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1 **Exercise for the intervertebral disc. A 6-month randomised controlled trial**
2 **in chronic low back pain**

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21 Tampere.

1 **ABSTRACT**

2

3 **Background Context:** Muscle, bone and tendon respond anabolically to mechanical forces.
4 Whether the intervertebral disc (IVD) can benefit from exercise is unclear.

5 **Purpose:** Examine whether exercise can beneficially affect IVD characteristics.

6 **Study Design/Setting:** Single-blinded 6-month randomised controlled trial
7 (ACTRN12615001270505) in an exercise and physiotherapy clinic.

8 **Patient Sample:** Forty patients with chronic non-specific low back pain (NSCLBP).

9 **Outcome Measures:** The primary outcome was lumbar IVD T2-time (MRI). Secondary
10 outcomes included IVD diffusion coefficient and IVD expansion with short-duration lying.

11 **Methods:** Twenty patients progressively loaded their lumbar IVDs (Exercise) via an exercise
12 program involving progressive upright aerobic and resistance exercises targeting the trunk and
13 major muscle groups and were compared to twenty patients who performed motor control
14 training and manual therapy (Control). Testing occurred at baseline, 3-months and 6-months.

15 **Results:** Seventeen Exercise and fifteen Control patients completed the interventions. There
16 was no group-by-time differences in T2-time of the entire IVD (Exercise 94.1 ± 10.0 ms vs.
17 Control 96.5 ± 9.3 ms, $p=0.549$). Exercise patients had shorter T2-time in the posterior annulus
18 at 6-months (82.7 ± 6.8 ms vs. 85.1 ± 8.0 ms, $p=0.028$). Exercise patients showed higher L5/S1
19 apparent diffusion coefficients and decreased IVD height at 3-months (both $p \leq 0.050$). After
20 adjustments for multiple comparisons, differences lost statistical significance. Per-protocol and
21 intent-to-treat analyses yielded similar findings.

22 **Conclusions:** This trial found that 6-months of exercise did not benefit the IVD of people with
23 NSCLBP. Based on this index study, future studies could investigate the effect of exercise on
24 IVD in different populations, with different type, duration and/or intensity of exercise, and
25 using different IVD markers.

1 INTRODUCTION

2

3 Most connective tissues are mechanosensitive.[1] Wolff [2] first described a ‘law’ of bone
4 adaptation to loading in 1892. Since then, successive studies have detailed muscle, bone and
5 tendon responses to exercise. Progressive resistance exercises maximize muscle
6 hypertrophy,[3] impact-loading exercises optimize bone mineral density and geometry[4, 5]
7 and burgeoning data favour loading magnitude over type of muscle contraction to increase
8 tendon cross-sectional area.[6] Whether intervertebral discs (IVD) respond to exercise training
9 is less well established.[7]

10

11 Loading of IVD tissue/cells in vitro resulted in an anabolic responses.[8, 9] Cyclical loads of
12 0.2-0.8 megapascal, at 0.1-1.0Hz for up to eight hours/day lead to an anabolic response.[8]
13 Animal studies reported beneficial modulation of the IVD with exercise; 3 months of exercises
14 in adult dogs improved IVD uptake of glucose, oxygen and glycogen.[10] Eight weeks of
15 treadmill- exercise in rats increased IVD matrix production[11] and cell numbers in the IVD
16 stem cell niche and the outer annulus.[12] A different study showed that 11 weeks of treadmill
17 exercises in rats increased IVD glycosaminoglycan concentration.[13] Moreover, treadmill
18 exercises of injured and sham IVDs in rats stimulated cell proliferation in both groups.[14]
19 These animal data support a positive impact of exercise on the IVD of quadrupeds.

20

21 Cross-sectional studies have been performed in humans. Highly physically active people had
22 longer lumbar IVD T2-time, on magnetic resonance imaging (MRI), a measure that correlates
23 with glycosaminoglycan and water content.[15] Similarly, long-distance runners and joggers
24 had longer lumbar IVD T2-time compared to sedentary people [16]. Long-distance runners
25 also had greater IVD to vertebral body height ratio compared to non-athletic referents, which

1 suggested IVD hypertrophy.[16] Finally, longer lumbar IVD T2-times were associated with
2 loading patterns in the range of fast walking to slow running.[16] Whilst these findings support
3 a beneficial effect of physical activity and exercise on IVD, prospective intervention studies
4 are required to establish causality.

