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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Multimodal high-intensity training to improve inspiratory muscle function in persons with chronic nonspecific low back pain

Luana Zago

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

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ABSTRACT

Background: Exercise therapy is effective in improving biopsychosocial outcomes in individuals with chronic nonspecific low back pain (CNSLBP), although overall treatment effects tend to be low to moderate. High-intensity training (HIT) has shown greater effectiveness compared to moderate-intensity training (MIT), but the underlying mechanisms remain unclear. A potential explanatory mechanism is inspiratory muscle (IM) function. This study aims to compare the effects of HIT and MIT on IM function in individuals with CNSLBP.

Methods: In this randomized controlled trial, 48 participants with CNSLBP were allocated to a 12-week supervised multimodal exercise program (24 sessions, twice weekly) at either HIT (n = 23) or MIT (n = 25) intensity. Primary outcomes were IM strength, endurance, and fatigue. Secondary outcomes included exercise capacity, physical disability, pain intensity, depression, and anxiety. Assessments were conducted pre- and post-intervention, and data were analyzed using linear mixed models.

Results: Both groups were comparable at baseline. The HIT group showed significant improvements in IM strength (+10%, $p = .045$), endurance (+31%, $p = .002$), $VO_2\text{max}$ (+15%, $p < .002$), disability (−40%, $p = .003$), pain (−49%, $p < .001$), and depression (−40%, $p = .038$). The MIT group improved in IM strength (+14%, $p = .006$), disability (−44%, $p < .001$), and pain (−38%, $p = .006$). Between-group differences favored HIT for IM endurance ($p = .029$) and exercise capacity ($p = .013$).

Conclusion: Both HIT and MIT improved IM function, with HIT showing greater benefits for endurance and capacity. IM function may underlie these effects and warrants further exploration within multimodal HIT programs, particularly in relation to psychosocial profiles.

Keywords: chronic nonspecific low back pain, high-intensity training, diaphragm function, randomised controlled trial

PREFACE

This master's thesis is positioned within the field of clinical musculoskeletal care pathways and rehabilitation guidelines, focusing on the complex challenge of rehabilitating individuals with chronic nonspecific low back pain (CNSLBP). This study explores the potential mechanisms behind high-intensity training (HIT) and its impact on diaphragm and inspiratory muscle (IM) function in individuals suffering from CNSLBP.

The thesis elaborates on specific aspects of the BREATHE-(H)IT trial, titled "Multimodal high-intensity training to improve diaphragm function in persons with chronic non-specific low back pain." This randomized controlled trial is led by Dr. Sim Klaps under the supervision of Prof. Dr. Annick Timmermans and Dr. Jonas Verbrugghe, and is supported by the Special Research Fund UHasselt (BOF21DOC15). It takes place at REVAL, the research facility of the Faculty of Rehabilitation Sciences and Physiotherapy in Diepenbeek.

CNSLBP is a leading cause of disability worldwide, with 10-20% of cases progressing to chronicity (Ferreira et al., 2023). While current rehabilitation methods, including exercise therapy, show moderate effectiveness, there remains a need for optimization (Oliveira et al., 2018). The BREATHE-(H)IT trial investigates the comparative effects of HIT and moderate-intensity training (MIT) on IM function and disease-related outcomes.

This thesis primarily examines the impact of these two training approaches on IM function and disease-related outcomes, based on preliminary data from the broader study. The findings are interpreted within the framework of the trial's objectives and under the guidance of the supervisory team. The study is expected to be completed this year, after which the complete results will be presented.

Throughout the research process, the students involved in this thesis actively contributed to data collection and assisted in the delivery of interventions to study participants. All activities were carried out under the supervision of Drs. Sim Klaps. Additionally, every four weeks, the students were invited to present specific aspects of the study. These presentations offered opportunities to deepen the understanding of scientific research processes and served as valuable preparation for the thesis defense.

Being involved in this study and collaborating with the research team has been a highly educational experience for each of us as students. Through our engagement, we developed essential research skills, including data analysis and scientific interpretation. Moreover, our involvement has provided us with in-depth knowledge of CNSLBP, a condition that is not only highly prevalent but also one we are likely to encounter frequently in our future careers as healthcare professionals.

We would like to express our heartfelt gratitude to our supervisor, Drs. Sim Klaps, for his tireless efforts, insightful guidance, and continuous support throughout our Master's journey. We also sincerely thank our promotor, Prof. Dr. Annick Timmermans, and co-promotor, Dr. Jonas Verbrugghe, for their valuable input and encouragement. We would like to extend our thanks to the Faculty of Rehabilitation Sciences and Physiotherapy at Hasselt University for providing us with this enriching opportunity and for promoting our development as future professionals and researchers. Finally, we would like to thank all the participants who took part in the study; their time, commitment, and willingness to contribute were essential to the progress of this research.

ChatGPT (developed by OpenAI) was utilized as a supportive writing tool to improve grammatical correctness and enhance the clarity of language throughout this thesis.

INTRODUCTION

Low back pain (LBP) is the leading cause of disability worldwide, often resulting in long-term functional disability and high healthcare utilisation (Ferreira et al., 2023). Approximately 84% of people experience LBP at least once in their lifetime (Balagué et al., 2012), with 90% of cases being non-specific, meaning no identifiable cause can be determined (Krismer & Van Tulder, 2007). Chronic LBP, defined as pain in the lumbar region persisting for over 12 weeks, occurs in 10-20% of cases (Maher, 2004), and if no identifiable cause can be determined it is referred to as chronic non-specific low back pain (CNSLBP) (Maher et al., 2017).

LBP is linked to respiratory symptoms such as hyperventilation, dyspnea, asthma, and allergies, with 32% of LBP cases having respiratory dysfunctions (Beeckmans et al., 2016). Furthermore, persons with CNSLBP may have reduced inspiratory muscle (IM) function, such as reduced muscle strength (Vermeersch et al., 2017), increased diaphragm fatigability (Janssens, Brumagne, et al., 2013), and reduced diaphragm endurance (Janssens et al., 2010). Kolář et al. (2012) also showed that persons with LBP have reduced diaphragm movement compared to healthy controls. Impairments in IM function, particularly of the diaphragm, may contribute to CNSLBP because the diaphragm is crucial for respiration and postural control (Hodges and Gandevia, 2000).

Exercise therapy is the primary treatment for CNSLBP patients, although its effects are often moderate (Oliveira et al., 2018). The intensity of training plays a crucial role in determining its effectiveness (Verbrugghe et al., 2019). High-intensity training (HIT) is a time-efficient, safe, and feasible method shown to be more effective than moderate-intensity training (MIT) in improving cardiorespiratory capacity, pulmonary function, muscle strength, mental health, and overall exercise capacity (Gibala et al., 2012; Verbrugghe et al., 2018, 2019; Dunham & Harms, 2012). Moreover, multimodal HIT has demonstrated greater reductions in disability, which is a key outcome in CNSLBP management (Verbrugghe et al., 2019). However, the underlying mechanisms driving these superior outcomes remain unclear. One potential explanation is that multimodal HIT elicits stronger improvements in IM function, which may play a mediating role in symptom reduction.

Although high-intensity inspiratory muscle training (IMT) enhances diaphragm function — improving strength, endurance, postural control, and pain relief — its effects on disability and psychosocial factors have not been consistently demonstrated (Janssens et al., 2015). In contrast, multimodal HIT training offers broader benefits, including improvements in disability and psychosocial outcomes (Verbrugghe et al., 2019; Klaps et al., 2022).

The primary research objective is to compare the effects of multimodal HIT and MIT on IM function, specifically strength, endurance, and fatigue, in persons with CNSLBP. The research question guiding this objective is: *Does HIT improve IM function (strength, endurance, and fatigue) more than MIT in individuals with CNSLBP?* The hypothesis is that HIT will lead to higher increases in diaphragm strength and endurance, as well as more significant reductions in diaphragm fatigue, compared to MIT.

The secondary research objective is to examine the effects of HIT versus MIT on exercise capacity, pain intensity, disability, anxiety, and depression in persons with CNSLBP. The research question here is: *Does HIT improve exercise capacity, pain intensity, disability, anxiety, and depression more than MIT in persons with CNSLBP?* It is hypothesised that HIT will result in greater improvements in these outcomes compared to MIT.

