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Acute Effects of a High-Intensity Interval Training Protocol on Pain Sensitivity and Inflammatory Markers in Persons with Chronic Nonspecific Low Back Pain: A Controlled Clinical Trial

Jonas Verbrugghe [1,*], Sim Klaps [1], Kenneth Verboven [1,2], Timo Meus [1], Kristof Kempeneers [3], Kristian Kjaer-Staal Petersen [4] and Annick Timmermans [1]

[1] REVAL—Rehabilitation Research Centre, Hasselt University, 3500 Hasselt, Belgium; sim.klaps@uhasselt.be (S.K.); kenneth.verboven@uhasselt.be (K.V.); timo.meus@uhasselt.be (T.M.); annick.timmermans@uhasselt.be (A.T.)
[2] Biomedical Research Institute (BIOMED), Faculty of Medicine and Life Sciences, Hasselt University, 3500 Hasselt, Belgium
[3] Jessa Hospital, 3500 Hasselt, Belgium; kristof.kempeneers@jessazh.be
[4] Center for Neuroplasticity and Pain, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, 9220 Aalborg, Denmark; kkp@hst.aau.dk
* Correspondence: jonas.verbrugghe@uhasselt.be; Tel.: +32-11269224

Abstract: Chronic nonspecific low back pain (CNSLBP) might be associated with increased pain sensitivity and inflammation. High-intensity interval training (HIIT) has been suggested to reduce pain outcomes and inflammatory markers, but its effects compared to moderate-intensity continuous training (MICT) remain unclear. This study aimed to evaluate the acute effects of HIIT on pain sensitivity and inflammatory markers in persons with CNSLBP compared to healthy controls (HCs) and to determine how these effects differ from MICT. Twenty persons with CNSLBP and twenty HCs were assessed before (PRE) and after (POST) a single HIIT and MICT protocol for pain sensitivity (cuff pressure pain threshold (cPPT), temporal summation of pain (TS), conditioned pain modulation (CPM)), and inflammatory markers (IL-6, TNF-α). Data were analyzed using one-way ANOVAs, paired *t*-tests, and correlation analyses. At PRE, persons with CNSLBP exhibited lower cPPT (28.2 ± 7.1, Δ = −5.5, $p = 0.040$), higher TS (1.11 ± 0.89, Δ = 0.79, $p = 0.042$), and lower CPM (36.2 ± 11.6, Δ = −10.0, $p = 0.023$) compared to HCs. HIIT resulted in PRE–POST improvements in cPPT (38.9 ± 12.6, Δ = 5.2, $p = 0.019$) in HCs. No PRE–POST differences were observed in pain processing in those with CLBP. No PRE or PRE–POST differences were observed in the inflammatory markers in either group. The current exploratory study suggests that a single HIIT session might have a beneficial effect on pain sensitivity in HCs but does not alter acute pain sensitivity or inflammatory markers in persons with CNSLBP. Further research is needed to clarify the involved mechanisms and explore the (relation with the) long-term effects of HIIT.

Keywords: chronic low back pain; exercise; high-intensity training; pain sensitivity; inflammation

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1. Introduction

Chronic nonspecific low back pain (CNSLBP) affects almost 10% of the adult population, with its prevalence continuing to rise [1,2]. It significantly impairs the physical and psychological functioning of an individual, leading to difficulties in performing activities of daily living, limitations in community participation, (symptoms of) depression and anxiety,

prolonged work absenteeism, and increased medical costs [3–5]. Consequently, CNSLBP is a pervasive societal issue consuming a substantial amount of healthcare resources [3].

Regular physical activity and structured exercise improve physical and psychological health [6,7]. Moreover, various forms of exercise therapy (ET) have proven to be effective in relieving pain associated with musculoskeletal disorders [8,9]. Hence, clinical practice guidelines, including those for persons with CNSLBP, systematically recommend ET as a therapeutic modality [10]. While ET might benefit CNSLBP, its pain-relieving effect is only approximately 15% and responses to exercise vary considerably [11,12]. Additionally, other studies showed no change or even brief exacerbations of pain following exercise [13]. These 'flare-ups' of acute pain are believed to be related to increased pain sensitivity in people with musculoskeletal pain [11].

Exercise-induced hypoalgesia (EIH), referring to a short-term endogenous pain-inhibiting response directly after exercise, is well documented in healthy persons [14]. EIH is measured by changes in pain thresholds before and after exercise and is often assessed using pressure pain thresholds (PPTs). Pre-treatment EIH (i.e., as a pain sensitivity measure) has been linked with the pain-relieving therapy of exercise and therefore might act as an early indicator of a person's potential responsiveness to ET [15]. However, while EIH is influenced by exercise type, dose, and intensity [16,17], the optimal intensity required to induce EIH in CNSLBP remains poorly understood [18]. Of interest, studies have shown that EIH can be affected in a variety of musculoskeletal disorders [13,19,20]. Likewise, persons with CNSLBP display alterations in pain sensitivity, including modified PPTs [21], which may, at least partly, explain individual differences in responses to acute exercise in this specific population [20]. However, very few studies have examined the relationship between exercise modalities and EIH in persons with CNSLBP.

Chronic pain conditions like CNSLBP are also increasingly associated with low-grade systemic inflammation [22]. For instance, elevated levels of pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been associated with chronic pain states [23]. In pre-clinical studies, these cytokines have been demonstrated to sensitize nociceptors at the peripheral and central levels [24,25]. As such, they represent potential therapeutic targets for pain modulation [26]. Interestingly, exercise induces significant acute inflammatory responses and can even lead to disproportional reactions in persons with chronic musculoskeletal pain [27–29]. However, it is unclear if this is associated with pain sensitivity outcomes (such as a disrupted EIH) in persons with CNSLBP. In addition, both inflammatory responses and pain sensitivity outcomes appear to be influenced by psychosocial factors in chronic pain disorders [30]. In particular, higher anxiety, pain catastrophizing, and depression have been associated with an altered inflammatory state in fibromyalgia and osteoarthritis [31,32]. Likewise, sleep disturbances have been associated with higher circulating IL-6 levels in CLBP [33].

