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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effects of high-intensity interval training on body composition, blood lipids, bone mineral density and an inflammatory blood marker in persons with nonspecific chronic low back pain

Amber Gevers
Stan Sniekers

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

PROMOTOR :
dr. Monique VAN ERUM

COPROMOTOR :
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We are also thankful to REVAL research centre for rehabilitation research of Hasselt University fundamental research and service in the domain of rehabilitation and physiotherapy for permitting us to utilise all the necessary facilities and equipment of the institution.

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We thank you.

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Research context

This master thesis is situated in the domain of musculoskeletal rehabilitation. The majority of the world's population will experience at least one episode of low back pain in their lifetime. Although a minority will evolve to a chronic state of low back pain, the socioeconomic burden should not be underestimated. Until this day there is no specific exercise therapy that has been identified as being beneficial for all people with nonspecific chronic low back pain (NSCLBP). No single exercise intervention seemed superior to another. With limited time being the most reported barrier, high-intensity interval training (HIT) could be favourable. To our knowledge, HIT has not been explored yet in persons with NSCLBP.

This preliminary randomized controlled trial (RCT) focused on the effects of different HIT-protocols on body composition, bone mineral density (BMD), blood lipid profile and the inflammatory blood marker in persons with NSCLBP.

This study was conducted under the supervision of dr. Monique Van Erum and Prof. dr. Frank Vandenabeele, as a part of a broader doctoral study from dr. Anouk Agten and drs. Jonas Verbrugghe: "Structural and functional effects of high-intensity interval training in patients with aspecific chronic low back pain" (study 15.142/reva15.14). This research project was supervised by Prof. dr. Bert Op 't Eijnde, Prof. dr. Annick Timmermans and dr. Monique Van Erum. All tests and training sessions were conducted at the REVAL research centre for rehabilitation research of Hasselt University fundamental research and service in the domain of rehabilitation and physiotherapy, located in Diepenbeek, Belgium.

This master thesis was completed by two last-year students of Rehabilitation Sciences and Physiotherapy at the University of UHasselt. The study design and method were developed by dr. Anouk Agten and drs. Jonas Verbrugghe. A convenience sampling was used to recruit study participants through brochures and social media. The data acquisition was fulfilled by dr. Anouk Agten and drs. Jonas Verbrugghe. To assure quality, the two master students Amber Gevers and Stan Sniekers wrote the article in cooperation. The data analysis was completed by Amber Gevers. An even amount of time and effort was invested by both master students. The supervised rehabilitation of the NSCLBP participants and testing of the NSCLBP participants and healthy controls (HC) itself were mostly done by dr. Anouk Agten and drs. Jonas Verbrugghe. When necessary, the two master students attended the rehabilitation and testing.

1 Abstract

Background: NSCLBP is a major health problem that has extended from the western society to the entire world. Until this day, no single intervention seemed to be superior to another. The effects of HIT have not yet been investigated in this population.

Objectives: The purpose of this preliminary RCT was to evaluate the effects of four different, twelve-week, HIT- protocols in persons with NSCLBP.

Participants: Thirty-two participants enrolled the present study, of which 14 subjects with NSCLBP and 15 HC. Participants with NSCLBP were randomly assigned to one of the HIT groups: HIT mobilization, HIT strength, HIT stabilization or HIT combined. Subjects of each training group performed an interval training session on a cycle ergometer at an individualised workload. Additional training was specific to each HIT group. The HC group did not enrol an exercise program. There were no dropouts during the study trial.

Measurements: Primary outcome measures were blood lipid profile, bone mineral density (BMD), body composition and an inflammatory blood marker. Secondary, sociodemographic baseline characteristics were obtained.

Results: There were no significant differences in baseline characteristics between persons with NSCLBP and HC. However, significantly more persons with NSCLBP had participated in a rehabilitation program for low back pain. None of the exercise training programs provided significant differences in the persons' blood lipid profile, BMD, body composition, and the inflammatory blood marker hs-CRP. Pre- and post-differences within and between groups showed no significant changes in the four intervention groups.

Conclusion: After twelve weeks, none of the outcome measures showed significant changes. More research is necessary to investigate the effects of different HIT-protocols in persons with NSCLBP and its possible superiority to other existing training interventions.

2 Introduction

Nonspecific chronic low back pain has increased substantially during the second half of the 20th century. This major health problem seems to have extended from the western society to the entire world (Balague, Mannion, Pellise, & Cedraschi, 2012; O'Sullivan, 2005). With its increasing medical expenditure and work absence, low back pain should not be underestimated (Gordon & Bloxham, 2016; O'Sullivan, 2005). Low back pain is defined as pain, muscle tension, or stiffness localised below the costal margin and above the inferior gluteal folds, with or without leg pain (sciatica) (Balague et al., 2012; Koes, van Tulder, & Thomas, 2006). Up to 84% of the population will experience at least one episode of low back pain during their lifetime. 90% of the population experiencing low back pain will have NSCLBP (Airaksinen et al., 2006; Balague et al., 2012). This pain is defined as symptoms without a clear specific cause. The diagnosis is based on the exclusion of specific pathologies, commonly referred to as “red flags” and is classified as chronic when the episode lasts longer than three months. Psychosocial factors, “yellow flags”, seem to have an important impact on the transition from acute to chronic low back pain (Balague et al., 2012; Koes et al., 2006). The diagnosis is based on the exclusion of specific pathologies, therefore the prevalence of NSCLBP can only be estimated at 23% (Airaksinen et al., 2006; Balague et al., 2012; Koes et al., 2006).

Physical inactivity is a modifiable risk factor for a variety of chronic diseases including obesity, CVD and bone and joint diseases, with a prevalence higher than all the other modifiable risk factors (Warburton, Nicol, & Bredin, 2006). The international guidelines for the treatment of people with chronic low back pain include: 1) discourage use of passive modalities, 2) short-term use of medication or manipulation, 3) supervised exercise therapy, 4) cognitive behavioural therapy and 5) multidisciplinary treatment (Koes et al., 2010). The current KNGF-guidelines make a distinction between nonspecific low back pain without dominant presence of psychosocial factors and nonspecific low back pain with dominant presence of psychosocial factors. The difference in treatment approach lies in the addition of cognitive behavioural therapy when yellow flags are present. Beside the differences between these two subgroups, both treatments recommend an active lifestyle and discourage any form of passivity (Royal Dutch Society for Physical Therapy [KNGF], 2013). Nevertheless, a recent review consisting of randomized controlled trials including active

exercise therapy could not establish any long-term clinically meaningful effects. Nor did one intervention seemed to be superior to another. Despite the variety in treatment approaches, people with LBP encounter an increase in disability and chronicity (O'Sullivan, 2005). A considerable number of chronic low back pain patients ends up in a vicious cycle leading to the development of deconditioning syndrome (Verbunt, Smeets, & Wittink, 2010).