METHODS

Study design

This study is a randomised controlled trial, in which persons with CNSLBP participated in a 12-week exercise therapy program in REVAL (Hasselt University, Diepenbeek, Belgium). The HIT group followed a high-intensity program, while the MIT group adhered to a comparable (i.e., identical content, duration, and frequency) training program at moderate intensity. Participants were evaluated before (referred to as "pre") and after (referred to as "post") the training program. The clinical trial was approved by the Medical Ethical Committee of Hasselt University (B1152021000029) and is registered at ClinicalTrials.gov (code: NCT05384457). All participants gave written informed consent. As the study is still ongoing, the preliminary results collected between July 2022 and March 2025 are discussed in this thesis.

Participants

Between February 2022 and December 2024, participants were recruited through the local distribution of flyers (e.g. in pharmacies, libraries, universities and facilities) in Limburg (BE) and advertisements on social media. Those who expressed interest were provided with a patient information letter and were invited to attend an intake session with one of the researchers (SK). During this session, the information letter was reviewed, study inclusion and exclusion criteria were assessed, and a study-specific screening regarding red flags for low back pain rehabilitation was completed.

The study included Dutch-speaking males and females between the ages of 18 and 65 with chronic low back pain (i.e. pain localised below the costal margin and above the inferior gluteal folds, with or without referred leg pain for at least twelve weeks (Maher, 2004). The pain also needed to be of a non-specific origin (i.e., pain not attributable to a recognizable, known, specific pathology, e.g., infection, tumour, osteoporosis, fracture, structural deformity, an inflammatory disorder, radicular syndrome, or cauda equina syndrome) (Airaksinen et al., 2006). In addition, participants were required to report a pain intensity of more than 3 on a 0–10 numeric rating scale at baseline. All participants had to verify this medical diagnosis from a general practitioner or medical specialist.

Persons were excluded from the study when they had a history of spinal fusion; the presence of musculoskeletal disorders other than CNSLBP that could affect the correct execution of the therapy program; baseline characteristics potentially influencing outcome assessments (such as having a pacemaker, acute/chronic respiratory disorder, or known balance/vestibular issues); severe comorbidities 'e.g. paresis or sensory disturbances of neurological origin, diabetes mellitus, rheumatoid arthritis); ongoing compensation claims; negative advice from the general practitioner regarding sports medical screening; pregnancy; or an inability to attend regular appointments. Table 1 in the appendix shows a detailed presentation of the eligibility criteria.

Randomisation and blinding

A research assistant, who was not involved in the study, picked a sealed, numbered envelope to achieve randomisation. This was used with a block size of two participants to ensure an equal group division (1:1 allocation ratio). To avoid performance bias, participants were informed that equal progression of outcomes was expected across both groups.

Measurements – Test moments

At baseline (T0), midway through (six weeks, T1), and after completing the training program (12 weeks, T2), participants were tested to assess any changes in outcome over time. Following the intervention period, two longitudinal assessments (at three months (T4) and after one year (T5)) were conducted to assess the evolution of outcome measures. In this thesis, only data collected from measurement time T0 (pre) is compared to data from measurement time T2 (post, after 12 weeks of training).

Outcome measures

Primary outcomes

1. *Inspiratory muscle strength*

Maximal inspiratory pressure (MIP) was measured with an electronic pressure transducer PowerBreathe KH2 (POWERbreathe International Ltd., type KH1, Warwickshire, UK) to assess IM strength. The highest mouth pressure over one second was defined as MIP. The standardised protocol was done according to Black and Hyatt's method (Carpenter et al., 1998). The MIP manoeuvre was repeated five times if the mean difference between the best and second-best inspiratory pressure was less than five percent. Otherwise, additional repetitions were performed until the difference was within five percent.

Absolute MIP values were converted into predicted MIP (MIPpred) values using the equations that were developed by Lista-Paz A. et al. (2023), accounting for age, sex and BMI. The participants' MIP were expressed as percentages of their predicted values. Additionally, for the cut-off score for IM weakness, a value of less than 80% of the MIPpred was used, according to the article by Azevedo I.G. et al (2023).

$$\text{MIP (women)} = 61,48 + 0,66 \times \text{age} + 1,55 \times \text{BMI} - 0,01 \times \text{age}^2$$

$$\text{MIP (men)} = 98,60 + 1,18 \times \text{age} + 0,76 \times \text{BMI} - 0,02 \times \text{age}^2$$

2. *Inspiratory muscle endurance*

A fixed intensity of 60% of MIP was used to measure the endurance time (Welch et al., 2018). Participants were instructed to inhale as explosively as possible at a frequency of 15 breathing cycles per minute and a half-duty cycle. The IM endurance time (in seconds) was calculated as the amount of time before task failure.

3. *Inspiratory muscle fatigue*

Inspiratory muscle fatigue (IMF) is defined as a temporary reduction in the ability to generate inspiratory muscle force due to contractile activity. The specific cut-off for a decrease in MIP to identify IMF varies across studies, but a commonly referenced decline to define exercise-induced IMF is a reduction of 10% (Klaps et al., 2025). To evaluate IMF in this study,

MIP assessments were conducted immediately before the cardiopulmonary exercise test (CPET), and at 0, 15, and 30 minutes post-CPET. IMF was calculated by comparing MIP values at these time points.

Secondary outcomes

1. Exercise capacity

A CPET is the gold standard for measuring cardiorespiratory fitness, with maximal oxygen uptake (VO₂max) serving as its primary indicator (Guazzi et al., 2017). VO₂max, the maximum oxygen uptake, was expressed in ml/min/kg (Buttar et al., 2019). During the CPET, breath-by-breath gas exchange was analysed using the Cortex MetaMax 3B.

The CPET protocol involved an incremental ramp test where the participant maintained a cadence of 75 RPM, with the wattage increasing by 15 watts every minute, starting from 30 watts. The test continued until the participant was unable to continue due to fatigue, with a respiratory exchange ratio of at least 1.10 indicating maximal effort (Thompson et al., 2013).

2. Disability

The Modified Oswestry Disability Index (MODI) is a validated and reliable questionnaire designed to assess the physical limitations a person experiences in daily life due to low back pain (Denteneer et al., 2018).

The MODI consists of 10 items and each item was scored on a six-point ordinal scale, ranging from 0 (no limitations) to 5 (maximum limitations). The raw scores (0-50) are multiplied by 2 to yield a total score ranging from 0 to 100, which represents the percentage of perceived disability (Beurskens et al., 1995). The interpretation of this integral score is as follows: a score of 20-40% indicates moderate limitations; 40-60% severe limitations; 60-80% significant limitations; and 80-100% reflects experiencing extreme disability (Vianin et al., 2008). The questionnaire is sensitive to clinical changes, with a minimal detectable change (MDC) of 5-6 points and a minimum clinically important difference (MCID) of 6 points (Fritz et al., 2001).

3. *Pain*

The Brief Pain Inventory (BPI) (Stanhope, 2016) was used to determine the participants' average pain intensity during the previous week, measured by the Numeric Pain Rating Scale (NRPS) on a scale from 0 to 10.

4. *Depressive mood*

Depressive mood was assessed using the Beck Depression Inventory (BDI), which consists of 21 items rated on an ordinal four-point scale (0-3).

Based on the total BDI score, with a maximum of 63 points, depressive mood can be categorised into four severity levels: no or minimal depression (0-13); mild depression (14-19); moderate to severe depression (20-28); severe depression (29-63). With a sensitivity of 0.77 (95% CI 0.69-0.83) and specificity of 0.92 (CI 0.79-0.97), the BDI is a valid tool to assess depressive mood (Goodarzi et al., 2016).

5. *Anxiety*

To assess anxiety levels, the State-Trait Anxiety Inventory (STAI) was used. This instrument consists of two subscales: one measuring *state anxiety* — anxiety related to specific events — and the other assessing *trait anxiety*, which reflects a more stable, personal predisposition to anxiety (Knowles & Olatunji, 2020). Each subscale consists of 20 items, each scored on an ordinal scale from 0 to 4. The total score reflects the severity of anxiety, with scores above 38.5 on the state anxiety subscale and above 45.5 on the trait anxiety subscale indicating high anxiety levels (de Lemos Zingano et al., 2019).

Interventions

Both groups received a multimodal exercise program of 12 weeks with two sessions per week. The program included a cardiorespiratory component on a cycle ergometer, as well as limb and core muscle strengthening exercises.