High-intensity interval training (HIIT) is an innovative ET modality that has been advocated as optimizing the treatment effects of ET. HIIT involves short bursts of vigorous exercise interspersed with periods of passive or active rest [34]. When performed systematically, it improves cardiovascular fitness along with multiple other positive outcomes on general health indicators [35]. Furthermore, recent systematic reviews have noted positive effects on diseases-related outcomes such as long-term pain intensity and disability, while providing interesting advantages in the treatment of chronic musculoskeletal pain populations including being time-efficient, increasing motivation, and limiting general exhaustion by the volume of the training [36,37]. Additionally, research also indicates that HIIT may improve acute pain sensitivity more as several indications of a dose–response effect of exercise intensity and EIH have been found [17]. As such, it is tempting to speculate that HIIT is a promising therapeutic intervention for CNSLBP [38]. However, given its vigorous nature, HIIT might also provoke excessive inflammatory responses in chronic pain conditions. Some studies have explored

the effects of HIIT on clinical pain and systemic inflammation [39], but there is a notable lack of research specifically addressing the acute effects of exercise intensity on these outcomes in individuals with CNSLBP.

Therefore, this exploratory study aimed to investigate to what extent (1) a single HIIT protocol affects acute pain sensitivity and inflammatory parameters in persons with CNSLBP, (2) the acute effect of a single HIIT protocol on pain sensitivity and inflammatory markers differs between persons with CNSLBP and healthy controls (HC), (3) the acute effect of a single HIIT protocol on pain sensitivity and inflammatory markers in persons with CNSLBP differs from a single moderate-intensity continuous training (MICT) protocol, and (4) the acute effect of a single HIIT protocol on pain sensitivity is correlated to the inflammatory markers in persons with CNSLBP.

2. Materials and Methods

2.1. Research Hypotheses

We hypothesized that (1) persons with CNSLBP display altered pain sensitivity (lower cuff pain pressure thresholds (cPPTs), more temporal summation (TS), and less conditioned pain modulation (CPM)) and higher inflammatory markers (higher interleukin-6 (IL-6) and higher tumor necrosis factor alpha (TNF-α) levels) at rest when compared to matched HCs; (2) HIIT leads to higher cPPT, less TS, and higher CPM and changes IL-6 and TNF-α levels in persons with CNSLBP; (3) HIIT improves cPPT, TS, and CPM to a greater extent compared to MICT; (4) a correlation between cPPT, TS, CPM, and IL-6, TNF-α exists in persons with CNSLBP; (5) this correlation is influenced by demographic (age, body composition) and psychosocial parameters (depression, stress, anxiety, sleep).

2.2. Study Design

An overview of the study design is displayed in Figure 1. This controlled clinical trial involved a cross-sectional assessment evaluating 20 persons with CNSLBP and 20 HCs. Persons with CNSLBP were recruited first. HCs were matched for age, sex, and body mass index (BMI) [40]. At least seven days before performing study assessments, each participant performed a standardized maximal cardiorespiratory exercise test (CPET) on a bike ergometer, used to design the individual HIIT/MICT protocols. Evaluation of CNSLBP consisted of two sessions, with 7–14 days in between. Each session was carried out at the same time of the day to optimize the analysis of inflammatory markers [41,42] and was designed identically, with exception of the performed HIIT/MICT protocol. To avoid the learning effect, each participant underwent the HIIT/MICT protocol in a random sequence. The evaluation for HCs consisted of one session. The design and content of this session was identical to that for CNSLBP with the exception of HCs only performing a HIIT protocol and not completing the questionnaires only applicable to CNSLBP (i.e., MODI, BPI, FABQ). All assessments were carried out at REVAL Research Center, Hasselt University (Hasselt, Belgium). The study protocol was approved by the medical ethical committee of Jessa Hospital (Hasselt, Belgium) and registered at clinicaltrials.gov (nr: NCT04902196).

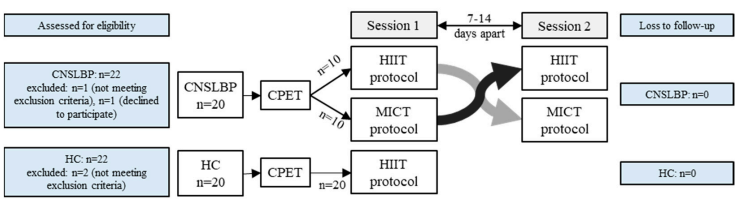


Figure 1. Study design. Abbreviations: HCs: healthy controls; CNSLBP: chronic nonspecific low back pain; CPET: cardiorespiratory exercise test; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training.

2.3. Participants

Persons with CNSLBP were recruited at the outpatient rehabilitation department of Jessa Hospital Campus Virga Jesse (Hasselt, Belgium). Eligible participants were informed about this study by a physician during regular consultation (at the start of a physical therapy trajectory). When interested, a study flyer and approval form for further contact was issued by the physician, signed by the patient, and returned to the researchers. The researchers contacted the potential participant, answered initial questions, and provided the information and consent form. HCs were recruited via convenience sampling (via flyers in classic/social media). Interested persons could contact the researchers via email. Following this, further questions were answered by the researchers, and the information and consent form was provided.

2.4. Inclusion/Exclusion Criteria

2.4.1. Inclusion Criteria for Persons with CNSLBP

- Primary complaint: CNSLBP, i.e., low back pain defined as pain in the area between the lower ribs and upper buttock crease, with or without radiation in the leg [43], chronic: current episode >12 weeks, mean pain intensity between 3 and 8/10, nonspecific: the main pain cannot be traced back to a known pathology;
- No other diagnosed acute or chronic disorders;
- Age: 18–65 years;
- Understanding of the Dutch language (written and spoken).