As demonstrated, inactivity leads to an accumulation of adipose tissue in which no less than 75 inflammatory proteins can be produced. These proteins are associated with the development of systematic low-grade inflammation (Nimmo, Leggate, Viana, & King, 2013). The increase in abdominal tissue is an independent risk factor for the development of cardiometabolic diseases (Amato, Guarnotta, & Giordano, 2013). Moreover, low back pain is associated with CVD. People with CVD had a higher prevalence of low back pain and disability as a result of low back pain. In presence of marked aortic calcification, low back pain is frequently more reported. A high level of triglycerides is also linked to low back pain and the same was found for high cholesterol and low density lipoprotein (LDL). C-reactive protein (CRP), an indicator of chronic inflammation, has been found to be associated with sciatica, which could be present in people with LBP. The combination of lipid storage and inflammation contributes to the development of atherosclerosis. Atherosclerosis compromises the vascular endothelial function, which could lead to an increased inability of the vessels to dilate. The development of an increased thickness of the carotid intima-media is already been established to be related to low back pain (Kauppila, 2009). Interestingly, cardiovascular health and a decrement of the adipose tissue can be promoted by exercise (Nimmo et al., 2013). Furthermore, the level of CRP also decreases after routine physical activity (Warburton et al., 2006).

The findings concerning BMD in individuals with LBP are inconclusive. Lee et al. (2013) and Snider et al. (2014) showed a significant higher BMD in the lumbar spine in subjects with chronic LBP compared to those without LBP (Lee et al., 2013; Snider, Johnson, Degenhardt, Snider, & Burton, 2014). The previous findings contrasted with the findings of a retrospective study by Al-Saeed et al. (2013), where significant lower hip and spine BMD were found (Al-Saeed, Mohammed, Azizieh, & Gupta, 2013). In a second larger pilot study of Snider et al. (2014), chronic LBP was not related to vertebral, nor regional BMD (Snider et al., 2014). Evidence shows that physical activity also prevents the age-associated decline in BMD and

reduces the risk and number of falls (Warburton, Nicol, Gatto, & Bredin, 2007). Even though physical activity is most important in growth period, it can make a difference in all periods of life (Bielemann, Martinez-Mesa, & Gigante, 2013).

To promote and maintain health, adults should participate in moderate aerobic physical activity, for at least five days a week for a minimum of 30 minutes or vigorous aerobic physical activity, 3 days a week for a minimum of 20 minutes. The updated recommendation from the American College of Sports Medicine and the American Heart Association now states that moderate –to vigorous-intensity activities lead to more health benefits (Haskell et al., 2007). Yet routine physical activity seems unreachable, with lack of time being frequently cited as the greatest barrier (Gibala, Little, Macdonald, & Hawley, 2012). HIT, characterised by a high intensity and low volume, is a time-efficient solution. HIT can be defined as an intermittent exercise with relatively short bouts of high-intensity workloads alternated by periods of passive rest or low-intensity activity (Gillen & Gibala, 2014; Tschakert & Hofmann, 2013). HIT is a relatively new concept intervention which could be the cause of lacking a standardized protocol. Despite this variability, positive effects in favour of HIT could be achieved in different studies indicating there is no need for a standardized exercise protocol (Tschakert & Hofmann, 2013).

NSCLBP is a multifactorial disease which explains the heterogeneity of this population. Until this day there is no specific exercise therapy which has been identified as being beneficial for all people with NSCLBP. This suggests that the intervention should not just focus on one specific area of physical activity. A combined exercise program, adjusted to the personal needs of the person, would be beneficial for rehabilitation of NSCLBP (Gordon & Bloxham, 2016).

To date, no studies have reported the effects of HIT in people with NSCLBP. The aim of this study is to investigate which intervention will have the most beneficial impact on blood lipid profile, BMD, body composition and the inflammatory blood marker hs-CRP.

3 Method

3.1 Subjects

Following detailed information and informed written consent, 16 subjects with NSCLBP were recruited from a convenience sample. Subjects were recruited through social media and informative brochures, with the contact details (e-mail and telephone number) given. Inclusion criteria were NSCLBP (current episode >12 weeks); 25 – 60 years old and able to understand Dutch (written and spoken). People with invasive neurosurgery in the past 18 months (with the exception of minimally invasive neurosurgery); radiculopathy (uni- or bilateral); comorbidities (paresis and sensory abnormalities with an underlying neurological source, diabetes mellitus, rheumatoid arthritis); increase in pain of >3/10 and/or pain >8/10 in the last 48 hours; ongoing compensations and/or work absence >6 months; rehabilitation or exercise therapy targeting the low back in the last 6 months were excluded from the study.

In addition to the subjects with NSCLBP, 16 HC were included. Inclusion criteria were no chronic complaints (persisting >3 months); no acute low back pain (<6 weeks): VAS >8/10 in the last 24 hours; 25-60 years old and able to understand Dutch (written and spoken). People undergoing rehabilitation or exercise therapy targeting acute diseases were excluded from the study.

This preliminary study used a RCT design and had been approved by the medical ethical committee of Hasselt University (protocol 14.87/REVA14.12). The clinical trial was registered at clinicaltrials.gov (NCT02786316).

3.2 Study Design

All tests and training sessions were conducted at the REVAL research centre for rehabilitation research of Hasselt University fundamental research and service in the domain of rehabilitation and physiotherapy, located in Diepenbeek, Belgium.

After an initial screening, participants with NSCLBP underwent baseline assessment (T0) and were reassessed after six (T1) and twelve weeks (T2) of rehabilitation. HC were only assessed at baseline (T0). Figure 1 represents the timeline of this study.