Multimodal HIT group

Cardiorespiratory training

The cardiorespiratory training consisted of a high-intensity interval training (HIIT) protocol on a cycle ergometer, beginning with a five-minute warm-up at low resistance. The main component consisted of five active bouts of one minute at 100% of the participant's $\text{VO}_{2\text{max}}$ and a cadence of 110 rpm, separated by five one-minute bouts of rest at 50% $\text{VO}_{2\text{max}}$ and a cadence of 75 rpm. Each session ended with a cooling-down of five minutes at low resistance to support recovery.

During session one, participants performed their first HIIT session. In session two, the cycling protocol was repeated without modifications. The first progression in the duration of the active interval time was introduced in session three, increasing the length of each active bout by ten seconds. This progression was maintained in session four. From session five onward, the protocol continued to progress by extending the active interval duration by an additional ten seconds after every two consecutive sessions, while the duration of the rest intervals remained unchanged.

A mid-program reassessment was conducted to evaluate individual progress and adjust training intensities accordingly. From session thirteen onward, cycling intensities were tailored to each participant based on the results of this reassessment, allowing for continued adaptation and progression in the cardiorespiratory component.

Limb Muscle Strengthening

The limb muscle strengthening program targeted both the upper and lower extremities. Participants performed six resistance exercises: three for the lower limbs (leg press, leg curl, and leg extension) and three for the upper limbs (chest press, arm curl, and vertical traction) (Figure 1). These exercises were executed at 80% of the participant's one-repetition maximum (1RM) for 12 repetitions per set.

In session one, the strength training equipment and exercises were introduced, allowing participants to become familiar with proper technique and machine operation. During

session two, a 1RM assessment was conducted to determine individual training loads. Sessions three and four included the first implementation of limb muscle strengthening exercises, with one set of each of the six exercises being performed. From session five onward, participants progressed to two sets per session. When participants were able to complete two sets of twelve repetitions without compensatory movement, the load was increased to a higher load, depending on the exercise and machine. The exercise protocol and progression model were maintained consistently throughout the entire program.

Core Muscle Strengthening

Core muscle strengthening exercises were based on previous literature and were performed in an isometric position. These six exercises included the glute bridge, glute clam, superman back extension, adapted plank, adapted side plank, and shoulder retraction with hip hinge (Figure 2). Each exercise was held for ten seconds, repeated ten times with a ten-second rest in between repetitions. Progression was determined by achieving a minimum core muscle activation of more than 60% maximal voluntary contraction (MVC) (Verbrugghe et al., 2019).

In session one, the concept of core muscle strengthening and its neuromuscular focus was introduced to optimize muscle activation, specifically targeting the multifidus and transversus abdominis. During session two, the six specific exercises were demonstrated and performed. In sessions three and four, participants performed one set of each exercise. From session five onward, this was increased to two sets per session. Progressions in exercise difficulty were made by adjusting the starting position and were implemented when participants correctly performed the exercises in two consecutive sessions.

Multimodal MIT group

The MIT group followed a similar 12-week multimodal exercise program but at moderate intensity and with lower volume. The cardiorespiratory training consisted of a 14-minute continuous session at 60% VO₂max and a cadence of 90 rpm, with progression made by adding 1'40" after two consecutive sessions. The limb strengthening exercises included the same exercises as in the HIT group, but performed once per session at 60% 1RM for 15 repetitions. Progression occurred when participants could correctly execute the set for two

consecutive sessions. The core muscle strengthening exercises targeted deep core muscles at an activation level below 60% MVC. Instead of modifying the starting position, progressions were made by increasing execution time by two seconds when exercises were correctly performed for two consecutive sessions.

Following each session, a fidelity checklist was used in both groups to ensure adherence to all practical considerations and safety regulations, as well as to maintain consistency in training program implementation and training volume across different therapists. This checklist (see appendix - table 2) was structured around four key principles of exercise fidelity (i.e., adherence, dosage, quality of intervention and participants responsiveness) (An et al., 2020).

Figure 1

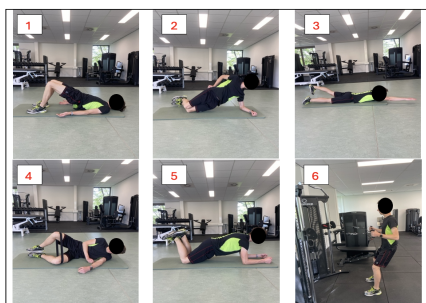
Limb Strengthening Exercises (Breathe-(H)IT Trial)



Note. (1) Leg curl – (2) Leg extension – (3) Leg press – (4) Arm curl – (5) Chest press – (6) Vertical traction

Figure 2

Core Muscle Strengthening Exercises (Breathe-(H)IT Trial)



Note. (1) Glute bridge – (2) Adapted side plank – (3) Superman back extension – (4) Glute clam – (5) Adapted plank – (6) Shoulder retraction with hip hinge

Sample size calculation

A sample size estimation was carried out in collaboration with CenStat (Hasselt University) to ensure sufficient statistical power for the study. This estimation considered:

- a) the effects of a twelve-week multimodal HIT program compared to a MIT program on VO₂max, measured during a cardiorespiratory fitness assessment (Verbrugghe et al., 2019).
- b) the outcome of an eight-week high-intensity IMT program compared to a low-intensity version on MIP, reflecting IM strength (Janssens et al., 2015).

These measures were chosen due to their relevance for respiratory function and potential to reflect changes in diaphragm performance. The calculation was based on a minimal clinically important difference of 3.5 ml/kg/min for VO₂max (Bonafiglia et al., 2022), 18 cmH₂O for MIP and 22.1% of the value of MIP_{pred} (Del Corral et al., 2023). A significance level of .05 and statistical power of 80% were applied to determine the sample size needed to detect group differences, leading to an initial estimate of 38 participants (n = 19 per group).

Adjustments were made to account for anticipated participants dropouts: 30% by the second time point (T2, after the intervention) and an additional 10% at T4 (one year follow-up). This resulted in a target recruitment of 64 individuals (n = 32 per group).

Data analysis

In this study, we aimed to assess the impact of multimodal HIT versus MIT on various primary and secondary outcome measures after completion of a 12-week exercise program.

Statistical analysis was performed using JMP Pro (version 17, SAS Institute Inc., Cary, USA). The difference in baseline characteristics drawing a comparison between the HIT and MIT group was assessed using independent t-tests for continuous variables (Body Mass Index (BMI), age, weight, length and duration of LBP) and Chi-square tests for categorical variables (sex). If the data did not meet the assumptions for normality, the Rank Sum test was used for continuous variables instead.

A linear mixed model (LMM) was used due to the study's repeated measurements design, allowing for the examination of both between- and within-group differences. This model incorporated fixed effects, including treatment group (HIT vs. MIT), time, and their interaction. Additionally, random effects, such as subjects, were included to account for intra-subject variability.

Several assumptions needed to be met for the model to be valid. Firstly, the residuals had to adhere to a normal distribution to satisfy the assumption of normality, which was assessed using visual inspection of the normal quantile plot (QQ-plot). Secondly, the residuals had to exhibit constant variance to meet the assumption of homoscedasticity, evaluated using the Brown-Forsythe test. Thirdly, observations had to be independent within groups to fulfil the assumption of independence. Finally, the relationship between dependent and independent variables had to be linear to satisfy the assumption of linearity. Cohen's *d* was calculated to estimate the effect size of all parameters. Post-hoc pairwise comparisons were performed using *t*-tests, as part of the mixed model analysis. Furthermore, the residuals were plotted to check for outliers among the results. A significance level of 5% ($p < .05$) was used for determining statistical significance.

Values in HIT and MIT were reported as mean (standard deviation). Delta was calculated as the difference between POST and PRE. Difference of deltas (DOD) was calculated as the difference between Delta HIT and Delta MIT. Cohen's *d* was calculated to showcase effect sizes.

RESULTS

Baseline characteristics

The baseline characteristics of the participants in the HIT (n = 23) and MIT (n = 25) groups were similar, with no statistically significant differences between both groups ($p > 0.05$). An overview of the participants' baseline characteristics is summarized in Table 1.

Table 1

Baseline Characteristics of Participants (n=48)

Variables	HIT (n=23)	MIT (n=25)	P-value
Sex (m/f)	12/11	16/9	0.406 ^a
Age (yr)	45.22 (13.36)	44.92 (14.67)	0.984 ^b
BMI (kg*m ⁻²)	25.60 (4.19)	26.28 (4.23)	0.577 ^a
Length (m)	1.75 (0.11)	1.75 (0.09)	0.928 ^a
Weight (kg)	78.15 (13.44)	80.70 (15.38)	0.544 ^a
Duration LBP (yr)	11.08 (7.21)	10.47 (9.14)	0.493 ^b

Note. Continuous variables are expressed as mean (standard deviation), categorical variables are expressed as a number. m/f = male/female; yr = years; BMI = body mass index; LBP = low back pain.