2.4.2. Inclusion Criteria for HCs

- No diagnosed acute or chronic disorders;
- No current musculoskeletal complaints;
- Age: 18–65 years;
- Understanding of the Dutch language (written and spoken).

2.4.3. Exclusion Criteria for CNSLBP and HCs

- Spinal surgery within last 18 months;
- Radiculopathy or sensory disturbances in lower extremities;
- Pregnancy;
- Ongoing compensation complaints >6 months;
- Previous ET for CNSLBP in last 6 months.

2.5. Contents of the Assessment

Each session had a total duration of 2.5–3 h (Figure 2). At the start of the first session, the following sociodemographics were collected descriptively: sex (male/female), age (years), working (yes/no), diet (yes/no), smoking (yes/no). The following sociodemographic data were only collected from persons with CNSLBP: history of CNSLBP (years). Next, six (CNSLBP) or four (HC) questionnaires were administered, two blood samples (PRE–POST exercise) were collected, and two QST measurements (PRE–POST exercise) were conducted. Questionnaires were discussed in advance with the participant and were completed alone by the participant in a quiet room with sufficient time. Participants were instructed to maintain their usual diet and avoid alcohol or intense physical activity for 48 h before testing. Testing was scheduled at a consistent time of day to control for circadian variations [41].

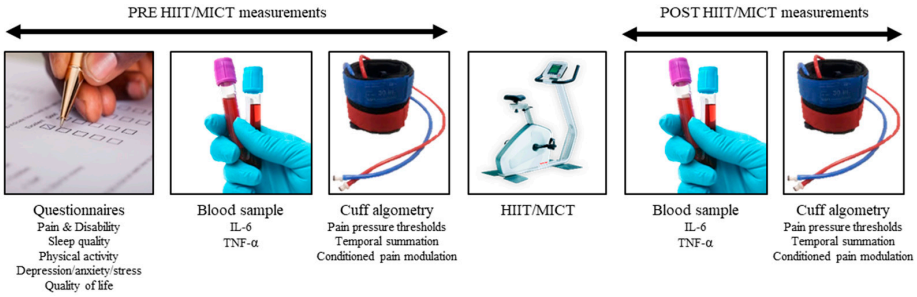


Figure 2. Content of a session. Abbreviations: IL-6: interleukin-6; TNF-α: cytokine tumor necrosis factor alpha; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training.

2.6. Research Parameters

2.6.1. Pain Sensitivity

To evaluate pain sensitivity, a computer-controlled cuff algometer and protocols from Cortex Technology and Aalborg University (Aalborg, Denmark) were used. The cuff algometer is a reliable tool used for the assessment of cPPT, TS, and CPM [44,45] and is equipped with two 13 cm wide tourniquets placed on both legs and connected to an electronic 100 mm visual analogue scale (VAS). Participants used the VAS to rate pressure-induced pain intensity and were instructed to press a button to release the pressure. The cuff was inflated automatically (1 kPa/s rate) until a maximum pressure limit (100 kPa) was reached. cPPT was assessed by rating pain intensity continuously on the VAS from the first sensation of pain up until measuring the greatest level of pain by rising pressure that a subject was prepared to endure. cPPT was defined as the moment of transition between strong and painful pressure (i.e., first time VAS exceeds 0). The pressure value at the termination of pressure inflation was defined as the pressure tolerance threshold (PTT). TS was assessed by delivering ten stimuli, each set to the PTT, to the dominant leg. Each stimulus lasted for one second with a one-second interval between them. Participants continuously rated pain intensity using a VAS, and TS was calculated as the difference in pain intensity between the first and tenth stimuli. CPM was evaluated by applying a conditioning pressure stimulus to the non-dominant leg while measuring cPPT on the dominant leg. The conditioning stimulus was set at 70% of the pain tolerance threshold. The CPM effect was determined as the difference between the conditioned cPPT and the unconditioned cPPT.

2.6.2. Venous Blood Samples

Two venous blood samples (serum, 5 mL) were collected at each session by venous puncture. POST blood samples were taken exactly two minutes after the finalization of the cardiopulmonary exercise test. All samples were kept at room temperature for two hours. Serum tubes were centrifuged at 1300× *g* for 15 min, after which serum aliquots were stored at −80 °C until further analysis. The human biological material used in this publication was provided by the University Biobank Limburg (UBiLim) [46]. Serum levels of IL-6 and TNF-α were determined using a flow-cytometry-based multiplex immunoassay (i.e., Biolegend®, San Diego, CA, USA, LegendPlex Multiplex Assay, inflammation panel 1). Concentrations are reported in picograms per milliliter (pg/mL).

2.6.3. Brief Pain Inventory Short Form (BPI-sf)

This reliable and valid nine-item questionnaire evaluates the severity of a patient's CNSLBP and the impact of this pain on the patient's daily functioning [47]. The patient is asked to rate the worst/lowest/mean/current pain intensity, list current treatments and perceived effectiveness, and judge the degree to which pain interferes with general

activity, mood, walking ability, normal work, relationships with other individuals, sleep, and quality of life on a 10-point numeric pain rating scale (NPRS).

2.6.4. Modified Oswestry Disability Index (MODI)

This reliable and valid questionnaire evaluates the limitations persons with CNSLBP experience in their daily activities due to their pain [48]. It consists of 10 items on a 5-point scale. A percentage of restriction can be indicated based of the total score.

2.6.5. International Physical Activity Questionnaire Short Form (IPAQ)

This reliable and valid seven-item questionnaire estimates the physical activity level of persons with CNSLBP [49]. A higher score corresponds to a more physically demanding activity level.

2.6.6. Fear Avoidance Beliefs Questionnaire (FABQ)

This reliable and valid questionnaire focuses on how a person's fear avoidance beliefs about physical activity and work may affect and contribute to CNSLBP and the resulting disability [50]. The FABQ consists of 16 items with a score from 0 to 7 (completely disagree to completely agree), with a total possible maximum score of 96. A higher score indicates more strongly held fear avoidance beliefs.