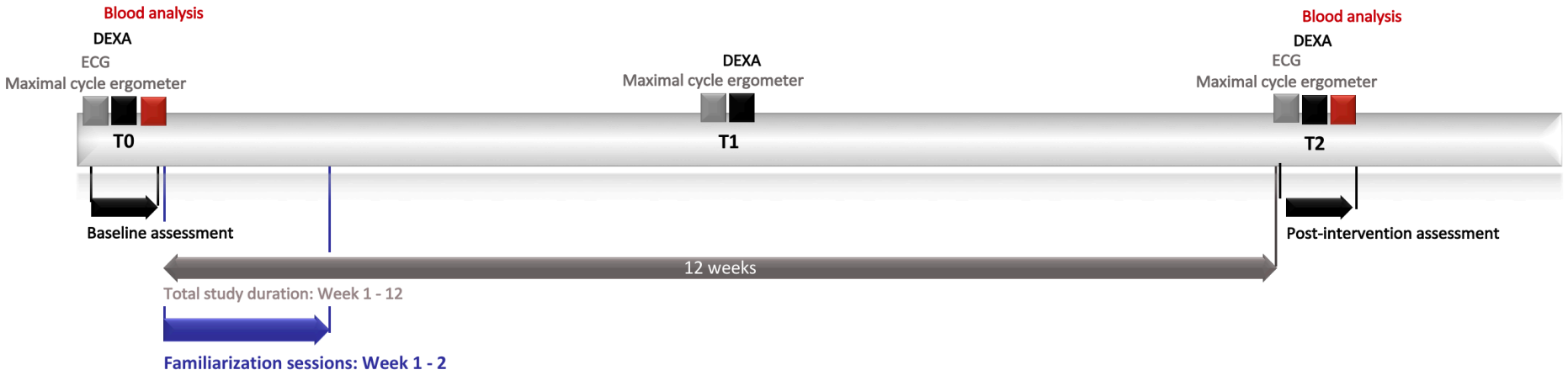

Figure 1. *Schematical presentation of the timeline*

To guarantee the subject's safety before performing a maximal cycle ergometer test, an electrocardiography (ECG) was performed by an experienced physician. The participants with NSCLBP were randomized into four training groups: 1) HIT mobilization, 2) HIT strength, 3) HIT stabilization or 4) HIT combined. The type of intervention is presented in table 1. Assignments were placed in opaque envelopes and distributed to participants after a participant passed the screening to ensure blinding of the randomisation. The different exercise programs all consisted of two supervised sessions of two hours per week for twelve consecutive weeks. The HC did not enrol in an exercise program. Meanwhile, all subjects were instructed to maintain their normal diet and physical activity habits during the study period.

Table 1. *Variables of each training group*

	Cardiovascular training	Maximal resistance training	Trunk stabilization training	Stretching
HIT mobilization	X			X
HIT strength	X	X[a]		
HIT stabilization	X		X[b]	
HIT combined	X	X	X	

The HIT mobilization group executes the protocol twice a session from the third week[a]
The HIT stabilization group executes the protocol twice a session from the third week[b]

3.3 Intervention

The first two weeks of training were familiarization sessions in which the participants got used to the new training stimuli related to the assigned HIT group. During these sessions, the supervisor gave extrinsic feedback on movement quality within the different training programs. Participants received information about the movement characteristics that led to the desired performance outcome to restrain compensations and enhance execution performance.

The rating of perceived exertion, measured by the Borg Rating of Perceived Exertion Scale (RPE scale) was the quantitative measure used to monitor the level of exertion during

physical activity. After each training session participants rated the intensity of the training on a numerical scale that ranged from 6 to 20.

The participants of the HIT mobilization group *(n*=3) underwent a physical reconditioning program consisting of high-intensity interval cardiovascular training by using a cycle ergometer and static self-stretching exercises. Throughout the training the supervisor focused on the maintenance of a good posture. The participants of the HIT strength group (*n*=4) underwent a physical reconditioning program consisting of high-intensity interval cardiovascular training by using a cycle ergometer and maximal resistance training at high intensity with the use of Technogym exercise machines. Throughout the training the supervisor focused on the maintenance of a good posture. The intensity was raised progressively when participants could execute two sets of twelve repetitions on two consecutive training sessions. When the weight was too high to perform eight repetitions with proper performance, the resistance was reduced. The six exercises of the maximal resistance training were executed twice a session from the third week. The participants of the HIT stabilization group (*n*=4) underwent a stabilization program of the trunk at high intensity consisting of high-intensity interval cardiovascular training by using a cycle ergometer and trunk stabilization training at maximal intensity which focused on core stability. The intensity was raised progressively when the participants could properly execute an exercise by providing a more difficult exercise with a higher percentage of muscle activation on the targeted muscle or increasing the duration of the exercise. The participants of the HIT combined group (*n*=3) performed a combination of the four HIT programs (except for stretching exercises), with the same training principles, as described above, consisting of high-intensity interval cardiovascular training by using a cycle ergometer, maximal resistance training at high intensity with the use of Technogym exercise machines and trunk stabilization training at maximal intensity which focused on core stability. The weight of the maximal resistance training was raised progressively when participants reached twelve repetitions of the same exercise on two consecutive training sessions. The six exercises of the maximal resistance training were, in contrast to the HIT strength group, executed once a session during the entire program to ensure an equal training volume in the HIT combined and HIT strength group. A detailed overview is given in table 2.

Table 2. *Detailed overview of the characteristics of the different intervention groups*

Variable	Cardiovascular training	Maximal resistance training	Trunk stabilization training	Stretching
Training group	HIT mobilization HIT strength HIT stabilization HIT combined	HIT strength[b, c] HIT combined	HIT stabilization[e] HIT combined	HIT mobilization
Protocol	5 high-intensity cycles: - Week 1: 1'00" - Week 2: 1'00" - Week 3: 1'10" - Week 4: 1'20" - Week 5: 1'30" - Week 6: 1'40" - Week 7: 1'00" - Week 8: 1'10" - Week 9: 1'20" - Week 10: 1'30" - Week 11: 1'40" - Week 12: 1'50" 5 active recovery cycles:	Six exercises[d]: 1. Vertical traction 2. Leg extension 3. Chest press 4. Leg press 5. Arm curl 6. Leg curl Week 1-2: quality control and 1-RM testing Week 3-12: 80% 1-RM (8 – 12 reps)	Week 1-2: muscle setting and quality control 1. Transversus abdominis 2. Multifidus 3. Gluteal 4. Thoracic 5. Posture Week 3-12: stabilization training[f] 1. Bridging 2. Clamming 3. Bird dog 4. Planking	Six stretching exercises[g]: 1. Gluteus maximus 2. Gluteus medius 3. Lumbar spine 4. Thoracic spine 5. Frontal abdominals 6. Side abdominals

	- Week 1-12: 1'00"		5. Sideplanking 6. Rowing	
Frequency and duration	2 sessions per week 12 weeks	2 sessions per week 12 weeks	2 sessions per week 12 weeks	2 sessions per week 12 weeks
Workload	High intensity: 100%W_{max}[a] Active recovery: 50%W_{max}[a]	80% 1-RM		

The first 6 weeks are based on the baseline assessment (T0) of maximal Wattage (W_{max}); from week 7 until week 12 are based on the assessment after 6 weeks (T1) of W_{max}[a]

The protocol was executed twice a session from the third week[b]

Resistance was increased when on 2 consecutive sessions ≥12 correct repetitions could be performed[c]

Alternating between low limb and upper limb resistance training[d]

The protocol was executed twice a session starting from the third week[e]

10x10 sec per exercise[f]

30 sec passive static self-stretching twice per side; spine: 2x10 repetitions[g]

3.4 Measurements

3.4.1 Primary outcome measures

The aim of the study was the investigation of blood lipid profile, BMD, body composition and an inflammatory blood marker in persons with NSCLBP. Previous outcomes were divided into three primary questions. i) Did differences exist, at baseline, between participants with NSCLBP and the HC? ii) Which differences were observed within the different exercise programs at pre- and post-exercise assessments in participants with NSCLBP? iii) Which differences were observed between the different exercise programs at pre- and post-exercise assessments in participants with NSCLBP?