^a P-value of parametric test. ^b P-value of non-parametric test.

Training outcomes

An overview of the training outcomes is given in table 2.

Significant improvements in MIP were observed in both the HIT and MIT groups. The HIT group demonstrated an increase of 9.03% ($p = .045$), while the MIT group showed an increase of 11.99% ($p = .006$). However, no significant difference was found between the two groups in MIP improvement ($p = .407$).

Significant increases in endurance were found exclusively in the HIT group, with an improvement of 75.75 seconds ($p = .002$). A significant difference in endurance improvement

was observed between the HIT and MIT groups, favouring the HIT group with a p -value of .029.

No significant differences were found in inspiratory muscle fatigue in either group for each time point after the CPET ($-5.12\% < +3.2\%$, $0.838 < p < 0.382$). Furthermore, no significant differences were observed between the HIT and MIT groups for any of the fatigue measurements (measurement 1: $p = .929$; measurement 2: $p = .293$; measurement 3: $p = .265$).

The HIT intervention resulted in a significant improvement in CPET performance, with an increase of 5.48 ml/kg/min ($p < .002$). A significant difference in CPET improvement was found between the HIT and MIT groups, favouring the HIT group with a p -value of .013.

Both the HIT and MIT interventions led to significant decreases in the MODI scores. The HIT intervention resulted in a significant decrease of 7.83 ($p = .003$), and the MIT intervention resulted in a significant decrease of 9.36 ($p < .001$). No significant difference in MODI score reduction was observed between the two groups ($p = .559$).

The HIT intervention led to a significant reduction in BPI scores (-2.39 , $p < .001$), while the MIT intervention also resulted in a statistically significant decrease of -1.64 points ($p = .006$). No significant difference was found between the HIT and MIT groups in their effects on BPI scores ($p = .287$).

The HIT intervention resulted in a significant decrease in BDI scores (3.30 , $p = .038$). No significant difference in BDI score reduction was found between the two groups ($p = .155$).

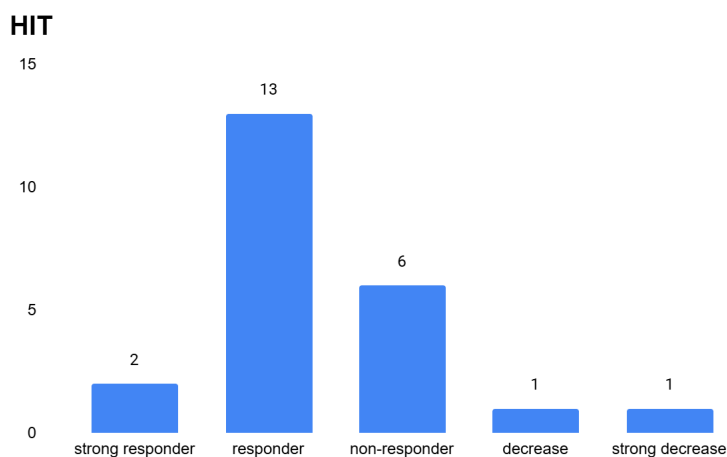
Neither the HIT nor the MIT interventions significantly decreased STATE scores (HIT: -5.09 , $p = .084$; MIT: -0.60 , $p = .830$). No significant difference in STATE score reduction was observed between the two groups ($p = .169$).

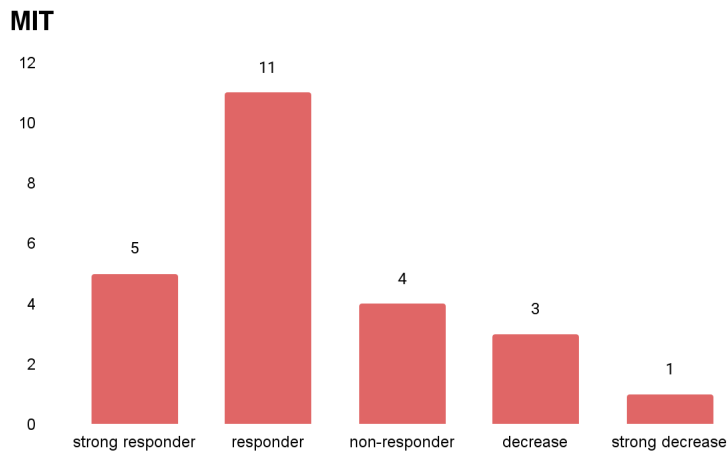
The HIT intervention resulted in a significant decrease in TRAIT scores (5.65 , $p = .037$). The MIT intervention did not significantly decrease TRAIT scores and showed an increase of 1.72 ($p = .504$). No significant difference in TRAIT score changes was found between the two groups ($p = .099$). A summary of the results is presented in Table 2.

A subanalysis was performed to give more insight into the effects of both interventions on the MIP. During this subanalysis, the participants were divided into subgroups depending on the amount of improvement in their MIP following the interventions. As stated by Del Corral et al. (2023), a minimum improvement of 18 cmH₂O (sensitivity, 61.5%; specificity, 96.6%) and 22.1% (sensitivity, 76.9%; specificity, 89.7%) of the predicted value for MIP is required to achieve a clinically meaningful change (MCID) in MIPpred. Participants reaching the threshold of 20% improvement in MIPpred are categorized as ‘strong responder’. Participants with an improvement between 5% and 20% were classified as ‘responders’, indicating a moderate but potentially meaningful effect, albeit below the MCID. Changes within a $\pm 5\%$ range were categorized as ‘non-responders’, assuming a possible measurement error. A decrease between 5% and 10% was labeled as ‘decrease’, suggesting a small reduction without clear clinical relevance. Lastly, participants with a decrease greater than 10% were placed in the ‘strong decrease’ group. While not meeting statistical significance thresholds, such a decline is considered noteworthy and may warrant further attention. See figure 3 for the distribution of the participants.

Figure 3

Subgroup Distribution based on MIP Change after Intervention





Note. Distribution of participants in the HIT group (blue) and participants in the MIT group (red).

The subanalysis revealed that most participants in both the HIT and MIT groups showed improvement after the interventions, even though this rarely reached the level of a minimal clinically important difference (MCID). However, in both groups were eight participants who did not improve in MIP, while some of them even showed a significant decrease in MIP. The participants who showed a decrease in MIP more than 5% were individually checked for deviations of other outcomes. Interestingly, these participants mostly had a MIP more than 100% of their predicted value prior to the study. In both groups, only one participant showed a decrease in MIP while already not achieving 100% of their MIPpred.

A graphic design with the results of all these participants compared with the average effects shows that there are a few deviations from these participants in relation to the average effects, but they show an overall effect comparable with the average effects (see appendix - figure 1).

Table 2

Results of the Outcome Measures Collected from Participants at PRE and POST together with Within and Between Group Differences

Outcome measures	HIT (n=23)			MIT (n=25)			Interaction	
	PRE	POST	DELTA	PRE	POST	DELTA	DOD	Cohen's d
Primary								
MIP %pred (%)	88,39 (23,19)	97,42 (20,00)	9,03 (10,31)*	87,71 (17,22)	99,71 (16,25)	11,99 (13,77)*	-2,96	0,24
Endurance (sec)	245,21 (102,04)	320,96 (115,47)	75,75 (81,21)*	260,51 (129,67)	290,65 (142,24)	30,13 (57,76)	45,62**	0,63
Fatigue %pred1 (%)	2,20 (10,31)	4,25 (11,93)	2,06 (13,09)	4,16 (22,75)	6,53 (24,44)	2,37 (10,82)	-0,31	0,03
Fatigue %pred2 (%)	5,85 (7,64)	6,97 (9,83)	1,12 (12,30)	8,70 (23,11)	3,58 (7,66)	-5,12 (25,45)	6,24	0,31
Fatigue %pred3 (%)	4,78 (6,24)	7,98 (8,39)	3,20 (10,56)	7,73 (23,18)	4,76 (6,90)	-2,97 (24,08)	6,17	0,33
Secondary								
VO2max (ml/kg/min)	36,74 (9,64)	42,22 (9,60)	5,48 (3,73)*	36,08 (8,36)	38,52 (9,36)	2,44 (4,31)	3,04**	0,71
MODI (%)	19,57 (11,35)	11,74 (8,03)	-7,83 (8,90)*	21,36 (8,65)	12,00 (10,97)	-9,36 (9,11)*	1,53	0,17
BPI (NPRS)	4,87 (1,91)	2,48 (2,37)	-2,39 (2,52)*	4,36 (1,52)	2,72 (1,72)	-1,64 (2,04)*	0,75	0,33
BDI (pts)	8,17 (7,06)	4,87 (5,05)	-3,30 (5,81)*	8,92 (6,25)	7,64 (6,38)	-1,28 (3,75)	-2,02	0,41
STAI - STATE (pts)	36,65 (9,91)	31,57 (9,03)	-5,09 (11,84)	34,24 (10,57)	33,64 (10,95)	-0,60 (10,38)	-4,49	0,54
STAI - TRAIT (pts)	39,83 (10,23)	34,17 (9,49)	-5,65 (8,86)	37,88 (12,72)	36,16 (10,98)	-1,72 (7,31)	-3,93	0,35