2.6.7. Depression Anxiety Stress Scale (DASS-21)

This reliable and valid scale examines depression, anxiety, and stress without the major impact of possible somatic factors in multiple clinical samples [51]. The 21 questions can be answered with 0 (not at all/never applicable), 1 (a little/sometimes applicable), 2 (quite/often applicable), or 3 (very definitely/mostly applicable). A qualification score of 1–5 (normal to very severe) is calculated for each scale.

2.6.8. Pittsburg Sleep Quality Index (PSQI)

This reliable and valid nineteen-item questionnaire evaluates last month's sleep quality grouped into seven domains: sleep latency time, sleep duration, sleep medication, daytime functioning, and sleep-related problems in multiple clinical samples [52]. Each domain is given a score from 0 to 3, and the global PSQI score ranges from 0 to 21. A score of >5 indicates poor sleep quality.

2.6.9. Exercise Capacity

A maximal cardiopulmonary exercise test (CPET) was performed on a cycle ergometer (eBike Basic, General Electric, Bitz, Germany) to evaluate exercise capacity [53]. During the CPET, workload gradually increased each minute (30 W + 15 W/min). Maximal oxygen uptake (VO_2max) was evaluated through breath-by-breath gas exchange analysis (MetaMax 3B, Cortex Biophysik, Leipzig, Germany) and heartrate monitoring (H10, Polar Electro, Kuopio, Finland). A minimum respiratory exchange ratio threshold of 1.10 was used to evaluate the proper validity of maximum effort. The body weight (kg) and height (m) of the participant were measured with a calibrated scale and height meter, respectively.

2.7. Intervention

2.7.1. HIIT Protocol

After a five-minute warm-up, a ten-minute HIIT protocol on a cycle ergometer was started, consisting of five one-minute bouts (110 revolutions per minute (rpm) at 100% VO_2max workload), separated by one minute of active rest (75 rpm at 50% VO_2max workload). This HIIT protocol was chosen because of its proven feasibility and long-term effectiveness on health-related and disease-specific outcomes in CNSLBP rehabil-

itation [54,55]. The work-to-rest ratio (1:1) was selected based on evidence suggesting that it balances metabolic and neuromuscular demands while ensuring sufficient recovery between bouts [56]. Intensity was set at 100% VO_2max to elicit maximal physiological responses, as supported by the existing literature on exercise-induced hypoalgesia [16].

2.7.2. MICT Protocol

After a 5 min warm-up, a 14 min MICT protocol on a cycle ergometer was started at a stable resistance (90 rpm at 60% VO_2max workload). This protocol was volume-adjusted to the HIIT protocol to provide an identical volume load stimulus [54].

2.8. Data Analysis

As this trial involved preliminary and exploratory data, an a priori power analysis prior could not be performed. A sample size of n = 20 per group was chosen based on comparison with other studies using identical designs and evaluating similar outcome measures [57,58]. No adjustments for multiple testing were performed. Data analysis was performed in SPSS (29.0.2.0, IBM Corp, New York, NY, USA). Data normality was checked (Shapiro–Wilk test) to determine whether parametric or nonparametric analyses would be performed. For aims one to three, PRE, POST, and PRE–POST (delta) evaluations were performed. A one-way ANOVA/Kruskal–Wallis test was used for comparisons between groups. A two-sided paired *t*-test/Wilcoxon test was used for comparisons between two sessions. To evaluate aim four, Pearson and Spearman correlation tests were executed to determine bivariate correlations between independent variables (PRE cPPT, delta cPPT, PRE TS, delta TS, PRE CPM, and delta CPM) and dependent variables (PRE IL-6, delta IL-6, PRE TNF-α, and delta TNF-α). For absolute values of r, 0–0.190 was regarded as very weak, 0.200–0.390 as weak, 0.400–0.590 as moderate, 0.600–0.790 as strong, and 0.800–1 as very strong correlation [59]. As these correlations might be confounded by other variables, partial correlations were also performed to evaluate the influence of either demographics (age, BMI) or psychosocial factors (DASS-21, PSQI) as covariates.

3. Results

3.1. Demographics

Twenty persons with CNSLBP (ten women, age = 44.5 ± 10.6 y) and twenty HCs (ten women, age = 44.5 ± 10.3 y) participated in this study. Persons with CNSLBP displayed moderate pain intensity (NPRS = 5.2 ± 2.3) and moderate disability levels (MODI = 10.3 ± 5.7). No differences were found between CNSLBP and HCs in any outcomes except for better sleep quality in the latter ($p < 0.001$). The detailed characteristics of all participants are presented in Table 1. No dropouts were noted during the clinical phase of this trial.

Table 1. Group demographics of CNSLBP and HCs.

	CNSLBP (n = 20)	HC (n = 20)	*p*-Value
Sex (F/M, %)	10/10	10/10	1.000
Age (years)	44.5 ± 10.6	44.5 ± 10.3	1.000
BMI (kg/m^2)	26.3 ± 4.9	26.4 ± 4.0	0.695 ǂ
Working (yes/no)	19/1	19/1	1.000
Diet (yes/no)	0/20	1/19	1.000
Smoking (yes/no)	20/0	20/0	1.000
LBP onset (years)	12.7 ± 10.4	/	-
Pain intensity (NPRS, 0–10)	5.2 ± 2.3	/	-
Disability level (MODI)	10.3 ± 5.7	/	-
Fear avoidance (FABQ, 0–96)	29.8 ± 14.2	/	-
Activity level (IPAQ, METS)	4740 ± 2843	3413 ± 2666	0.185

Table 1. *Cont.*

	CNSLBP (n = 20)	HC (n = 20)	*p*-Value
Depression (DASS-21, 0–42)	2.4 ± 3.5	1.6 ± 3.0	0.483 ǂ
Anxiety (DASS-21, 0–42)	1.4 ± 1.3	2.0 ± 1.7	0.352 ǂ
Stress (DASS-21, 0–42)	4.6 ± 4.7	3.1 ± 2.7	0.302 ǂ
General health (SF-36, %)	66.6 ± 19.0	74.7 ± 15.0	0.151
Sleep quality (PSQI, 0–21)	15.2 ± 6.1	8.0 ± 5.1	>0.001
CRF (VO_2max, mL/kg/min)	30.6 ± 10.3	33.0 ± 9.1	0.457 ǂ

