023 and concluded when the final participants completed the 12-week follow-up assessment. Descriptive baseline characteristics of the participants are presented in Table 1.

3.2. Adherence

Participants demonstrated a mean (SD) training adherence of 70.4% (20.4%), equivalent to two of the three prescribed training sessions per week. Mean running speed was 9.5 (1.8) km per hour, and running distance per session (excluding walking) averaged 2.0 (1.2) km, increasing from 1.1 (0.4) km in week 1 to 2.7 (1.6) km in week 12.

Table 1
Baseline characteristics of participants.

	Intervention (n = 20)	Control (n = 20)
Age, years	33.6 (5.3)	32.2 (7.0)
Female, n (%)	10 (50)	10 (50)
Pain intensity, Visual Analogue Scale (0-100)	30.8 (23.3)	40.1 (20.9)
Body mass index, kg/m^2	29.6 (6.9)	29.0 (7.5)
Smoking status, n (%)		
Current	2 (10)	0 (0)
Former	1 (5)	3 (15)
Never smoked	17 (85)	17 (85)

Data are mean (SD) or count (percentage within group).

3.3. Inflammatory markers

Changes in CRP, TNF-α and IL-8 are presented in Table 2. No significant between-group differences were detected for any of the inflammatory markers over the 12-week period. Within the control group, CRP levels showed a statistically significant 32% reduction from baseline to 12 weeks. No significant within-group changes were observed for IL-8 or TNF-α in either group.

3.4. Correlations between inflammatory markers, pain intensity, and mental health

Change-score correlations between inflammatory markers and pain intensity or mental health were calculated separately for the intervention and control groups (Table 3). No between-group differences in correlations were measured. Overall, correlations were weak to moderate in magnitude.

3.5. Harms

As reported in detail elsewhere (Neason et al., 2025), nine

Table 2
Changes in inflammatory markers after run-walking intervals compared to waitlist from baseline to 12 weeks.

Variable	Intervention (n = 20)				Control (n = 20)				Group-by-time	
	Mean (SD)	EMM (SE)	Δ Mean (95% CI)	*p*	Mean (SD)	EMM (SE)	Δ Mean (95% CI)	*p*	β (95% CI)	*p*
CRP										
Baseline	1.65 (2.16) mg/L	1.18 (0.29)†			6.75 (10.08) mg/L	2.59 (0.64)†				
12-week	1.55 (1.93) mg/L	1.12 (0.28)†	0.95 (0.71, 1.26)†	0.694	3.12 (4.21) mg/L	1.75 (0.45)†	**0.68 (0.50, 0.92)†**	**0.013**	0.34 (−0.07, 0.74)◆	0.109
IL-8										
Baseline	13.62 (14.68) pg/mL	8.81 (2.09)†			8.21 (3.74) pg/mL	7.51 (1.83)†				
12-week	20.60 (45.06) pg/mL	6.88 (1.68)†	0.78 (0.41, 1.50)†	0.448	16.59 (20.19) pg/mL	8.42 (2.18)†	1.12 (0.57, 2.22)†	0.738	−0.36 (−1.30, 0.58)◆	0.443
TNF-α										
Baseline	16.19 (13.65) pg/mL	16.19 (2.48) pg/mL			12.80 (7.24) pg/mL	12.80 (2.55) pg/mL				
12-week	15.40 (11.95) pg/mL	14.92 (2.51) pg/mL	−1.27 (−4.62, 2.08) pg/mL	0.446	13.21 (10.51) pg/mL	12.82 (2.60) pg/mL	0.01 (−3.52, 3.55) pg/mL	0.994	−1.29 (−6.15, 3.58) pg/mL	0.595

Data are sample size, observed mean (SD), estimated marginal mean (EMM) (SE), within-group mean change from baseline (95% CI), within-group *p*-value, group-by-time β coefficient (95% CI) and group-by-time *p*-value from linear mixed models.† Estimated marginal means (SE) and change scores (Δ Mean, 95% CI) were log-transformed for statistical analysis and back-transformed to the original scale. The Δ mean of back-transformed values represents a multiplicative factor for interpretability (value < 1 indicates a decrease, while a value > 1 indicates an increase relative to baseline). ◆β (95% CI) was log-transformed for statistical analysis. CRP, C-reactive protein; IL-8, interleukin-8; TNF-α, Tumour necrosis factor-α.