Abbreviations. DOD = Difference of deltas; MIP %pred = measured maximal inspiratory pressure compared to predicted maximal inspiratory pressure via calculation, given as a percentage; VO2max = maximum oxygen consumption/uptake; MODI = Modified Oswestry Disability Index; BPI = Brief Pain Inventory; NPRS = Numeric Pain Rating Scale; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory.

* P < 0.05 compared with PRE. ** P < 0.05 HIT compared with MIT, using a Student's t-test.

DISCUSSION

The aim of this study was to compare the effects of multimodal HIT and MIT on IM function, exercise capacity, disability, pain, depressive mood, and anxiety. The results indicate that both HIT and MIT lead to improvements in MIP and scores on the MODI. However, the HIT intervention also results in significant improvements over time in IM endurance, VO_2 max, as well as on the BPI and the BDI. Notably, the HIT program has a significant advantage over MIT in improving IM endurance and VO_2 max.

MIPpred

Following any intervention, a significant increase in MIP was observed in both groups. However, no significant difference in MIP improvement was found between the HIT and MIT groups. This is different from the hypothesis, as we expected that the HIT-protocol would significantly improve more. Gomes Neto et al. (2018) and the studies of Janssens et al. (2013; 2015) found greater improvements in the high-intensity group when comparing high- and low-intensity IMT protocols. Subanalysis of both groups in this trial shows some important factors which could explain the difference with the hypothesis. While there is a significant increase in MIP in both groups, some participants did decrease following the interventions. Two participants in the HIT intervention showed a decrease in MIP following the intervention, while even four participants in the MIT showed a decrease in MIP. Interestingly, only one participant from both groups did decrease in MIP while already having a MIP less than 100% of the predicted value. IMT literature suggests that both moderate- and high-intensity protocols result in similar improvements in IM strength and endurance in well-trained individuals (Rehder-Santos et al., 2021). This suggests a possible ceiling effect in well-conditioned individuals, where higher intensities may not proportionally lead to greater benefits. The large part of the participants in this study, who showed no improvement or even worsening in change in MIPpred following the intervention, might explain the inconsistency between this study and the studies of Gomes Neto et al. (2018) and Janssens et al. (2013;2015). Another interesting aspect is that the previously described studies did use IM training protocols, while the current study does only use whole-body training. Despite using a different type of training, a significant benefit in IM strength is visible.

As suggested by the results and the previously referred studies, high-intensity whole-body training could offer greater physical benefits than MIT, as demonstrated by the within-group progressions in MIPpred. While within-group improvements were significant, the absence of a significant between-group difference in MIP may indicate that respiratory muscle adaptations require a more specific training approach which is not only dependent on training intensity. Therefore, future research could explore the potential additive effect of incorporating targeted IMT into a high-intensity whole-body exercise program. This combined approach may optimize both diaphragm-specific outcomes and broader functional and psychological benefits in individuals with CNSLBP.

Substantial inter-individual variability was observed when analyzing the pre-intervention MIP values. As Klaps et al. (2025) suggested, future research should include participants through criteria based on the MIP. Participants exhibiting such weakness before the intervention may experience greater improvements compared to those with normal IM strength. Future research is needed to conduct subgroup analyses, where we can start looking at baseline and evolution of MIP values within the HIT / MIT group. Thus, there could be some links between MIP values and other (secondary) outcome measures.

Inspiratory muscle endurance

Regarding IM endurance time, the HIT intervention resulted in a significant improvement, while no such effect was observed in the MIT group. A significant difference between those groups was observed. Several possible underlying mechanisms can explain this.

Firstly, the cardiorespiratory component of the HIT group was characterized by short bouts of high-intensity cycling. Due to its demanding ventilatory effort, it could trigger the inspiratory muscles more than the MIT group (Romer & Polkey, 2008). As described by Nakahara et al. (2020), high-intensity interval training extends the time spent above the respiratory compensation threshold more effectively than moderate-intensity continuous training, thereby eliciting a greater ventilatory and metabolic stimulus for respiratory muscle adaptation. This might explain their ability to perform the endurance test for a longer period.

Besides, it might be possible that the number of core muscle strength training sets, the level of effort per set, and the extent of core muscle activation has an impact on the effectiveness of a training protocol. Schoenfeld et al. (2018) and Hughes et al. (2018) suggest that training intensity and effort per set may be more important than total session duration. This could help explain why HIT leads to greater improvements than MIT in endurance-related outcomes. Additionally, Gomez et al. (2009) found that repeated abdominal muscle activation – e.g. sit-ups – can increase the intra-abdominal pressure, potentially leading to structural overload and fatigue of the diaphragm. Regarding our study, it might be possible that the core strength exercises of the HIT protocol, which are progressed in a higher %MVC of the core muscles, can give a rise in intra-abdominal pressure regulations with more diaphragm adaptations as a result.

Inspiratory muscle fatigue

The present analysis revealed that neither the HIT nor the MIT intervention led to significant improvements in the IMF. Several explanations may account for this finding. First, the CPET protocol used in this study was incremental, which may not have induced sufficient or sustained respiratory muscle loading to elicit IMF. Archiza et al. (2018) suggest that constant-load protocols are more effective and reliable for provoking diaphragm fatigue, as they allow exercise to be maintained at intensities of 80–85% of VO_2max for extended periods. In this study, thresholds were reached to induce IMF, but the duration of exercising above this intensity may be too short as suggested by Klaps et al. (2025). Similarly, Hardy et al. (2024) emphasize that the duration of high-intensity bouts must be sufficiently long to provoke diaphragm fatigue. During their study, they compared a HIT-interval protocol with high-intensity bouts of five minutes on average with a prolonged HIT-interval protocol with high-intensity bouts of ten minutes on average. This prolonged protocol did significantly produce more diaphragmatic fatigue. The 1 to 1.4-minute intervals used in the HIT exercise protocol may therefore have been too brief to induce meaningful physiological adaptations related to IMF.

Additionally, findings by Klaps et al. (2025) provide further context, showing no significant differences in IMF between individuals with CNSLBP and healthy controls. This suggests that

diaphragm fatigability may not be a prominent characteristic in this patient population, which could partially explain the absence of detectable improvements following the intervention. Interestingly, Klaps et al. (2025) also reported that individuals with a higher VO₂max, longer time to exhaustion and maximal workload during the CPET exhibited lesser IMF, suggesting that the combination of exercise duration and the exercise intensity could play an important role. Another consideration for future research is to conduct subgroup analyses stratified by baseline disability or pain severity to examine whether individuals with higher symptom severity experience differential improvements in IM function.

Exercise capacity

This thesis highlights the clear advantages of training at higher intensities. Exercise capacity, as measured by VO₂max, improved significantly in the HIT group, whereas no such improvement was observed in the MIT group. These findings align with prior research. Although both endurance training and high-intensity training result in VO₂max improvements, the gains are consistently greater with HIT (Milanović et al., 2015; Verbrugghe et al., 2019). Additional studies further support these observations. Despite lower total training volumes, HIT has been shown to yield equal or even superior results compared to moderate-intensity protocols, regardless of participants' baseline fitness levels (Atakan et al., 2021). Verbrugghe et al. (2019), using an identical HIT protocol in a similar population, likewise confirmed the superior efficacy of HIT in enhancing exercise capacity. These improvements in VO₂max are thought to result from a range of physiological adaptations, including increased mitochondrial density, improved cardiac output, and enhanced oxygen utilization.