Abbreviations: CNSLBP: chronic nonspecific low back pain; HCs: healthy controls; F: female, M: male, BMI: body mass index; NPRS: numeric pain rating scale; MODI: Modified Oswestry Disability Scale; FABQ: Fear Avoidance Behaviour Questionnaire; IPAQ: International Physical Activity Questionnaire; METS: metabolic equivalents; DASS-21: Depression, Anxiety and Stress Scale—21 Items; SF-36: Short Form Health Survey; CRF: cardiorespiratory fitness. ǂ nonparametric testing.

3.2. Pain Processing

Due to technical issues during the data collection from one person with CNSLBP and two HCs, the cuff algometry outcomes were based, respectively, on n = 19 and n = 18 participants. The details are presented in Table 2. At PRE, persons with CLBP showed significantly lower cPPT (Δ = −5.5; $p = 0.040$), TS (Δ = −0.79; $p = 0.042$), and CPM (Δ = −10.0; $p = 0.023$) in comparison to HCs. After performing a HIIT protocol, no significant PRE–POST differences were found in cPPT (Δ = 0.8; $p = 0.717$), TS (Δ = −0.41; $p = 0.121$), or CPM (Δ = −0.5; $p = 0.831$) in the persons with CNSLBP. Conversely, HCs showed significant PRE–POST improvements in cPPT (Δ = 5.2; $p = 0.019$) after a HIIT protocol. However, no between-group PRE–POST differences were found in either cPPT (Δ = 4.4; $p = 0.119$), TS (Δ = 0.40; $p = 0.412$), or CPM (Δ = 0.1; $p = 0.977$) after a HIIT protocol. Furthermore, no between-group PRE–POST differences in cPPT (Δ = 0.4; $p = 0.601$), TSP (Δ = 0.2; $p = 0.371$), or CPM (Δ = 3.1; $p = 0.289$) were found in persons with CNSLBP performing a HIIT or a MIT protocol.

Table 2. Pain sensitivity outcomes before and after a HIIT and MIT protocol in persons with CNSLBP and HCs.

	HIIT			MICT	
QST Variables	**CNSLBP (n = 19)**	**HC (n = 18)**	**Between-Group CLBP–HC Δ [CI] (*p*)**	**CNSLBP (n = 19)**	**Between-Group HIIT–MICT Δ [CI] (*p*)**
PRE cPPT	28.2 ± 7.1	33.7 ± 8.1	5.5 [0.3;10.8] (0.040)	29.3 ± 9.1	1.0 [−2.2;4.2] (0.512)
POST cPPT	28.9 ± 11.8	38.9 ± 12.6	9.9 [1.5;18.3] (0.022)	30.5 ± 10.9	1.4 [−4.3;6.3] (0.690)
Delta	0.8 ± 8.4	5.2 ± 7.8	4.4 [−1.2;10.0] (0.119)	1.3 ± 9.6	0.4 [−5.9;6.3] (0.601)
Within-group PRE–POST (*p*)	0.717	0.019		0.609	
PRE TS	1.11 ± 0.89	0.32 ± 1.23	0.79 [0.03;1.55] (0.042)	0.75 ± 1.26	0.3 [−0.8;0.3] (0.322)
POST TS	0.70 ± 1.04	0.31 ± 1.62	0.39 [−1.36;0.58] (0.417)	0.28 ± 0.97	0.0 [−0.6;0.3] (0.941)
Delta	0.41 ± 0.99	0.01 ± 1.67	0.40 [−0.58;1.38] (0.412)	0.47 ± 0.74	0.2 [−0.8;0.3] (0.371)
Within-group PRE–POST (*p*)	0.121	0.980		0.023	
PRE CPM cPPT	36.2 ± 11.6	46.3 ± 13.3	10.0 [1.5;18.7] (0.023)	36.4 ± 14.6	0.6 [−7.3;6.1] (0.844)
POST CPM cPPT	35.7 ± 13.9	45.6 ± 16.4	9.9 [0.3;21.6] (0.044)	38.2 ± 15.5	2.4 [−4.6;3.3] (0.469)
Delta	−0.5 ± 10.3	−0.7 ± 14.8	0.1 [−9.0;8.7] (0.977)	1.8 ± 7.1	3.1 [−2.9;3.1] (0.289)
Within-group PRE–POST (*p*)	0.831	0.850		0.330	

All values are reported in kPa. Abbreviations: QST: quantitative sensory testing; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; CNSLBP: chronic nonspecific low back pain; HCs: healthy controls; CIs: confidence intervals; cPPT: cuff pressure pain threshold; TS: temporal summation of pain; CPM: conditioned pain modulation.

3.3. Inflammation

Due to a number of outcomes falling under the limit of detection of the ELISA kit [60], IL-6 outcomes were based, respectively, on n = 14 (CNSLBP) and n = 17 (HC) participants, and TNF-α outcomes were based, respectively, on n = 14 (CNSLBP) and n = 12 (HC) participants. No significant differences were found between patient characteristics with missing data and the final dataset for any outcome. Details of these outcomes are presented in Figure 3. At PRE, no differences were found between persons with CNSLBP and HCs in either IL-6 (Δ = 0.6; p = 0.810) or TNF-α (Δ = 3.6; p = 0.255) (panels A–B). After performing a HIIT protocol, no significant PRE–POST differences were found in either IL-6 or TNF-α in either persons with CNSLBP (respectively, Δ = 2.0; p = 0.055 and Δ = 9.7; p = 0.237) and HCs (respectively, Δ = 3.1; p = 0.249 and Δ = −1.0; p = 0.542) (panels A–B). Furthermore, no between-group differences in IL-6 (Δ = 1.1; p = 0.700) or TNF-α (Δ = 10.7; p = 0.117) were found in persons with CNSLBP and HCs (panels C–D). Moreover, no between-group differences in IL-6 (Δ = 1.0; p = 0.358) or TNF-α (Δ = 8.7; p = 0.251) were found in persons with CNSLBP performing a HIIT or a MIT protocol (panels C–D). A table containing the full dataset is available in Supplementary Materials.