Table 3
Change-score correlations between biomarkers and outcomes by group.

Biomarker	Outcome	*r* Intervention	*r* Control	*p*
CRP	Anxiety (DASS-21)	−0.05	0.05	0.781
CRP	Depression (DASS-21)	0.06	0.27	0.543
CRP	Stress (DASS-21)	−0.23	0.28	0.142
CRP	Pain intensity (VAS)	−0.21	0.42	0.0663
IL-8	Anxiety (DASS-21)	−0.22	−0.41	0.561
IL-8	Depression (DASS-21)	0.10	0.01	0.803
IL-8	Stress (DASS-21)	0.05	−0.14	0.592
IL-8	Pain intensity (VAS)	0.14	0.08	0.863
TNF-α	Anxiety (DASS-21)	0.01	−0.09	0.787
TNF-α	Depression (DASS-21)	0.00	−0.01	0.964
TNF-α	Stress (DASS-21)	0.04	−0.34	0.287
TNF-α	Pain intensity (VAS)	0.29	0.11	0.626

Data are correlation coefficients (r) and *p* values. CRP, C-reactive protein; IL-8, interleukin-8; TNF-α, Tumour necrosis factor-α; DASS-21, Depression, Anxiety, and Stress Scale-21.

non-serious, study-related adverse events occurred in the intervention group, including seven lower limb injuries, one cardiac syncope related to a pre-existing condition, and one exacerbation of LBP. These events resulted in 20 missed training sessions, with all but one participant resuming the run-walk interval program within a week.

4. Discussion

This study is the first to investigate the effects of a run-walk interval training program on inflammatory markers in adults with non-specific chronic LBP. We found that (1) the run-walk interval program did not produce between-group changes in CRP, TNF-α, or IL-8 compared to waitlist control; and (2) the associations between changes in inflammatory markers and changes in pain intensity or mental health did not differ between the intervention and control groups.

We observed no significant within-group or between-group changes in TNF-α or IL-8 following the 12-week run-walk intervention. For CRP, a reduction was observed in the control group, whereas no change occurred in the intervention group. However, the absence of a group-by-time interaction indicates that the run-walk intervention did not result in greater reductions in CRP compared with the control condition. The decrease in CRP observed among controls may be attributable to their higher baseline CRP levels, consistent with regression to the mean. Overall, these findings suggest that the program did not induce a detectable systemic inflammatory response in the markers assessed.

To date, no studies have specifically examined the effects of running or aerobic exercise on inflammation in chronic LBP. Therefore, our findings can only be compared with two RCTs that investigated strength-based exercise interventions in this population (Nambi et al., 2020; Oghumu et al., 2023). Nambi et al. (2020) reported reductions in CRP, TNF-α, IL-2, IL-4, and IL-6 following four weeks of high-frequency isokinetic trunk training. However, units of measurement were not reported, and results were inconsistently presented, leading Puerto Valencia et al. (2024) to evaluate the study as not reliable. In contrast, Oghumu et al. (2023) found no change in several inflammatory markers not assessed in our trial (IL-1α, IL-18 receptor 1, IL-18 receptor accessory protein, and cyclooxygenase-2), whereas IL-6 increased following both lumbar stabilisation and graded activity training over ten weeks. Taken together, the absence of prior evidence and the findings of the present study suggest that a run-walk interval training does not alter systemic CRP, TNF-α, or IL-8 in adults with chronic LBP.

Importantly, the characteristics of the intervention should be considered when interpreting these findings (Cerqueira et al., 2020; Rose et al., 2021). The program was delivered over 12 weeks, with participants completing on average two of the three prescribed 30-min sessions per week at a mean (SD) running speed of 9.5 (1.8) km/h, corresponding to a slow-to-moderate intensity and an average running distance (excluding walking) of 2.0 (1.2) km per session (Neason et al., 2025). It therefore remains possible that running interventions of longer duration, higher frequency, or greater intensity or other types of exercise (e.g., strength training) may elicit different inflammatory responses in individuals with chronic LBP (Cerqueira et al., 2020).