While these findings are encouraging, future research is needed to further optimize HIT protocols—specifically with regard to optimal training intensity, session duration, and the duration of an active bout—to maximize both safety and effectiveness in clinical populations such as individuals with CNSLBP. Adjusting the intensity – for instance, targeting 85-90% of VO₂max instead of maximal efforts – may allow participants to sustain high-intensity efforts for longer periods. Moreover, extending session duration to maintain exercise above a critical intensity threshold, alongside optimising the work-to-rest ratio, could further maximize the

effectiveness of HIT interventions. Helgerud et al. (2007) suggested that 4 bouts of respectively at 4 minutes at 90-95% of the maximal heart rate, separated by 3 minutes at 70% of the maximal heart rate, can improve VO₂max more efficiently compared to lactate-threshold training intensities.

Psychosocial outcomes and disability

When examining psychosocial outcomes and disability, both the HIT and MIT interventions led to improvements on the MODI and BPI, while only the HIT group showed additional positive changes on the BDI scale. Despite these findings, only the improvements on the MODI reached clinical significance, defined as a minimum difference of 6 points according to Fritz et al. (2001). This suggests that both interventions had a meaningful impact on disability perception. While the HIT group appeared to show more consistent improvement across all psychosocial measures—except for the MODI—there was no statistically significant difference between the two groups, preventing firm conclusions regarding the superiority of HIT. Whole-body training – particularly at higher intensities – appears to offer broader benefits beyond respiratory function alone. In the present study, the HIT intervention also led to significant improvements in pain intensity (BPI), depressive symptoms (BDI), and disability (MODI). Interestingly, although HIT was associated with these improvements, disability also improved significantly following the MIT intervention. This contrasts with findings by Verbrugghe et al. (2019), who reported significant improvements in disability only after HIT. Additionally, the relative improvements in disability were less pronounced in our study than those observed by Verbrugghe et al. (2019).

A possible explanation for the better improvement in the HIT protocol is given by Thum et al. (2017). This study concluded that, despite the higher physical efforts, high intensity training gave more enjoyment to participants when compared to moderate intensity training. This might explain why participants in the HIT group showed slightly better improvements in the BDI, BPI, STATE and TRATE questionnaires. These questionnaires are used to measure psychosocial outcomes as pain at the moment, anxiety, depressive mood, etc. The possibly more enjoyment experienced during the HIT protocol might elevate their positive mental status. This might also explain why the MODI did not improve more in the HIT group, as this

questionnaire does look more into activities of daily living. However, in a trial by Paolucci et al. (2018), low-, moderate-, and high-intensity training (LIT, MIT, and HIT) protocols were compared to evaluate their effects on psychosocial outcomes. Both the MIT and HIT protocols led to improvements, with greater benefits observed in the MIT group. The authors suggested that the high physical stress of the HIT protocol might explain why MIT yielded better outcomes. Consequently, HIT might still offer psychosocial benefits, provided that participants find the exercise enjoyable.

Further research is needed to determine which training intensity offers the greatest benefits for patients with different personality traits. Pain experiences are, as is shown by Larsen et al. (2013), greatly modulated by psychosocial factors. Integrating a biopsychosocial approach is recommended for managing CNSLBP in clinical practice (Hartvigsen et al., 2018).

Strengths and limitations

One of the main strengths of this study is the use of a highly standardized and structured training protocol, supported by a detailed fidelity checklist. This enhanced the internal validity and reproducibility of the study. Medical confirmation by a general practitioner or specialist enhances the reliability of the study population. Additionally, the topic is both clinically and socially relevant, given the global burden of CNSLBP and the need for more effective rehabilitation strategies. Although based on preliminary results, this randomized controlled trial indicates that the reliability and generalizability of the findings could be enhanced by increasing the sample size. Randomization of participants helped to reduce allocation bias. While participants were aware of their group allocation, they were informed that equal improvements were expected across both groups, which may have reduced performance-related bias. The multimodal nature of the intervention, combining cardiorespiratory, strength, and core stability components, allowed for a comprehensive approach to functional rehabilitation, which increases its applicability in real-world settings. Furthermore, the use of validated outcome measures and a combination of physiological, functional, and psychosocial assessments provided a broad and reliable evaluation of intervention effects. Lastly, the results of these interventions might be applicable to other musculoskeletal pathologies, such as those with chronic neck pain. In a similar study by Colak et al. (2024) MIP was measured in patients with chronic neck pain and asymptomatic

controls. As there was a significant decrease in MIP in the participants with chronic neck pain, they suggested that there is a need for future research to determine the effectiveness of IMT for the treatment of chronic neck pain.

Despite its strengths, the study also has some limitations that should be acknowledged. There is a potential for selection bias, as participants who volunteered were likely more motivated and inclined toward exercise, possibly affecting the generalizability of the results to the broader population of individuals with CNSLBP. The exclusion of participants with other conditions, such as neurological or respiratory disorders, leads to an initially lower proportion of participants with IM dysfunctions, as this is a confounding factor which could influence the effect of the interventions. Although the International Physical Activity Questionnaire was used at baseline to estimate activity levels across different settings (e.g., work, domestic), physical activity during the intervention was monitored but not analyzed, which may have confounded the results. Variations in activity levels could have influenced inspiratory muscle outcomes, potentially leading to an overestimation of the intervention's effectiveness. Lastly, future research could include an additional inclusion criterion based on the percentage of MIPpred, enabling a more detailed investigation within a specific prevalence category.

CONCLUSION

Both HIT and MIT improved IM function and some psychosocial outcomes, with HIT showing significantly greater improvements in VO_2max and endurance. These findings suggest that improvements in IM function may be one of the underlying mechanisms driving the effects of both HIT and MIT. Future research should investigate the role of IMT within multimodal HIT programs, particularly in individuals with different psychosocial characteristics, to better understand its potential benefits in more severe profiles.

REFERENCES

- Airaksinen, O., Brox, J. I., Cedraschi, C., Hildebrandt, J., Klaber-Moffett, J., Kovacs, F., ... & COST B13 Working Group on Guidelines for Chronic Low Back Pain. (2006). European guidelines for the management of chronic nonspecific low back pain. *European spine journal*, 15(Suppl 2), s192.
- An, M., Dusing, S. C., Harbourne, R. T., Sheridan, S. M., & START-Play Consortium. (2020). What really works in intervention? Using fidelity measures to support optimal outcomes. *Physical therapy*, 100(5), 757-765.
- Archiza, B., Welch, J. F., Geary, C. M., Allen, G. P., Borghi-Silva, A., & Sheel, A. W. (2018). Temporal characteristics of exercise-induced diaphragmatic fatigue. *Journal of applied physiology*, 124(4), 906-914.
- Atakan, M. M., Li, Y., Koşar, Ş. N., Turnagöl, H. H., & Yan, X. (2021). Evidence-based effects of high-intensity interval training on exercise capacity and health: A review with historical perspective. *International journal of environmental research and public health*, 18(13), 7201.
- Azevedo, I. G., da Câmara, S. M., Maciel, A. C., Vieira, E. R., Espinoza, C. F., Pichún, S. M., ... & Sousa, S. L. D. O. (2023). Relationship between inspiratory muscle strength and balance in women: a cross-sectional study. *Plos one*, 18(2), e0280465.
- Balagué, F., Mannion, A. F., Pellisé, F., & Cedraschi, C. (2012). Non-specific low back pain. *The lancet*, 379(9814), 482-491.
- Beeckmans, N., Vermeersch, A., Lysens, R., Van Wambeke, P., Goossens, N., Thys, T., ... & Janssens, L. (2016). The presence of respiratory disorders in individuals with low back pain: A systematic review. *Manual therapy*, 26, 77-86.
- Beurskens, A. J., de Vet, H. C., Köke, A. J., van der Heijden, G. J., & Knipschild, P. G. (1995). Measuring the functional status of patients with low back pain: assessment of the quality of four disease-specific questionnaires. *Spine*, 20(9), 1017-1028.
- Bonafiglia, J. T., Swinton, P. A., Ross, R., Johannsen, N. M., Martin, C. K., Church, T. S., ... & Gurd, B. J. (2022). Interindividual differences in trainability and moderators of cardiorespiratory fitness, waist circumference, and body mass responses: a large-scale individual participant data meta-analysis. *Sports Medicine*, 52(12), 2837-2851.
- Buttar, K. K., Saboo, N., & Kacker, S. (2019). A review: Maximal oxygen uptake (VO2 max) and its estimation methods. *Ijpesh*, 6(6), 24-32.
- Carpenter, M. A., Tockman, M. S., Hutchinson, R. G., Davis, C. E., & Heiss, G. (1999). Demographic and anthropometric correlates of maximum inspiratory pressure: The Atherosclerosis Risk in Communities Study. *American journal of respiratory and critical care medicine*, 159(2), 415-422.
- Colak, G. Y., Ozyurek, S., Sengul, Y. S., & Kalemci, O. (2024). Differences of diaphragmatic muscle contraction between female patients with chronic neck pain and asymptomatic controls: A case-control study based on ultrasonography. *Musculoskeletal Science and Practice*, 69, 102894.
- de Lemos Zingano, B., Guarnieri, R., Diaz, A. P., Schwarzbald, M. L., Wolf, P., Lin, K., & Walz, R. (2019). Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) and The State-Trait Anxiety Inventory (STAI) accuracy for anxiety disorders detection in drug-resistant mesial temporal lobe epilepsy patients. *Journal of Affective Disorders*, 246, 452-457.