Body composition and bone mineral density

Anthropometric data (body composition and BMD) were collected from each subject by using dual-energy X-ray absorptiometry (DEXA) scanning (Delphi W S/N 70331, version 13.0:7, Hologic) with the patient lying supine. Bone and soft tissue analysis were performed by an experienced researcher. Research parameters exploring body composition included body mass index (BMI), subtotal fat mass, subtotal lean mass, subtotal fat percentage (%BF) and android/gynoid ratio. BMD measures were taken from the thoracic (BMD T-spine) and lumbar spine (BMD L-spine). Besides previous parameters, subtotal BMD and z-score were assessed as well.

Inflammatory blood marker and blood lipids

Venous blood samples were taken by an experienced physician at the right arm and were obtained by drawing the blood directly into tubes. Before the blood samples were centrifuged for 10 minutes at 1500g/3000rpm, the samples clotted at room temperature for 30 minutes. Subsequently, serum was transferred into six cryovials (500µl) and stored at -80°C for later analysis which included a measurement of blood lipids and the inflammatory blood marker hs-CRP. High density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), total cholesterol (TC), and TC/HDL were obtained as blood lipids.

3.4.2 Secondary outcome measurements

On the first visit, following baseline sociodemographic characteristics were obtained: age, gender, body mass index (BMI), lifestyle (diet and smoking habits), the onset of low back pain and any specific rehabilitation history for LBP.

3.5 Statistics

Analysis was carried out with JMP Pro version 12.2.0. All the data is presented as mean ± standard deviation.

The baseline characteristics of persons with NSCLBP and the HC were assessed with Fisher Exact for categorical variables, while ordinal data was analysed using the Wilcoxon Method. The baseline characteristics of the four intervention groups of the persons with NSCLBP were analysed with Kruskal-Wallis. When a significant difference was found, multiple comparison was used. To counteract the disadvantage of multiple comparisons, a Bonferroni Correction was applied.

Wilcoxon Method was utilised to investigate the differences in BMD, body composition, the inflammatory blood marker and blood lipids between persons with NSCLBP and HC, at baseline and following treatment. To assess the pre- and post-treatment differences within the four intervention groups, the Wilcoxon Signed-Rank Test was used. The pre- and post-treatment differences between the four different groups were determined by using the Kruskal-Wallis Test of the delta values.

4 Results

Subjects

Thirty-two participants enrolled the study, of which 16 persons with NSCLBP and 16 HC. Two subjects of the NSCLBP group were excluded even before training started, both due to illness. The remaining fourteen participants with NSCLBP were randomly allocated to one of the four intervention groups. There were no dropouts during the twelve-week training period. Data acquisition was obtained from all participants for all outcome measures, but one. Blood sample analysis was missing from one participant in the HIT combined group. Consequently, the data analysis of the blood lipid profile and inflammatory blood marker was inaccessible. All sixteen HC were part one control group. During baseline testing, baseline characteristics were incomplete from one of the participants, all data was excluded for analysis. Furthermore, blood analysis was missing from two other participants, nevertheless the residual data of the subjects were analysed. The flowchart can be found in figure 2.

The characteristics of both populations are shown in table 3. No significant differences were observed between persons with NSCLBP and HC in age, gender, BMI, PASIPD, diet and smoking habits. However, significantly more persons with NSCLBP had participated in a rehabilitation program for low back pain (p = 0,0007).

Table 3. *Baseline characteristics of the different intervention groups*

	NSCLBP (n = 14)	HC (n = 15)	p-Value
Age (yrs)	47 ± 7.21	40.67 ± 10.17	0.06
Gender			0.45
Female	8 (57.14)	11 (73.33)	
Male	6 (42.86)	4 (26.67)	
BMI (kg/m2)	24.86 ± 3.89	25,10 ± 1.85	0.21
PASIPD	16.02 ± 8.44	22,95 ± 8.14	0.05
Diet (no/yes)			
No	12 (85.71)	15 (100)	0.22
Yes	2 (14.29)	0 (0)	
Smoking (no/yes)			1.00
No	12 (85.71)	13 (86.67)	
Yes	2 (14.29)	2 (13.33)	
Rehabilitation (no/yes)			
No	6 (42.86)	15 (100)	0.0007
Yes	8 (57.14)	0 (0)	

Baseline characteristics of the two groups. Values are Mean ± SD or N (%). Boldface values indicates significance differences (P<0.05).