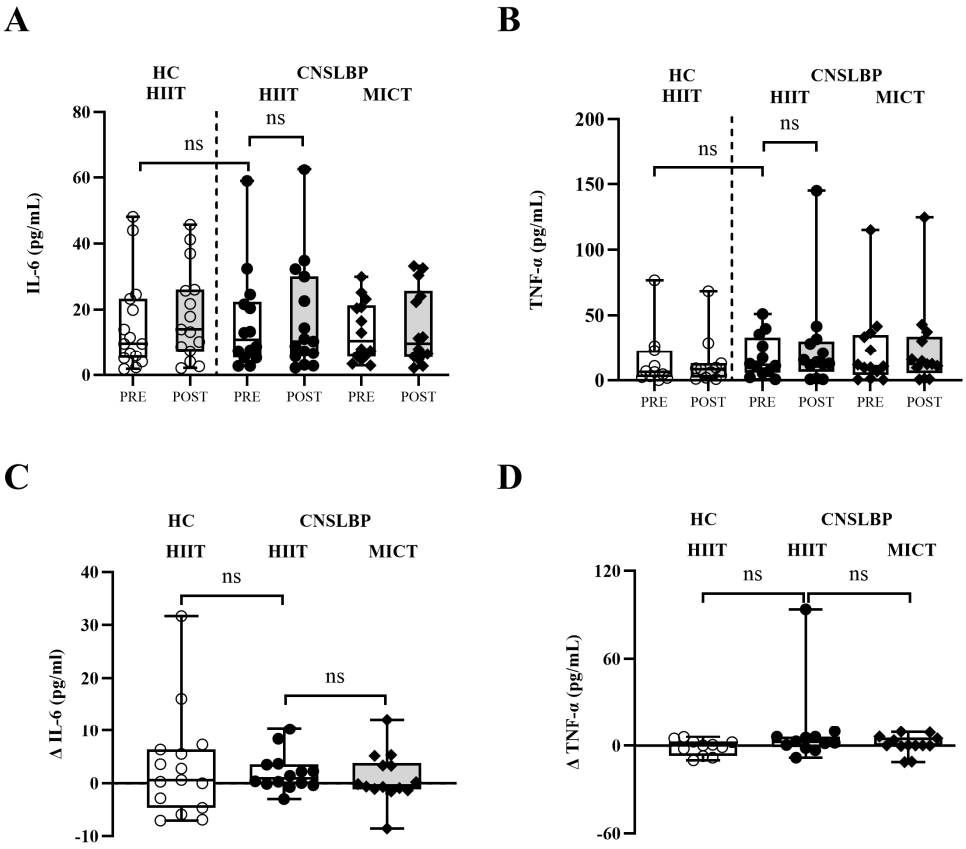


Figure 3. Overview of the inflammation outcomes (panels **A**–**D**). Abbreviations: IL-6: interleukin-6; TNF-α: cytokine tumor necrosis factor alpha; HCs: healthy controls; CNSLBP: chronic nonspecific low back pain; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training; ns: non-significant.

3.4. Relationship Between Pain Processing and Inflammation

The correlations between pain sensitivity and inflammatory markers in persons with CNSLBP are presented in Table 3. Significant moderate-to-strong relationships were found between PRE IL-6 and delta CPM (r = 0.724, p = 0.003), PRE TNF-α and delta TS (r = 0.613, p = 0.034), PRE TNF-α and delta CPM (r = 0.569, p = 0.043), and delta TNF-α and PRE cPPT (r = −0.690, p = 0.013). The other correlations were non-significant. Two partial

correlation analyses were performed. The first, confounding for age and BMI (Table 4), showed very strong significant correlations between PRE IL-6 and delta cPPT (r = 0.756, $p = 0.030$), PRE IL-6 and delta CPM (r = 0.853, $p = 0.007$), PRE TNF-α and cPPT (r = 0.721, $p = 0.043$), and PRE TNF-α and delta TS (r = 0.838, $p = 0.009$). The second, confounding for depression, stress, anxiety, and sleep (Table 5), showed no significant correlations between pain sensitivity and inflammatory markers.

Table 3. Correlations between pain sensitivity outcomes and inflammatory markers at PRE and PRE–POST (delta) after HIIT in persons with CNSLBP.

	Inflammatory Markers			
QST Variables	**PRE IL-6**	**Delta IL-6 ┼**	**PRE TNF-α**	**Delta TNF-α ┼**
PRE cPPT	0.068	0.264	0.148	−0.690 *
Delta cPPT	0.446	0.489	0.343	0.112
PRE TS	−0.011	0.046	−0.298	0.120
Delta TS	0.424	−0.203	0.613 *	0.182
PRE CPM	−0.147	0.060	−0.100	−0.459
Delta CPM	0.724 *	0.363	0.569 *	0.536

All values are displayed as r values. Abbreviations: QST: quantitative sensory testing; cPPT: cuff pressure pain threshold; TS: temporal summation of pain; CPM: conditioned pain modulation; IL-6: interleukin-6; TNF-α: cytokine tumor necrosis factor alpha. * significant $p > 0.05$. ┼ nonparametric testing.

Table 4. Partial correlations between pain sensitivity outcomes and inflammatory markers at PRE and PRE–POST after HIIT corrected for age and BMI in persons with CNSLBP.