- Del Corral, T., Fabero-Garrido, R., Plaza-Manzano, G., Fernández-de-Las-Peñas, C., Navarro-Santana, M. J., & López-de-Uralde-Villanueva, I. (2023). Minimal clinically important differences in inspiratory muscle function variables after a respiratory muscle training programme in individuals with long-term post-COVID-19 symptoms. *Journal of clinical medicine*, 12(7), 2720.
- Denteneer, L., Van Daele, U., Truijen, S., De Hertogh, W., Meirte, J., & Stassijns, G. (2018). Reliability of physical functioning tests in patients with low back pain: a systematic review. *The Spine Journal*, 18(1), 190-207.
- Dunham, C., & Harms, C. A. (2012). Effects of high-intensity interval training on pulmonary function. *European journal of applied physiology*, 112, 3061-3068.
- Ferreira, M. L., De Luca, K., Haile, L. M., Steinmetz, J. D., Culbreth, G. T., Cross, M., ... & Mahmoodpoor, A. (2023). Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *The Lancet Rheumatology*, 5(6), e316-e329.
- Fritz, J. M., & Irrgang, J. J. (2001). A comparison of a modified Oswestry low back pain disability questionnaire and the Quebec back pain disability scale. *Physical therapy*, 81(2), 776-788.
- Gibala, M. J., Little, J. P., MacDonald, M. J., & Hawley, J. A. (2012). Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of physiology*, 590(5), 1077-1084.
- Gomes Neto, M., Ferrari, F., Helal, L., Lopes, A. A., Carvalho, V. O., & Stein, R. (2018). The impact of high-intensity inspiratory muscle training on exercise capacity and inspiratory muscle strength in heart failure with reduced ejection fraction: a systematic review and meta-analysis. *Clinical Rehabilitation*, 32(11), 1482-1492.
- Gomez, C. L., Strongoli, L. M., & Coast, J. R. (2009). Repeated abdominal exercise induces respiratory muscle fatigue. *Journal of Sports Science & Medicine*, 8(4), 543.
- Goodarzi, Z., Mrklas, K. J., Roberts, D. J., Jette, N., Pringsheim, T., & Holroyd-Leduc, J. (2016). Detecting depression in Parkinson disease: a systematic review and meta-analysis. *Neurology*, 87(4), 426-437.
- Guazzi, M., Bandera, F., Ozemek, C., Systrom, D., & Arena, R. (2017). Cardiopulmonary exercise testing: what is its value? *Journal of the American College of Cardiology*, 70(13), 1618-1636.
- Hardy, T. A., Chadwick, M. R., Ferguson, C., Cross, T. J., & Taylor, B. J. (2024). Differential effects of exercise intensity and tolerable duration on exercise-induced diaphragm and expiratory muscle fatigue. *Journal of Applied Physiology*, 136(6), 1591-1603.
- Hartvigsen, J., Hancock, M. J., Kongsted, A., Louw, Q., Ferreira, M. L., Genevay, S., ... & Woolf, A. (2018). What low back pain is and why we need to pay attention. *The Lancet*, 391(10137), 2356-2367.
- Hodges, P. W., & Gandevia, S. C. (2000). Activation of the human diaphragm during a repetitive postural task. *The Journal of physiology*, 522(1), 165-175.
- Hughes, D. C., Ellefsen, S., & Baar, K. (2018). Adaptations to endurance and strength training. *Cold Spring Harbor perspectives in medicine*, 8(6), a029769.
- Janssens, L., Brumagne, S., McConnell, A. K., Hermans, G., Troosters, T., & Gayan-Ramirez, G. (2013). Greater diaphragm fatigability in individuals with recurrent low back pain. *Respiratory physiology & neurobiology*, 188(2), 119-123.

Janssens, L., Brumagne, S., Polspoel, K., Troosters, T., & McConnell, A. (2010). The effect of inspiratory muscles fatigue on postural control in people with and without recurrent low back pain. *Spine*, 35(10), 1088-1094.

Janssens, L., McConnell, A. K., Pijnenburg, M., Claeys, K., Goossens, N., Lysens, R., ... & Brumagne, S. (2015). Inspiratory muscle training affects proprioceptive use and low back pain. *Medicine & science in sports & exercise*, 47(1), 12-19.

Klaps, S., Haesevoets, S., Verbunt, J., Köke, A., Janssens, L., Timmermans, A., & Verbrugghe, J. (2022). The influence of Exercise Intensity on Psychosocial outcomes in Musculoskeletal disorders: a systematic review. *Sports health*, 14(6), 859-874.

Klaps, S., Verbrugghe, J., Goossens, N., Meus, T., Köke, A., Verbunt, J., ... & Janssens, L. (2025). Maximal inspiratory pressure and exercise-induced inspiratory muscle fatigue in chronic nonspecific low back pain. *Respiratory Medicine*, 236, 107887.

Knowles, K. A., & Olatunji, B. O. (2020). Specificity of trait anxiety in anxiety and depression: Meta-analysis of the State-Trait Anxiety Inventory. *Clinical psychology review*, 82, 101928.

Kolář, P., Šulc, J., Kynčl, M., Šanda, J., Čákr, O., Andel, R., ... & Kobesová, A. (2012). Postural function of the diaphragm in persons with and without chronic low back pain. *Journal of orthopaedic & sports physical therapy*, 42(4), 352-362.

Krismer, M., & Van Tulder, M. (2007). Low back pain (non-specific). *Best practice & research clinical rheumatology*, 21(1), 77-91.

Larsen, E. L., Nielsen, C. V., & Jensen, C. (2013). Getting the pain right: how low back pain patients manage and express their pain experiences. *Disability and rehabilitation*, 35(10), 819-827.

Lista-Paz, A., Langer, D., Barral-Fernández, M., Quintela-del-Río, A., Gimeno-Santos, E., Arbillaga-Etxarri, A., ... & González-Doniz, L. (2023). Maximal respiratory pressure reference equations in healthy adults and cut-off points for defining respiratory muscle weakness. *Archivos de Bronconeumología*, 59(12), 813-820.

Maher, C. G. (2004). Effective physical treatment for chronic low back pain. *Orthopedic Clinics*, 35(1), 57-64.

Maher, C., Underwood, M., & Buchbinder, R. (2017). Non-specific low back pain. *The Lancet*, 389(10070), 736-747.

Milanović, Z., Sporiš, G., & Weston, M. (2015). Effectiveness of high-intensity interval training (HIT) and continuous endurance training for VO₂max improvements: a systematic review and meta-analysis of controlled trials. *Sports medicine*, 45, 1469-1481.

Nakahara, H., Ueda, S. Y., & Miyamoto, T. (2020). Low frequency severe-intensity interval training markedly alters respiratory compensation point during incremental exercise in untrained male. *Frontiers in Physiology*, 11, 1100.

Oliveira, C. B., Maher, C. G., Pinto, R. Z., Traeger, A. C., Lin, C. W. C., Chenot, J. F., ... & Koes, B. W. (2018). Clinical practice guidelines for the management of non-specific low back pain in primary care: an updated overview. *European Spine Journal*, 27, 2791-2803.

Paolucci, E. M., Loukov, D., Bowdish, D. M., & Heisz, J. J. (2018). Exercise reduces depression and inflammation but intensity matters. *Biological psychology*, 133, 79-84.