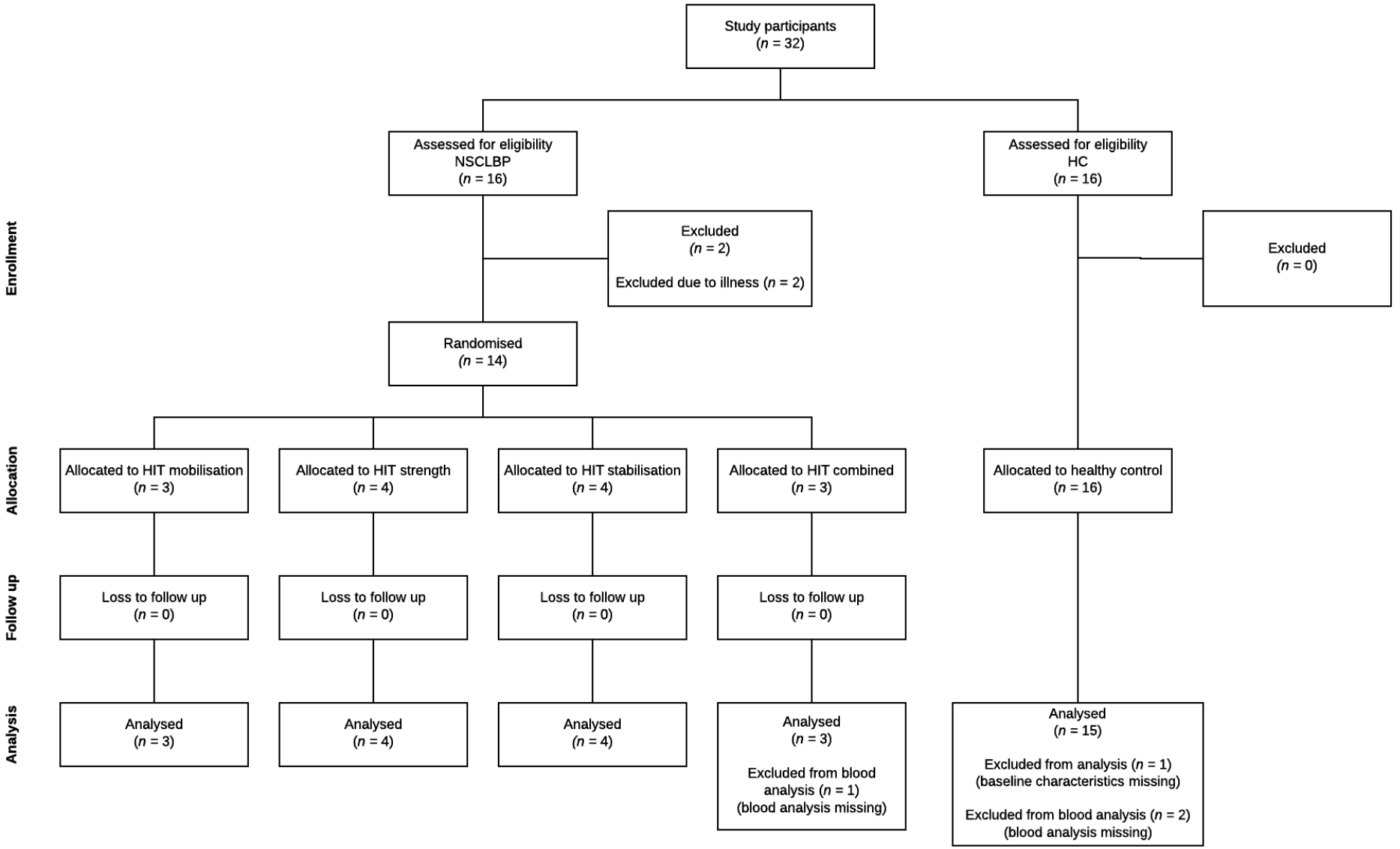

Figure 2. *Consort flow diagram concerning enrolment, allocation, follow-up and analysis of subjects*

Baseline differences between the four training groups are shown in table 4. The four intervention groups, existing of persons with NSCLBP, were well matched for gender, BMI, years of onset, PASIPD, diet and smoking habits, as well as previous rehabilitation experiences. Although age was significantly different between the four intervention groups (*p*=0,04), more specific between HIT strength and HIT stabilization group (*p*=0.03), this significant difference was no longer evident after a Bonferroni's adjustment (*p*>0,0083).

Table 4. *Baseline characteristics of the different intervention groups*

	HIT mobilization	HIT strength	HIT stabilization	HIT combined	p-Value
Age (yrs)	50.67 ± 3,21	44.75 ± 2.63[a]	52.75 ± 3.30[a]	38.67 ± 10.01	0.04
Gender					0.89
Female	1 (33)	2 (50)	3 (75)	2 (33)	
Male	2 (67)	2 (50)	1 (25)	1 (67)	
BMI (kg/m2)	24.37 ± 1.49	25.75 ± 4.85	22.71 ± 1.27	27.04 ± 6.33	0.56
Onset (years)	15.67 ± 17.00	20.33 ± 2.52	3.25 ± 2.63	5.00 ± 4.36	0.08
PASIPD	14.33 ± 7.75	12.46 ± 6.55	16.50 ± 8.52	21.81 ± 12.23	0.63
Diet					0.19
No	3 (100)	2 (50)	4 (100)	3 (100)	
Yes	0 (0)	2 (50)	0 (0)	0 (0)	
Smoking					0.82
No	3 (100)	3 (75)	4 (100)	2 (67)	
Yes	0 (0)	1 (25)	0 (0)	1 (33)	
Rehabilitation					0.89
No	2 (67)	2 (50)	1 (25)	1 (33)	
Yes	1 (33)	2 (50)	3 (75)	2 (67)	

Baseline characteristics of the two groups. Values are Mean ± SD or N (%). Boldface values indicates significance differences (p<0.05).
The nonparametric comparison for each pair using Wilcoxon Method showed a significant difference between HIT strength and HIT stabilization for age (P=0,03). With a Bonferroni's adjustment (P=0,0083) this significant difference no longer exists.[a]

Differences between persons with NSCLBP and HC

No differences were found between the two populations for the outcomes blood lipid profile, BMD, body composition and the inflammatory blood marker hs-CRP before and after training. (Table 5)

Table 5. *Differences between persons with nonspecific chronic low back pain and healthy controls pre- and post-treatment*

	NSCLBP (*n* = 14)		HC (*n* = 15)[a]	*p*-Value	
	Pre	Post		Pre	Post
Body composition					
Subtotal Fat Mass	18.58 ± 5.92	18.28 ± 5.80	18.32 ± 3.17	0.71	0.60
Subtotal Lean Mass	50.08 ± 9.78	50.42 ± 10.47	51.92 ± 10.33	0.62	0.62
BMI	24.86 ± 3.89	24.95 ± 4.00	25.09 ± 1.87	0.23	0.20
%BF	26.37 ± 6.33	25.88 ± 6.41	25.87 ± 4.73	0.91	0.90
Android/Gynoid	1.23 ± 0.39	1.19 ± 0.40	0.98 ± 0.27	0.13	0.21
Bone density					
Subtotal BMD	1.12 ± 0.12	1.11 ± 0.12	1.12 ± 0.13	0.84	0.88
BMD T-spine	1.03 ± 0.15	1.04 ± 0.14	0.96 ± 0.13	0.28	0.27
BMD L-spine	1.21 ± 0.17	1.20 ± 0.19	1.17 ± 0.21	0.84	0.65
Z-score	1.04 ± 1.13	0.99 ± 1.05	1.29 ± 1.32	0.79	0.76
Lipid profile					
HDL	58.77 ± 16.72	57.08 ± 15.04	60.38 ± 11.97	0.63	0.49
LDL	116.58 ± 25.49	122.08 ± 25.74	123.54 ± 28.67	0.43	0.87
TC	203.46 ± 23.81	202.77 ± 21.08	204.00 ± 31.43	0.87	0.88
TG	155.46 ± 148.54	135.31 ± 99.49	100.39 ± 37.45	0.46	0.25
TC/HDL	3.76 ± 1.30	3.82 ± 1.16	3.47 ± 0.82	1.00	0.66
Inflammatory blood marker					
Hs-CRP	1.06 ± 0.52	1.21 ± 0.83	1.61 ± 1.22	0.24	0.30

Values are Mean ± SD. Boldface values indicate significant differences (p<0.05).
Blood samples to measure inflammatory blood marker and lipid profile were obtained from 13 healthy controls.[a]

Pre- and post-differences within groups

There were no significant changes within the four intervention groups, as well as in the pooling of the four intervention groups. The differences in body composition following a twelve-week HIT intervention are represented in table 6. Table 7 provides the data concerning BMD following treatment. The changes in blood lipid profile are shown in table 8. The change in the inflammatory blood marker hs-CRP is shown in table 9.

Pre- and post-differences between groups

There were no significant differences between the four intervention groups concerning blood lipid profile, BMD, body composition and the inflammatory blood marker hs-CRP. However, in the BMD of the lumbar spine, a significant change was found (p=0,0326). More specific, this difference existed between the HIT strength and HIT stabilization group (p=0,0304). HIT stabilization resulted in a significant larger decrement in BMD of the lumbar spine than HIT strength. With a Bonferroni correction that difference no longer was evident. A more detailed overview can be found in tables 10, 11, 12 and 13.