5
6 Our aim was to conduct the first-ever randomised controlled trial (RCT) on the effect of
7 exercise training on IVD in humans. We assessed this in people with non-specific chronic low
8 back pain (NSCLBP) as firstly, demonstrating the capacity to improve IVD characteristics in
9 a clinical population group, with pain that may in part stem from IVD degeneration, would
10 have wider implications, when compared to otherwise healthy population groups, at both the
11 individual (e.g. reduced disability and increased health-related quality of life) and societal level
12 (e.g. reduced healthcare costs).[17] Secondly, the exercise training principle of initial values
13 suggests that physiological adaptations are greater in patients with lower baseline values,[18]
14 which supports that degenerated IVDs may have greater capacity, if plausible, to improve
15 through appropriately prescribed exercise training. Thirdly, patients with NSCLBP are often
16 sedentary but have the potential to increase physical activity levels.[19] We included people
17 aged 25-45 years, an age range where IVD adaptations may be more likely than older
18 individuals.[2] Notably, the notion that IVDs can undergo ‘regeneration’ once established
19 degeneration has occurred remains an ongoing debate within the field.[20] This being the index
20 study, the minimum duration of exercises to obtain measurable effects on IVD in humans is
21 unknown. Tendon adaptations were measured after 3-4 months,[21] while exercise
22 interventions for bone typically measured changes in bone mineral density after 9-12
23 months.[5] We set the duration of the exercise intervention at 6 months. We designed an
24 exercise intervention following existing recommendations for IVD,[7] This intervention
25 integrated progressive spinal loading and spine-specific physical activity into a general strength

1 and conditioning program. The control intervention was expected to minimally load the IVD
2 as it involved low intensity motor control training and manual therapy. Lumbar IVD outcomes
3 included T2-time, apparent diffusion coefficient and rate of IVD expansion in short-duration
4 lying.[22] Our primary hypothesis was that six months of exercise would increase IVD T2-
5 times compared to control intervention in patients with NSCLBP.

1 **METHODS**

2

3 This was a single-blinded 6-month RCT that examined the efficacy of exercise compared to
4 control in 40 adults with NSCLBP. The study was conducted from December 2015 to
5 December 2016 in Melbourne, Australia. The study was registered with the Australian New
6 Zealand Clinical Trials Registry (ACTRN12615001270505, date registered: 20/11/2015) and
7 approved by the institutional ethics review board. All patients provided informed written
8 consent prior to participation. The full study protocol was published[23] and is presented in
9 brief below.

10

11 **Patients**

12

13 Forty men and women aged 25-45 years with NSCLBP (i.e. greater than three months with no
14 definitive underlying pathology) were included. Exclusion criteria included: 1) history of spinal
15 surgery, 2) history of traumatic injury to spine (e.g. fracture and car accident), 3) scoliosis
16 previously requiring medical consultation, 4) symptoms of nerve root compression, 5) current
17 treatment for NSCLBP, 6) engaging in more than 150 minutes per week of moderate-vigorous
18 exercise training, 7) participation in formal organised sport, 8) participation in gym-based
19 exercise training more than once per week, 9) current smoker, and 10) implants unsuitable for
20 MRI. Pain intensity of the low back was measured with a 100-point visual analogue scale.[24]
21 The modified Oswestry disability index was used to measure patient disability due to
22 NSCLBP.[25] All patients underwent offsite randomisation procedures by a researcher who
23 had no contact with volunteers. A randomisation schedule (using block randomisation with
24 random block lengths and stratification for sex obtained from www.random.org) was
25 implemented.

1 **Exercise: General strength and conditioning**

2

3 The exercise intervention consisted of fifty two 1-hour one-on-one gym-based sessions with
4 an exercise physiologist (i.e. tertiary trained clinical exercise allied health professionals).[26]
5 During the first three months, patients attended two sessions per week. During the second 3-
6 month period, participant could self-select to attend either 1-2 sessions per week. Sessions
7 included aerobic and resistance exercises, which were progressed in a time-contingent manner.
8 During the first six weeks, patients were required to complete 5-10 minutes of mental rehearsal
9 of movements they nominated as being fearful for them. Prescribed exercises closely followed
10 prior recommendations[7] for the beneficial modulation of IVD: (a) loading was dynamic,
11 rather than static, which aimed to facilitate the transfer of nutrients between vertebral bodies
12 and IVDs,[8] (b) axial loading was emphasised, with extreme ranges of motion, torsional
13 activities and flexion with compression avoided,[8] (c) the speed at which the concentric and
14 eccentric isotonic exercises were completed remained between 6-60 cycles per minute,[8] (d)
15 exercises were chosen[27] that loaded the IVD in range of 0.2-0.8 megapascal, corresponding
16 to intradiscal pressure of 0.3-1.2 megapascal.[8] In each session, participants performed 20
17 minutes of treadmill aerobic exercise, beginning at an intensity of 65-70% maximal heart rate
18 in the first two weeks and increasing to 65-85% of maximal heart rate. Resistance exercise
19 were structured throughout the week to challenge lifting (e.g. squat, deadlift), pushing (e.g.
20 standing cable chest press, dumbbell chest press), pulling (e.g. Split stance cable row, single
21 leg opposite arm cable row), trunk flexion (e.g. partial curl ups, Bosu-ball crunches) and trunk
22 extension (e.g. Supine bridge, supine swiss-ball bridge). Exercise technique and body posture
23 were monitored by the exercise physiologist and feedback provided where needed. Moreover,
24 patients allocated to exercise were required to complete 20-40 minutes of home-based aerobic