No study to date has examined whether changes in inflammatory markers coincides with improvements in pain intensity in chronic LBP or mental health following exercise training. Therefore, we examined whether the associations between changes in inflammatory markers (CRP, TNF-α, or IL-8) and changes in pain intensity or mental health differed between groups as a secondary aim. No significant correlations were found, indicating that the run-walk interval training did not alter these associations. This result likely reflects the non-significant impact of the run-walk interval program on inflammatory markers, consequently limiting our ability to assess changes in its associations with pain intensity or mental health.

Overall, these null results are particularly noteworthy, as they demonstrate that a clinically meaningful improvement in pain intensity in individuals with chronic LBP, as measured in the primary analysis of

this study (Neason et al., 2025), does not occur in parallel with changes in CRP, TNF-α, or IL-8. Consequently, while the run-walk interval training produced clinically meaningful short-term improvements in pain intensity, these changes do not appear to be mediated by resting systemic levels of CRP, TNF-α, or IL-8. Notably, this does not negate a potential role for inflammatory processes in chronic LBP that may operate through other mechanisms, tissues, or temporal dynamics not captured by the present biomarker assessment, as discussed in the following section (Brown et al., 2018; Hiyama et al., 2022; Sluka et al., 2018). From a clinical perspective, these results provide reassurance that a 12-week low-intensity run-walk interval training can provide meaningful pain relief in chronic LBP (Neason et al., 2025) without the need to elicit or target measurable responses of the biomarkers assessed. Clinicians may safely introduce an individualised, guided, and conservative run-walk programme, beginning with short running intervals and gradually increasing duration and intensity, to allow physiological adaptation while minimising the risk of symptom exacerbation. Specific details on programme structure, feasibility, and adherence can be found in the original trial report (Neason et al., 2025). This underscores the intervention's feasibility, accessibility, and low-cost, highlighting its value as a therapeutic strategy based on symptomatic benefits rather than biomarker modification (Neason et al., 2025). Importantly, this does not preclude a role for inflammation in the pathophysiology of chronic LBP as discussed in the following paragraph.

Several possible explanations may account for the absence of detectable changes in inflammatory markers despite improvements in pain intensity. Specifically, inflammatory processes relevant to chronic LBP may be relatively stable over time (Chang et al., 2023), temporally dissociated from short-to medium-term changes in pain intensity (DeVon et al., 2014), or inadequately captured by the biomarkers measured in this study. Supporting this, a longitudinal study observed no significant change in CRP, TNF-α, or IL-8 over 6-months in individuals with acute LBP, even when symptoms improved or persisted (Chang et al., 2023). The timing of biomarker assessment may also have influenced results (Brown et al., 2018). Blood samples were collected three to seven days after the final exercise session, which may have missed transient or acute post-exercise inflammatory responses that typically occur within hours to days following exercise and resolve rapidly thereafter (Brown et al., 2018). As a result, short-lived fluctuations in cytokine concentrations induced by the training sessions may not have been captured by the present sampling schedule. Our sampling strategy was chosen to avoid capturing acute fluctuations and instead assess chronic adaptations. However, this approach limits our ability to comment on short-term inflammatory dynamics that may still be relevant to pain modulation or training adaptation. Furthermore, systemic cytokine concentrations may not reflect local inflammatory activity within spinal or paraspinal tissues (Hiyama et al., 2022). Alternatively, exercise-induced adaptations may occur at the level of inflammatory receptor sensitivity (Favere et al., 2021), intracellular signalling pathways (Walzik et al., 2024), or immune cell phenotypes (Brauer et al., 2021; Meyer-Lindemann et al., 2023), rather than through changes in systemic inflammation. Such mechanisms would not be detected using the present biomarker panel but may nonetheless influence pain processing and recovery (Sluka et al., 2018). In addition, resistance training may exert its analgetic effect through non-inflammatory mechanisms (e.g., activation of endogenous pain-modulation systems including enhanced descending inhibition (Murtezani et al., 2011), engagement of opioid and serotonergic pathways (Ma and Mumtaz, 2025), improvements in neuromuscular control (Maurus et al., 2019), reductions in kinesiophobia, maladaptive pain-related behaviours or increasing pain self-efficacy (Powell et al., 2025). While much of the mechanistic evidence derives from studies in healthy individuals or mixed chronic pain populations, research in chronic LBP supports these mechanisms (Blanco-Giménez et al., 2024; Farragher et al., 2024). For example, RCTs found improvements in pain sensitisation, kinesiophobia, catastrophising, and self-efficacy after 12 weeks of strength training in a chronic LBP sample (Blanco-Giménez et al., 2024; Farragher et al., 2024), and evidence from exercise-based interventions suggests that exercises can enhance muscle morphology, reflecting structural and motor control adaptations that may contribute to clinical improvements (Pillastrini et al., 2015). Future studies may address these considerations by using repeated, temporally sensitive biomarker assessments, incorporating measures of local inflammatory activity, and exploring alternative biological mechanisms beyond systemic inflammation to better elucidate how exercise training influences pain intensity in chronic LBP.