	Inflammatory Markers			
QST Variables	**PRE IL-6**	**Delta IL-6 ┼**	**PRE TNF-α**	**Delta TNF-α ┼**
PRE cPPT	−0.053	0.294	0.253	−0.575
Delta cPPT	0.756 *	0.398	0.721 *	0.171
PRE TS	−0.108	0.074	−0.384	0.198
Delta TS	0.646	0.108	0.838 *	0.492
PRE CPM	−0.267	−0.306	0.193	−0.606
Delta CPM	0.853 *	0.306	0.668	0.556

All values are displayed as r values. Abbreviations: QST: quantitative sensory testing; cPPT: cuff pressure pain threshold; TS: temporal summation of pain; CPM: conditioned pain modulation; IL-6: interleukin-6; TNF-α: cytokine tumor necrosis factor alpha. * significant $p > 0.05$. ┼ nonparametric testing.

Table 5. Partial correlations between pain sensitivity outcomes and inflammatory markers at PRE and PRE–POST after HIIT corrected for depression, stress, anxiety (DASS-21), and sleep (PSQI).

	Inflammatory Markers			
QST Variables	**PRE IL-6**	**Delta IL-6 ┼**	**PRE TNF-α**	**Delta TNF-α ┼**
PRE cPPT	0.807	−0.182	0.326	−0.107
Delta cPPT	0.846	0.358	0.737	0.486
PRE TS	−0.817	0.420	−0.567	−0.694
Delta TS	0.234	0.042	0.750	0.221
PRE CPM	0.726	−0.213	0.058	−0.713
Delta CPM	0.705	−0.014	0.809	0.304

All values are displayed as r values. Abbreviations: QST: quantitative sensory testing; cPPT: cuff pressure pain threshold; TS: temporal summation of pain; CPM: conditioned pain modulation; IL-6: interleukin-6; TNF-α: cytokine tumor necrosis factor alpha. * significant $p > 0.05$. ┼ nonparametric testing.

4. Discussion

This study is the first clinical trial to investigate the acute effects of a single HIIT session on pain sensitivity and inflammatory markers in persons with CNSLBP compared to HCs. In addition, this study examined the differential impact of HIIT versus MICT in persons with CNSLBP. This study found that persons with CNSLBP displayed lower cPPT, more TS, and lower CPM compared to HCs at rest. Following a HIIT session, HCs showed improvements in cPPT, indicating a potential exercise-induced hypoalgesia effect, which was not seen for persons with CNSLBP. Additionally, there were no differences in the effects on pain sensitivity between HIIT and MICT within the CNSLBP group. Moreover, no differences in baseline levels of IL-6 or TNF-α were found between persons with CNSLBP and HCs, and this was not modified by the HIIT or MICT protocols Finally, correlation analyses in the CNSLBP group showed significant relationships between pain sensitivity and inflammation. These were found to be strongly confounded by psychological factors.

4.1. Interpretation and Implications

Previous research has already reported increased pain sensitivity in persons with CNSLBP at rest when compared to HC [61,62]. Additionally, several studies have demonstrated a potential EIH effect in HCs [13]. There is still a debate regarding whether this effect is present in patients with CNSLBP [62].

The current study did find a higher pain sensitivity in persons with CNSLPB compared to HCs and corroborated the EIH effect in HCs. But, this effect was not present in persons with CNSLBP. This suggests that a single HIIT session may not be sufficient to elicit measurable improvements in pain sensitivity in this chronic pain population. These findings are supported by a recent clinical trial by Pinho et al. [63]. However, in the latter, only PPTs were analyzed, and dynamic QST outcomes such as TS or CPM were not included. Hence, the current study provided a more comprehensive analysis of pain modulation processes that might show EIH. The limited impact of HIIT in persons with CNSLBP contrasts the impact in HCs, where HIIT did lead to improvements, corroborating that this training modality enhances acute pain tolerance and pain modulation in non-clinical individuals. Indeed, similar results with higher-intensity protocols in HCs have been shown previously [16].

The findings regarding the comparison between HIIT and MICT indicate that both protocols had similar minimal effects on pain sensitivity within persons with CNSLBP, suggesting that the intensity of exercise may not be a critical determinant for this outcome in this disorder. Nonetheless, it remains unclear if applying different modalities (especially at specific intensities) would alter these findings. Previous trials have reported inconsistent results, with some showing unchanged pain sensitivity following strength training [58], while others have demonstrated increased EIH after aerobic [64] and stabilization training [65]. Notably, these studies had to differentiate between local and remote site effects, suggesting the involvement of distinct underlying mechanisms. Beyond the relationship with inflammation discussed in the present study, other neurophysiological (e.g., increased local blood flow [65] and activation of the endogenous opioid system [13]) and psychological (heightened anxiety and pain catastrophizing [66]) factors have been proposed. However, these theoretical models require validation in future trials. Additionally, many studies lack clear intensity definitions, limiting comparability across trials. Implementing standardized reporting templates, such as the CERT [67], could help address this issue and improve cross-study comparisons. Altogether, these inconclusive findings in CNSLBP remain in clear contrast with the positive outcomes on EIH found through performing several exercise modalities, including aerobic, stabilization, and strength training, in other chronic musculoskeletal disorders such as osteoarthritis, shoulder pain, and patella femoral

pain [20] and the overview literature showing a stronger impact through high-intensity protocols [16]. This variability highlights the need for further research into the underlying mechanisms governing disorder-specific responses to exercise.

Likewise, these results contrast the outcomes after repeated-exposure and structured training programs, where an added value of exercise intensity on pain sensitivity in both persons with CNSLBP [68] and HCs [69] has been displayed. Hence, it remains unclear if (absent) acute EIH effects have any predictive value on long-term pain sensitivity [70]. Such an evaluation has only been performed in persons with knee osteoarthritis, where a high EIH before a standardized ET program was associated with a larger pain improvement after treatment [15], suggesting that EIH might be an early "precursor" for a positive response to long-term exercise therapy. However, long-term changes to pain sensitivity can be caused by a plethora of biopsychosocial factors other than the used training paradigm, further complicating the interpretation of such results [20]. Large-scale research integrating all such factors is needed [70].