1 training in the form of walking or jogging three times per week throughout the study. Given
2 the nature of the intervention, neither the patients, nor clinicians, were able to be randomised.

3

4 **Control: motor control training and manual therapy**

5 The control intervention consisted of twelve 30-minute one-on-one physiotherapy-led
6 sessions.[23] Ten sessions (1-2 per week) were delivered during the first three months and two
7 sessions were provided in the second three months. Manual therapy was provided at the
8 discretion of the clinician and included posterior-anterior and transverse mobilisations using
9 rotation, as well as soft tissue manipulation within the lumbar and pelvic regions. The aim of
10 manual therapy was to reduce segmental hypomobility and facilitate pain modulation of
11 symptomatic spinal levels. Motor control training targeted transversus abdominis, multifidus
12 and pelvic floor musculature in non-weight bearing activities. Progression was on a pain-
13 contingent basis. Including transversus abdominis and multifidus contraction in specific
14 functional activities was only included in treatment if these specific functional activities were
15 part of the patient's goals. There was no prescription of physical activity. Similar to the exercise
16 intervention, blinding was not feasible for the patient, nor clinician.

17

18 **Magnetic resonance imaging and blinded analysis**

19

20 A 3T Phillips Ingenia scanner (Amsterdam, Netherlands; software release 4.1.3.4) was used
21 with a spinal coil for all scans. The following sequences were performed at baseline, three
22 months and six months:

- 23 • To measure the rate of IVD expansion with lying a first T2-weighted sagittal scan was
24 used (15 slices, thickness: 3mm, interslice distance: 1.5mm, repetition time: 2600ms,
25 echo time: 70ms) encompassing the entire lumbar spine.

- 1 • For quantifying IVD T2-time, a spin-echo multi-echo sequence was used with eight
2 echo times (15.75, 36.75, 57.75, 78.75, 99.75, 120.75, 141.75 and 162.75ms) from 12
3 sagittal anatomical slices each (thickness: 3mm, interslice distance: 1.5mm, repetition
4 time: 2000ms, field-of-view: 281x281mm, image resolution: 0.366mm per pixel)
5 encompassing the entire lower spine from left to right.
- 6 • For quantifying the apparent diffusion co-efficient (ADC) a single shot echo-planar
7 diffusion weighted imaging sequence was used (15 slices, thickness: 3mm, interslice
8 distance: 1.5mm, B factors: 0 and 400, repetition time: 9000ms, echo time: 76ms,
9 number of excitations/averages: 8). The scanner software then calculated the ADC map
10 from these diffusion weighted images.
- 11 • To complete the measure of the rate of IVD expansion with lying a second T2-weighted
12 sagittal scan was performed with the same settings.[22] This scan co-localised with the
13 diffusion weighted imaging scan. The time between the first and second T2-weighted
14 scan was constant across the study (Baseline: 29min, 3 months: 28min, 6 months:
15 28min).

16

17 MRI files allocation and study time-point were blinded to the assessor using a random number
18 prior to image analysis (obtained from www.random.org). The order of the two T2-weighted
19 scans was also blinded applying an additional random number to each of these scans. Pfirrmann
20 grade was assessed on the baseline T2-weighted images by a radiologist.