4.1. Strengths and limitations

Strengths of this study are its rigorous randomised controlled design, use of validated outcome measures, low attrition rate, and investigation of an intervention that is feasible at the population level due to its accessibility, low costs and non-reliance on specialised equipment. However, several limitations must be acknowledged. First, this study was an a priori secondary analysis, and the original sample size was not calculated for inflammatory marker outcomes, which may have limited the statistical power to detect small effects. Given the modest sample size, statistical analyses were considered exploratory and warrants replication in larger samples, ideally those a priori designed to investigate the relationships between inflammatory markers, pain intensity, and mental health. Second, the run-walk interval program did not include objective measures of training intensity (e.g., heart rate or other physiological measures) or control for concurrent physical activity outside the intervention, limiting certainty regarding the precise dosing of the intervention. Consequently, inter-individual variability in exercise intensity may have resulted in heterogeneous physiological loading, such that some participants may not have reached an intensity threshold required to elicit measurable systemic inflammatory adaptations. In contrast, others may have experienced greater physiological stress, thereby influencing cytokine responses. Third, while we focused on three relevant inflammatory markers in chronic LBP, a broader panel of cytokines (e.g., IL-6, IL-10, IL-1β) may provide a more comprehensive picture of immune activity. Fourth, unmeasured factors such as diet or medication use may have influenced inflammatory markers (Koop et al., 2021). Lastly, given the study sample consisted of young and middle-aged adults (mean [SD] age 32.8 [6.2] years), the findings may not be generalisable to older populations.

4.2. Conclusions

The run-walk interval program did not elicit a measurable systemic inflammatory response in CRP, IL-8, and TNF-α compared to waitlist control in adults with non-specific chronic LBP, nor did it alter the associations between these inflammatory markers with changes in pain intensity or mental health. These findings suggest that clinically meaningful improvements in pain may occur independently of the specific systemic inflammatory markers assessed at the exercise training dose studied. Overall, this study provides evidence supporting the inflammatory safety of low-intensity running with respect to CRP, IL-8, and TNF-α in chronic LBP, and highlights its potential as an accessible, low-cost intervention capable of delivering meaningful clinical benefits without necessarily altering the systemic biomarkers measured.

CRediT authorship contribution statement

Romina Gollan: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **Luana C. Main:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition. **Jamie L. Tait:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Data curation. **Claire L. Samanna:** Writing – review & editing, Project administration, Data curation. **Christopher Neason:** Writing – review & editing, Project administration, Data curation. **Daniel L. Belavý:** Writing – review &

editing, Methodology, Funding acquisition, Conceptualization. **Matthew J. Clarkson:** Writing – review & editing, Methodology. **Ulrike H. Mitchell:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Niamh L. Mundell:** Writing – review & editing, Methodology. **Scott D. Tagliaferri:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Jeremy M. Drake:** Writing – review & editing, Methodology, Formal analysis. **Patrick J. Owen:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethics approval

Ethics approval was provided by the Deakin University Human Research Ethics Committee (ID: 2022-162) on September 26, 2022.

Trial registration

Australian New Zealand Clinical Trials Registry: ACTRN12622001276741. Registered on September 29, 2022.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

The authors declare that they have no competing interests.

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