- Rehder-Santos, P., Abreu, R. M., Signini, É. D. F., da Silva, C. D., Sakaguchi, C. A., Dato, C. C., & Catai, A. M. (2021). Moderate-and High-Intensity Inspiratory Muscle Training Equally Improves Inspiratory Muscle Strength and Endurance—A Double-Blind Randomized Controlled Trial. *International Journal of Sports Physiology and Performance*, 16(8), 1111-1119.
- Romer, L. M., & Polkey, M. I. (2008). Exercise-induced respiratory muscle fatigue: implications for performance. *Journal of applied physiology*, 104(3), 879-888.
- Schoenfeld, B. J., Contreras, B., Krieger, J., Grgic, J., Delcastillo, K., Belliard, R., & Alto, A. (2018). Resistance training volume enhances muscle hypertrophy but not strength in trained men. *Medicine and science in sports and exercise*, 51(1), 94.
- Stanhope, J. (2016). Brief pain inventory review. *Occupational Medicine*, 66(6), 496-497.
- Thompson, P. D., Arena, R., Riebe, D., & Pescatello, L. S. (2013). ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription. *Current sports medicine reports*, 12(4), 215-217.
- Thum, J. S., Parsons, G., Whittle, T., & Astorino, T. A. (2017). High-intensity interval training elicits higher enjoyment than moderate intensity continuous exercise. *PloS one*, 12(1), e0166299.
- Verbrugghe, J., Agten, A., O. Eijnde, B., Olivieri, E., Huybrechts, X., Seelen, H., ... & Timmermans, A. (2018). Feasibility of high intensity training in nonspecific chronic low back pain: A clinical trial. *Journal of back and musculoskeletal rehabilitation*, 31(4), 657-666.
- Verbrugghe, J., Agten, A., Stevens, S., Hansen, D., Demoulin, C., Eijnde, B. O., ... & Timmermans, A. (2019). Exercise intensity matters in chronic nonspecific low back pain rehabilitation. *Medicine & Science in Sports & Exercise*, 51(12), 2434-2442.
- Vermeersch, A., Janssens, L., Thys, T., Goossens, N., Van Wambeke, P., Brumagne, S., & Lysens, R. (2017). Preliminaire studie over het belang van de opsporing van ademhalingsproblemen bij patiënten met lage rugpijn. *Tijdschrift voor Geneeskunde*, 73(9), 529-540.
- Vianin, M. (2008). Psychometric properties and clinical usefulness of the Oswestry Disability Index. *Journal of chiropractic medicine*, 7(4), 161-163.
- Welch, J. F., Archiza, B., Guenette, J. A., West, C. R., & Sheel, A. W. (2018). Sex differences in diaphragmatic fatigue: the cardiovascular response to inspiratory resistance. *The Journal of physiology*, 596(17), 4017-4032.

APPENDIX

Table 1

Eligibility Criteria (Breathe-(H)IT Trial)

Eligibility criteria	
Inclusion criteria	Rationale
18 to 65 year old	Study aimed at the adult working population
Low back pain for at least 12 weeks	Only the management of chronic low back pain is studied
Nonspecific origin	Specific pathological causes of low back pain can require specific care
Pain score > 3/10 (NRPS)	Ensures clinical relevance, reduces floor effects, and allows detection of meaningful treatment-related changes.
Exclusion criteria	Rationale
Invasive surgery (i.e. spinal fusion)	Specific invasive procedures of the lower back can require specific care table 1
A musculoskeletal disorder apart from CNSLBP that can affect the correct execution of the therapy program	Limiting the amount of factors acting on low back pain, not due to intervention
Comorbidities	Limiting the amount of factors acting on low back pain, not due to intervention
Ongoing compensation claims	Excluding motivation to contribute other than improvement of the pathology itself
Negative advice regarding sports medical screening	A negative advice from the GP does not allow the performance of a maximal cardiopulmonary exercise test
Pregnancy	Pregnancy-related low back pain is treated as a pathology with a specific cause and is thus not eligible for this study
Not able to attend regular therapy appointments	Limiting nonattendance to therapy due to reasons not linked to chronic low back pain

Table 2*Fidelity Checklist in the Multimodal HIT Group*

ADHERENCE		
Cardiorespiratory training in general	YES	NO
1: A file with the bicycle ergometer resistance values, saddle height and maximum wattage of the CPET is kept		
2: The participant is positioned correctly on the bicycle ergometer		
3: The therapist adjusts the resistance of the bicycle ergometer himself/herself		
4: The participant completes 5 minutes warm up		
5: The participant completes 5 minutes cooling down		
Remarks 'NO':		
Cardiorespiratory training HIT		
6: The participant completes 5 bouts of ... minute at 100% $VO_{2\max}$ workload and 110 rates per minute		
7: The participant completes 5 bouts of one minute active rest at 50% $VO_{2\max}$ workload and 75 rates per minute		
8: Exercise intensity is monitored at 9 timepoints in terms of heart rate and wattage		
Remarks 'NO':		
Resistance training		
9: A file with the results of the 1RM-testing is kept		
10: The therapist selects the correct weight/resistance for each exercise based on the 1RM-testing		
11: Actual intensity of each exercise is the same compared with its intended intensity (i.e. correct percentage 1RM)		
12: Actual repetitions of each exercise is the same compared with its intended repetitions		
13: Actual sets of each exercise is the same compared with its intended sets		
Remarks 'NO':		
Lumbar stabilization training		
14: Actual repetitions of each exercise is the same compared with its intended repetitions		
15: Actual sets of each exercise is the same compared with its intended sets		
Remarks 'NO':		
DOSAGE		
16: Session last at least 60 minutes		
QUALITY OF INTERVENTION DELIVERY		
In general		
17: An exercise manual with standardized instructions is provided for all therapists		
18: Intervention is provided by a trained therapist		
19: Therapist avoids distractions such as walking away, talking to other therapists, etc.		
Encouragement		

20: Therapist uses verbal encouragement at least 3 times during each exercise component		
21: Therapist acknowledges success after each successful training component		
22: Therapist uses verbal cues for changing intensity during HIT cardiorespiratory training		
PARTICIPANT RESPONSIVENESS		
23: Effort level is monitored after each exercise component in terms of rate of perceived exertion (BORG-scale)		
24: Motivation level is monitored at the start of the training session		

Fidelity Checklist in the Multimodal MIT Group

ADHERENCE		
Cardiorespiratory training in general	YES	NO
1: A file with the bicycle ergometer resistance values, saddle height and maximum wattage of the CPET is kept		
2: The participant is positioned correctly on the bicycle ergometer		
3: The therapist adjusts the resistance of the bicycle ergometer himself/herself		
4: The participant completes 5 minutes warm up		
5: The participant completes 5 minutes cooling down		
Remarks 'NO':		
Cardiorespiratory training MIT		
9: The participant completes ... minutes at 60% VO_{2max} workload and 90 rates per minute		
10: Exercise intensity is monitored at 6 timepoints in terms of heart rate and wattage		
Remarks 'NO':		
Resistance training		
11: A file with the results of the 1RM-testing is kept		
12: The therapist selects the correct weight/resistance for each exercise based on the 1RM-testing		
13: Actual intensity of each exercise is the same compared with its intended intensity (i.e. correct percentage 1RM)		
14: Actual repetitions of each exercise is the same compared with its intended repetitions		
15: Actual sets of each exercise is the same compared with its intended sets		
Remarks 'NO':		
Lumbar stabilization training		
16: Actual repetitions of each exercise is the same compared with its intended repetitions		
17: Actual sets of each exercise is the same compared with its intended sets		
Remarks 'NO':		
DOSAGE		

18: Session last at least 60 minutes		
Remarks 'NO':		
QUALITY OF INTERVENTION DELIVERY		
In general		
19: An exercise manual with standardized instructions is provided for all therapists		
20: Intervention is provided by a trained therapist		
21: Therapist avoids distractions such as walking away, talking to other therapists, etc.		
Remarks 'NO':		
Encouragement		
22: Therapist uses verbal encouragement at least 3 times during each exercise component		
23: Therapist acknowledges success after each successful training component		
Remarks 'NO':		
PARTICIPANT RESPONSIVENESS		
24: Effort level is monitored after each exercise component in terms of rate of perceived exertion (BORG-scale)		
26: Motivation level is monitored after the training session		
Remarks 'NO':		

Figure 1

Graphical Representation of Subanalysis of Participants with MIP Decline