The absence of any differences in the inflammatory responses between the two groups both at rest and postexercise challenges the hypothesis of a general, more pronounced pro-inflammatory state in persons with CNSLBP. Altered systemic levels of pro- or anti-inflammatory biomarkers have been widely discussed in the literature. A recent systematic review by Morris et al. showed no differences in IL-6 and TNF-α [22] between persons with CNSLBP and HCs, while Van Den Bergh et al. and Pinto et al. found positive correlations of IL-6 and TNF-α with the presence of nonspecific low back pain [27,71]. As the latter reviews included both acute and chronic low back pain, specific categorizing of the timing of clinical pain (i.e., acute/chronic) seems imperative to correctly evaluate such outcomes. Furthermore, the current evidence remains limited and of low methodological quality, postulating the need for additional supportive data to facilitate more in-depth analyses. Given these mixed findings, future research might also focus on the importance of extensive phenotyping of persons with CNSLBP to identify specific subgroups with an inflammatory-driven pain mechanism [72]. Such tailored approaches may help uncover the subset of patients for whom inflammation actually plays a significant role [73]. In other fields of musculoskeletal pain research, it has been demonstrated that there is a substantial inter-person variability in inflammatory markers [74,75], and evidence suggests that this variability might be able to guide therapy [76]. Moreover, while IL-6 and TNF-α were selected as key inflammatory markers due to their more established relevance in exercise and chronic pain, the importance of assessing additional markers such as IL-1β, CRP, and IL-10 should also be recognized [22,71,77]. As such, future research might aim to include a broader range of biomarkers to evaluate a broader inflammatory profile and provide a more detailed understanding of the inflammatory response to high-intensity exercise in chronic pain populations.

The findings from the current study regarding HIIT and MICT responses indicate that neither exercise protocol significantly affected the inflammatory markers within CNSLBP. This was an unexpected outcome as, at least in HCs, the impact of acute exercise on systemic IL-6 levels has been demonstrated [78,79] and in high-intensity (interval) exercise conditions [80–82]. Furthermore, baseline values of IL-6 and TNF-α in both groups (but especially in the HCs) were much higher than reported in the literature [83,84]. However, as high variability in inflammatory biomarkers has been noted in general, which can even increase in chronic pain [71,85], it is unclear if this affected the outcome.

Finally, the observed correlations between specific pro-inflammatory markers and cuff algometry outcomes suggests a link between inflammation and pain sensitization in CNSLBP. This association has been widely studied in animals [86] and has only just recently been confirmed in humans [87]. But, due to the lack of broader significant correlations, the current

results remain speculative, and other variables not included in this study could heavily influence this relationship. Through correcting for either age and BMI or DASS-21 and PSQI outcomes, we were able to show that the latter strongly impacted the association between systemic inflammation and pain sensitivity. Hence, we believe that the positive correlation found in this analysis should at this moment be interpreted with caution. A more inclusive evaluation of psychological factors confounding this relationship seems essential.

4.2. Strengths and Limitations

This study was strengthened by its inclusion of a well-defined CNSLBP sample with a matched HC group, as deemed paramount for the qualitative evaluation of EIH [20], as well as the comprehensive assessment of both pain sensitivity outcomes and systemic inflammatory markers. Additionally, the comparison of HIIT and MICT protocols provides important insights into the value of different exercise intensities [13].

This study also has limitations. First, the small sample size and technical issues leading to incomplete data could have reduced the statistical power in detecting significant differences. However, statistical power remained sufficient to evaluate strong correlations ($r > 0.600$) [88]. Since all significant correlations in this study approached or exceeded this threshold, the data that were used to interpret these results remained valid. Nonetheless, these correlation analyses also showed some strong correlations ($r > 0.600$) that were not significant, which could be caused by the high variability in a small dataset [89]. Furthermore, not all confounders could be included in one all-encompassing partial correlation analysis due to limits in the remaining degrees of freedom of the analysis (minimum $dF = 3$). Bigger datasets could also enable a shift toward elaborate cluster analyses [90] to provide supportive information regarding different overarching patient profiles. Second, the MICT protocol was only performed by persons with CNSLBP, making a direct comparison with HCs related to this protocol impossible. Third, participants were not required to fast before testing, which could have influenced the inflammatory marker outcomes. Dietary intake and substances like coffee or medication may impact the levels of inflammatory markers such as IL-6 and TNF-α, potentially masking or altering the true effects of exercise on these markers [91]. Additionally, studies should incorporate a broader range of inflammatory markers and consider individual variability in inflammatory responses to exercise [28,71]. Third, some confounders (such as the DASS-21 subscores [92]) showed very low baseline scores, limiting their clinical relevance in this sample. A dataset with more pronounced scores for these factors might have more impact on the final results. Lastly, some data points were missing for both the pain processing ($n = 3$, 8%) and inflammation ($n = 23$, 29%) outcomes due to technical issues or limitations of the assessment sensitivity. Given the small sample size, we did not perform a formal sensitivity analysis or use imputation techniques. However, we did carefully examine the distribution of the missing data and found no significant profile differences or systematic patterns suggesting bias. As such, we ensured that the missing data did not meaningfully impact the overall trends in the results.

5. Conclusions

This study provides novel insights into the acute effects of HIIT on pain sensitivity and inflammation in persons with CNSLBP. Baseline differences in pain sensitivity were found in persons with CNSLBP compared to HCs. No improvements in either outcome were observed after HIIT in the CNSLBP group. However, the findings of decreased cPPTs in the HCs suggest that HIIT still has beneficial nociceptive effects in specific populations. Finally, no differences in pain sensitivity or inflammatory markers were found between HIIT and MICT protocols in persons with CNSLBP. Future research should consider larger sample sizes for more elaborate evaluations, additional biomarkers, more transparent exercise

protocols, and comparison with outcomes from longer intervention periods to gain a more comprehensive understanding of the effects of various exercise intensities on pain and inflammation in persons with CNSLBP.

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