Table 6. *Differences in body composition within intervention groups pre- and post-treatment*

Group (*n*)	HIT mobilization (3)	HIT strength (4)	HIT stabilization (4)	HIT combined (3)	All HIT (14)
Subtotal Fat Mass					
Pre	17.76 ± 1.54	17.80 ± 5.25	16.44 ± 0.92	23.31 ± 11.73	18.58 ± 5.92
Post	17.70 ± 1.64	17.68 ± 5.84	16.73 ± 1.77	21.72 ± 11.67	18.28 ± 5.80
Pre-post (p-value)	0.75	0.88	0.88	0.25	0.39
Subtotal Lean Mass					
Pre	50.24 ± 7.30	56.46 ± 13.51	46.30 ± 9.93	46.43 ± 4.08	50.08 ± 9.78
Post	50.85 ± 8.12	57.90 ± 14.34	45.59 ± 9.39	46.43 ± 4.84	50.42 ± 10.47
Pre-post (p-value)	1.00	0.25	0.63	1.00	0.43
BMI					
Pre	24.37 ± 1.49	25.75 ± 4.85	22.71 ± 1.27	27.04 ± 6.33	24.86 ± 3.89
Post	24.46 ± 1,47	26.18 ± 5.30	22.93 ± 1.15	26.50 ± 6.55	24.95 ± 4.01
Pre-post (p-value)	1.00	0.38	0.38	0.25	0.50
%BF					
Pre	25.57 ± 4.63	23.43 ± 6.75	26.23 ± 4.50	31.30 ± 9.26	26.37 ± 6.33
Post	25.30 ± 4.94	22.83 ± 7.05	26.50 ± 5.30	29.70 ± 9.17	25.88 ± 6.41
Pre-post (p-value)	0.50	0.38	0.88	0.25	0.12
Android/Gynoid					
Pre	1.36 ± 0.50	1.37 ± 0.38	1.14 ± 0.47	± 0.19	1.23 ± 0.39
Post	1.31 ± 0.42	1.32 ± 0.43	1.12 ± 0.50	0.98 ± 0.27	1.19 ± 0.40
Pre-post (p-value)	0.75	0.63	0.63	1.00	0.29

Values are Mean ± SD. Boldface values indicate significant differences (p<0.05).

Table 7. *Differences in bone mineral density within intervention groups pre- and post-treatment*

Group (*n*)	HIT mobilization (3)	HIT strength (4)	HIT stabilization (4)	HIT combined (3)	All HIT (14)
Subtotal BMD					
Pre	1.15 ± 0.10	1.19 ± 0.16	1.05 ± 0.10	1.06 ± 0.09	1.12 ± 0.12
Post	1.12 ± 0.10	1.20 ± 0.16	1.07 ± 0.11	1.06 ± 0.08	1.11 ± 0.12
Pre-post (p-value)	0.25	1.00	0.25	1.00	0.25
BMD T-spine					
Pre	0.99 ± 0.11	1.17 ± 0.08	1.05 ± 0.13	0.84 ± 0.04	1.03 ± 0.15
Post	1.04 ± 0.13	1.12 ± 0.18	1.05 ± 0.11	0.93 ± 0.14	1.04 ± 0.14
Pre-post (p-value)	0.25	0.38	0.88	0.75	0.25
BMD L-spine					
Pre	1.18 ± 0.22	1.29 ± 0.12	1.24 ± 0.24	1.09 ± 0.05	1.21 ± 0.17
Post	1.29 ± 0.27	1.28 ± 0.12	1.12 ± 0.22	1.11 ± 0.16	1.20 ± 0.19
Pre-post (p-value)	0.25	0.88	0.13	0.75	0.25
z-score					
Pre	1.10 ± 1.05	1.63 ± 1.33	0.95 ± 0.74	0.33 ± 1.50	1.04 ± 1.13
Post	0.80 ± 1.00	1.57 ± 1.25	1.00 ± 0.75	0.40 ± 1.32	0.99 ± 1.05
Pre-post (p-value)	0.25	0.75	1.00	0.75	0.25

Values are Mean ± SD. Boldface values indicate significant differences (p<0.05).

Table 8. *Differences in blood lipid profile within intervention groups pre- and post-treatment*

Group (*n*)	HIT mobilization (3)	HIT strength (4)	HIT stabilization (4)	HIT combined (2)[b]	All HIT (14)
HDL					
Pre	61.00 ± 29,51	54.50 ± 13.00	65.75 ± 14.59	50.00 ± 5.66	58.77 ± 16.72
Post	55.00 ± 21.70	52.50 ± 12.71	65.00 ± 16.63	53.50 ± 9.19	57.08 ± 15.04
Pre-post (p-value)	0.25	0.50	1.00	0.50	0.46
LDL					
Pre	105.50 ± 28.99[a]	113.00 ± 16.99	121.50 ± 30.87	125.00 ± 45.25	116.58 ± 25.49
Post	102.00 ± 24.04[a]	121.00 ± 23.93	121.50 ± 22.05	145.50 ± 40.31	122.08 ± 25.74
Pre-post (p-value)	1.00	0.50	0.75	0.50	0.22
TC					
Pre	205.67 ± 27.43	195.50 ± 18.23	210.00 ± 21.68	203.00 ± 49.50	203.46 ± 23.81
Post	192.67 ± 12.58	195.00 ± 24.29	209.00 ± 15.56	221.00 ± 33.94	202.77 ± 21.08
Pre-post (p-value)	0.50	1.00	1.00	0.96	0.96
TG					
Pre	244.67 ± 305.13	139.25 ± 118.61	113.00 ± 21.43	139.00 ± 48.08	155.46 ± 148.54
Post	220.33 ± 195.00	108.00 ± 62.90	112.50 ± 28.35	108.00 ± 14.14	135.31 ± 99.49
Pre-post (p-value)	1.00	0.63	1.00	0.50	0.39
TC/HDL					
Pre	3.87 ± 1.80	3.85 ± 1.34	3.40 ± 1.34	4.15 ± 1.48	3.76 ± 1.30
Post	3.87 ± 1.40	3.95 ± 1.41	3.43 ± 1.09	4.25 ± 1.34	3.82 ± 1.16
Pre-post (p-value)	1.00	0.75	1.00	1.00	0.47

Values are Mean ± SD. Boldface values indicate significant differences (p<0.05).
In one subject the LDL could not be measured, because TG was > 400 mg/dl.[a]
No blood sample was taken from one subject of the HIT combined group.[b]

Table 9. *Differences in the inflammatory blood marker within intervention groups pre- and post-treatment*

Group (*n*)	HIT mobilization (3)	HIT strength (4)	HIT stabilization (4)	HIT combined (2)[a]	All HIT (14)
Hs-CRP					
Pre	0.54 ± 0.00	0.87 ± 0.35	1.33 ± 0.65	1.43 ± 0.23	1.06 ± 0.52
Post	0.34 ± 0.19	1.22 ± 0.59	1.81 ± 0.95	0.90 ± 0.78	1.21 ± 0.83
Pre-post (p-value)	0.50	0.25	0.25	0.50	0.38

Values are Mean $\pm$ SD. Boldface values indicate significant differences ($p<0.05$).
No blood sample was taken from one subject of the HIT combined group.[a]

Table 10. *Differences in body composition between intervention groups pre- and post-treatment*

Groups (*n*)	Subtotal Fat Mass	Subtotal Lean Mass	BMI	%BF	Android/Gynoid
Between group comparison (4)	0,1912	0,4787	0,3104	0,2574	0,9895

Values are p-values. Boldface values indicate significant differences (p<0.05).

Table 11. *Differences in bone mineral density between intervention groups pre- and post-treatment*

Groups (*n*)	Subtotal BMD	BMD T-spine	BMD L-spine	Z-score
Between group comparison (4)	0,1623	0,4927	0,0326[a]	0,3136

Values are p-values. Boldface values indicate significant differences (p<0,05). The nonparametric comparison for each pair using Kruskal-Wallis Test showed a significant difference between HIT strength and HIT stabilization for BMD L-spine (p=0,0304). With a Bonferroni's adjustment (p=0,0083) this significant difference no longer exists.[a]

Table 12. *Differences in blood lipid profile between intervention groups pre- and post-treatment*

Group (*n*)	HDL	LDL	TC	TG	TC/HDL
Between group comparison (4)	0,1751	0,2291	0,1895	0,6485	0,9851

Values are p-values. Boldface values indicate significant differences (p<0.05).

Table 13. *Differences in the inflammatory blood marker between intervention groups pre- and post-treatment*

Group (*n*)	Hs-CRP
Between group comparison (4)	0,2301

Values are p-values. Boldface values indicate significant differences (p<0.05).

5 Discussion

This preliminary RCT examined differences in blood lipid profile, BMD, body composition, and an inflammatory blood marker between healthy persons and persons with NSCLBP along with the effects of the relative new training principle HIT on the previous mentioned outcome measures in people with NSCLBP. Four different kinds of HIT-protocols were explored in this study population. To our knowledge no other study has explored these effects of HIT in persons with NSCLBP.

This study showed no differences between healthy persons and persons with NSCLBP in blood lipid profile, BMD, body composition and the inflammatory blood marker hs-CRP. Within the different intervention groups, no significant changes were obtained after twelve weeks of HIT in one of the four previous mentioned domains. Also, when comparing the results between the four HIT groups, none of the interventions seemed to be superior to another, in exception of the effect on lumbar BMD. A significant difference was found without a Bonferroni correction between the HIT strength group and HIT stabilization group, in which the HIT stabilization group showed a significant larger decrement in BMD of the lumbar spine.

Strengths and limitations

A strength of the doctoral study is the randomized and evenly distribution of the experimental group into four different HIT-protocols. In each training group, the subjects perform an interval training session on a cycle ergometer at an individualised workload of 100% W_{max} during high intensity, and 50% W_{max} during active recovery. Additional training is specific to each HIT group. Because of the lack of a standardized HIT-protocol, different metabolic effects might be elicited among different HIT variants. Also, the training volume of each experimental group is equal. In this way, a comparison between different HIT-protocols can be made. Due to the preliminary design of this study, the sample size was restricted which led to a distribution of the experimental group into four small HIT groups of three to four participants. Because of the limited persons in each intervention group, not only pre- and post-exercise effects in the assigned group of the subjects with NSCLBP were assessed, results of the four intervention groups were pooled as well. Because of the small sample size a nonparametric statistical analysis was applied and a Bonferroni correction was used to avoid Type I errors with the use of multiple comparison tests. During these twelve weeks, no

dropouts were observed, suggesting adherence was high. Furthermore, no adverse events were reported, implying HIT is a safe training method.

In the current study, several limitations can be enumerated. Based on the recommendations of the American College of Sports Medicine and American Heart Association, in which they state a minimum exercise dosage of vigorous aerobic physical activity of 20 minutes, three days a week, the frequency of two days a week used in these HIT-protocols might be insufficient to trigger training adaptations. Because of the chosen study design, it was more likely that people with an active lifestyle participated in the current study. Therefore, it is possible that the subjects in the NSCLBP group were more motivated and in better health than average persons with NSCLBP who live a more passive lifestyle and are physically deconditioned. It is possible that greater effects were found if less active subjects participated in the study. The majority of the NSCLBP subjects received previous rehabilitation for their low back pain. Although this study excluded subjects who had undergone previous rehabilitation or exercise therapy targeting the low back in the past six months, the experience with similar exercises could not be prevented. This advantage could underestimate the results that were found. Another study limitation was the absence of a control group consisting of persons with NSCLBP who participated in a moderate-intensity continuous exercise program to make the comparison with a HIT-protocol. After enrollment into the study, blinding was inconceivable for the participants and researchers. Also, test results could have been perturbed because multiple researchers conducted the testing. Interrater reliability was not assessed. This intervention only provided a physical intervention as well. A more patient-specific intervention with the addition of cognitive behavioral therapy for people with pronounced yellow flags could enhance treatment effects.

Bone mineral density

BMD did not differ between the NSCLBP group and HC group at baseline. Previous RCTs did not yet measure BMD as an effect parameter after HIT. Moreira et al. (2014) stated that a six-month exercise intervention is needed to detect a clinical significant effect on BMD (Moreira et al., 2014). This preliminary RCT observed the effects after twelve weeks of HIT, which could be the clarification of the nonsignificant findings. Furthermore, Borer et al. (2005) numerated seven principles which have an increasing effect on BMD: (1) dynamic

mechanical stimulation, (2) supra-threshold intensity, (3) strain frequency and strain intensity, (4) brief but intermittent exercise, (5) unusual pattern of bone loading, (6) availability of nutrient energy and (7) calcium and cholecalciferol availability (Borer, 2005). Moreira et al. (2014) agreed by stating that gravitational loading is essential for stimulating bone growth. They have also found that people who participated in non-impact sports, like cycling and swimming, often had a low BMD (Moreira et al., 2014). So, an underestimation is expected with the use of a cycle ergometer HIT-protocol. A high-impact HIT-protocol could possibly lead to more beneficial effects.

Although BMD did not show any significant changes between persons with NSCLBP and HC, possible explanations for a higher BMD in persons with NSCLBP have been described. Morphologic changes, as bony sclerosis and osteophytes, could be the reason for an increased BMD measured by DEXA scanning in people with chronic LBP. The prevalence of these morphological changes increases with age. LBP has also been shown to limit daily activities, which negatively affect BMD (Snider, Johnson, Degenhardt, & Snider, 2011). Al-Saeed et al. (2013) found that obese persons had a higher BMD compared to persons with normal weight, suggesting a positive effect of being obese on BMD (Al-Saeed et al., 2013). Despite conflicting results, Moreira et al. (2014) stated that a six-month exercise intervention is needed to detect a clinical significant effect on BMD (Moreira et al., 2014). This randomized preliminary clinical trial took twelve weeks, which could be the clarification of the nonsignificant findings.

Endocrine influences, measured with blood analysis, might lead to a better perspective of the effects of HIT on bone growth even before six months of exercise. Growth hormone (GH), insulin-like growth factor (IGF-1), insulin-like growth factor-binding protein 3 (IGFBP-3), leptin, estrogen, parathyroid hormone (PTH), cholecalciferol (vitamin D_3), calcium, acidic fibroblast growth factor (aFGF), transforming growth-factor beta (TGFβ), bonemorphogenetic proteins, thyroid hormone (T3), glucocorticoids, estradiol and cortisol might all have an impact on blood profile before significant changes in BMD can be measured (Borer, 2005).

Body composition

Multiple RCTs have investigated the effects of HIT on body composition, mostly in a population with cardiovascular risks. Although results were inconclusive, the effects were

either positive or nonsignificant in favour of the HIT group (Astorino, Schubert, Palumbo, Stirling, & McMillan, 2013; Fisher et al., 2015; Hallsworth et al., 2015; Schjerve et al., 2008; Stensvold, Slordahl, & Wisloff, 2012; Trapp, Chisholm, Freund, & Boutcher, 2008; Tsekouras et al., 2008). A recent systematic review and meta-analysis showed no significant effects of HIT on body mass, BMI and %BF after less than twelve weeks of HIT in persons with a normal weight and in overweight/obese. The effect on body composition after twelve weeks of HIT or more, has not been investigated sufficiently enough to draw a conclusion on the effect in normal weight populations. Either way, this study revealed no significant changes after twelve weeks of HIT on body mass, BMI and %BF in persons with NSCLBP, and other body composition measurements (Batacan, Duncan, Dalbo, Tucker, & Fenning, 2017).

Multiple factors can influence this outcome parameter. Sedentary people showed a positive correlation between the initial amount of fat mass and fat loss (Trapp et al., 2008). Despite dietary intake, which was not assessed in the present study, a previous study by Astorino et al. (2013) used an isocaloric diet, in which the percentage of carbs, lipids and proteins were considered, but did not find a significant weight reduction. This finding was probably due to underreporting of the food intake of the study participants (Astorino et al., 2013). Deighton et al. (2013) demonstrated a suppressed appetite right after sprint exercise, but an elevated appetite after sprint exercise trials in comparison to endurance exercise, which could clarify the increase in food intake (Deighton, Barry, Connon, & Stensel, 2013). The previous could be one of the reasons why persons in the intervention group did not lose weight. This is in contrast with a possible mechanism explained by Batacan et al. (2017), in which is stated that the generation of catecholamines might lead to an elevated fat oxygenation, decreased appetite right after exercise, as well as an increased oxygen consumption resulting in an elevated fat loss (Batacan et al., 2017).

The findings in the present study can also be explained by a recent review by Wewege et al. (2017). They stated that physical activity was only mildly effective in reducing body weight when not adding a dietary intervention in overweight/obese people (Wewege, van den Berg, Ward, & Keech, 2017). Shiraev et al. (2012) suggests the addition of a weight management program to a HIT-protocol to lose weight. While caloric restriction is more effective in stimulating weight loss, physical activity is more effective for diminishing visceral fat deposits. A reduction in abdominal and visceral fat is possible with or without total weight

loss in comparison to continuous moderate exercise (Shiraev & Barclay, 2012). A possible explanation given by Batacan et al. (2017), could be the gain in muscle mass after HIT, which compensates for the decrease in fat mass. HIT is known to activate a higher amount of type II muscle fibres leading to muscle hypertrophy (Batacan et al., 2017). Visceral fat is known to have an impact on cardiovascular health. In the present study only DEXA scanning was used without a direct measurement of visceral fat content through the 'gold-standard' CT or MRI scanning, which could mask the effect on visceral fat adiposity. Additionally, Shiraev et al. (2012) found that solely HIT running significantly reduced body fat and body mass which could clarify the findings in the current study (Shiraev & Barclay, 2012). A possible underlying factor for this physiological change could be the increased muscle mass activation during running, which is accompanied by an elevated energy expenditure compared to cycling. Nonetheless, it remains unknown if such HIT running protocol is suitable for persons with LBP.

Inflammatory blood marker

Adipose tissue might lead to the development of systemic low-grade inflammation, because of its production of inflammatory proteins. Hs-CRP did not show a significant effect after twelve weeks of HIT in both obese men as well as men and women with metabolic syndrome (Schjerve et al., 2008; Stensvold et al., 2012). In people with acute specific low back pain, hs-CRP was found to be increased, which was correlated with pain intensity (Rannou et al., 2007). On the contrary, this association could not be observed in persons with chronic specific low back pain (Park & Lee, 2010; Rannou et al., 2007). The development of atherosclerosis can be a result of the combination of an increase in blood lipids and inflammation. Atherosclerosis diminishes the blood perfusion to the lumbar vertebras, which leads to ischemia and pain (Kauppila, 2009).

The amount of muscle mass recruited during exercise is an important factor for the magnitude of the anti-inflammatory effect. For this reason, whole-body exercise, like rowing or running, could be a more appropriate way to stimulate both lower and upper body simultaneously (Nimmo et al., 2013).

This study focused solely on the inflammatory blood marker hs-CRP, even though other inflammatory blood markers have been described as a measure of inflammation. For example, other RCTs using a HIT-protocol also investigated chemokine ligand 2 (CCL2), tumor

necrosis factor-alpha (TNF-α), interleukins and leukocyts (Dorneles et al., 2016; Schjerve et al., 2008; Stensvold et al., 2012). Stensvold et al. (2012) and Schjerve et al. (2008) did not find any significant changes in (hs-)CRP after twelve weeks of HIT in obese men and inactive men and women with metabolic syndrome respectively (Schjerve et al., 2008; Stensvold et al., 2012).

Blood lipid profile

The findings of this study are in line with findings of Batacan et al. (2017), in which no significant effects on TC, HDL and TG were found in persons with normal weight after twelve weeks of HIT or more. The same results were obtained for overweight/obese persons. Although the exact cause remains unravelled, a hypothesis could be that HIT inhibits the release of fatty acids when the level of catecholamines rises (Batacan et al., 2017). Nevertheless, the study of Shiraev et al. (2012) showed a superiority of HIT in comparison to continuous moderate exercise, when examining triglyceride, HDL and LDL-HDL ratio (Shiraev & Barclay, 2012).

6 Conclusion

The absence of a clear definition and standardization of HIT demands clarification so comparisons of study results can be made. In the current preliminary RCT, no differences were found between persons with NSCLBP and HC for blood lipid profile, BMD, body composition and the inflammatory blood marker hs-CRP. There were no significant changes within and between the four intervention groups, as well as in the pooling of the four HIT groups. To trigger training adaptations, we suggest a more patient-specific approach with a minimum frequency of three days a week. Studies should investigate multiple inflammatory blood and bone markers to get a broader perspective on the effects of HIT. A comparison with a high-impact sport might lead to new insights and a dietary intervention should be incorporated to establish its influence. HIT remains a relative new, interesting domain in the rehabilitation of NSCLBP which should be explored more in depth in future investigations.

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