21

22 ImageJ 1.38x (<http://rsb.info.nih.gov/ij/>) was used to perform all quantitative MR measures. In
23 the sagittal spin-echo multi-echo images every IVD from T11/T12 to L5/S1 was measured.
24 After segmenting the IVD, an ImageJ plugin (“ROI Analyzer”;
25 <https://github.com/tjrantal/RoiAnalyzer> and

1 <https://sites.google.com/site/daniellbelavy/home/roianalyser>) was used to rotate the IVDs to
2 horizontal and to measure their area and height. The IVD volume was calculated by linear
3 interpolation of the area data from all slices. The slice number with the spinous process of each
4 vertebrae was noted. Lordosis angle was calculated as the difference between the angle to the
5 horizontal of the region of interest traced around the L5/S1 IVD and that of a region of interest
6 traced around the L1/2 IVD. With the exception of IVD volume, the morphometric data from
7 three central images at the spinous process for each lumbar IVD were averaged. Signal intensity
8 was obtained of the entire IVD as well as five equidistant subregions of the IVD from anterior
9 to posterior (Figure 1). T2-time was calculated via a linear fit to the natural logarithm of the
10 image intensity in each of the eight MR echo times.

11

12 IVD height on T2-weighted images was assessed in a similar fashion: a region of interest was
13 traced manually around each IVD and the same custom written ImageJ plugin used to calculate
14 average IVD height on the central three slices. The coordinates of the regions of interest were
15 saved for each measurement. The change in IVD height between the first and second T2-
16 weighted scan was calculated as in prior work.[22]

17

18 To automate the analysis of ADC maps, the coordinates regions of interest saved from the co-
19 localised T2-weighted images were used. Custom written software in “R” (version 3.4.2,
20 www.r-project.org) was used to rescale the coordinates of the regions of interest to the pixel
21 resolution and position on the ADC maps. Then a custom written ImageJ macro was used to
22 load each rescaled region of interest coordinates and corresponding ADC map image. The
23 image intensity, and hence ADC, was calculated for each region of interest (whole IVD). ADC
24 values were averaged from the three slices positioned around the spinous process for each IVD.

25

1 **Statistical analyses**

2

3 The “R” statistical environment (version 3.4.2, www.r-project.org) was used for all statistical
4 analyses. An intent-to-treat analysis approach was first implemented. A linear-mixed effects
5 model with allowances for heterogeneity of variance according to study date were performed.
6 Then repeated-measures analysis of variance examined for differences between group over
7 time and *a priori* T-tests were performed comparing each follow-up time-point to baseline. An
8 alpha-level of 0.05 was taken for statistical significance. To minimize the risk of type I errors
9 and aid interpretation of the findings, P-values were also adjusted by the false discovery rate
10 method.[28] The primary analysis considered data averaged from all lumbar IVDs. A per-
11 protocol analysis was then completed.

12

13 Assuming an alpha of 0.05, power of 0.8 and mean(SD) average lumbar IVD T2-time of
14 100.6(12.4)ms and adjusting[29] for a correlation(95% confidence interval) of 0.98(0.95-1.00)
15 (coefficient of variation[95% confidence interval]: 1.8[1.5-2.1]%; unpublished repeatability
16 data from the senior author’s lab collected from twelve men across nine repeated time-points
17 over the course of one year. This is an appropriate number of measures for this sample size to
18 adequately establish reliability),[30] 18 patients in each group (total: n=36) were required to
19 detect a 2.2% (effect size: 0.17) net difference in average lumbar IVD T2-time between-groups
20 at the third time-point (i.e. 6-month).

1 RESULTS

2

3 Forty patients (exercise: n=20, control: n=20) were randomized. Baseline demographic, pain
4 intensity and disability data are shown in Table 1. Mean attendance was 31/52 sessions (60%)
5 for exercise and 9/12 sessions (77%) for control. Eight patients withdrew from the study
6 between baseline and 6-month follow-up (ex: n=3; co: n=5; Figure 2).

7

8 No group by time effect was observed for whole lumbar IVD T2-time (Table 2, Figure 3). A
9 within-group reduction of 2.9% and 3.7% in T2-time of the subregion representing the posterior
10 annulus was observed at six months for the exercise and control group, respectively, albeit only
11 the exercise group reached statistical significance (Table 2). A group by time effect was
12 revealed for L2-L3 IVD posterior nucleus T2-time (net mean percent difference after six
13 months exercise compared to control: -0.7%) and L4-L5 IVD anterior annulus (net mean
14 percent difference after six months exercise compared to control: -11%) (Supplementary Table
15 1). T2-time also differed within-group after three months of exercise for L2-L3 IVD posterior
16 nucleus (-3.9%) and after six months for L1-L2 IVD posterior annulus (-9.2%) and L4-L5 IVD
17 anterior annulus (-7.3%; Supplementary Table 1). Within-group differences were similarly
18 observed after three months of control for L2-L3 IVD anterior annulus (-4.8%; Supplementary
19 Table 1). Importantly, none of these between- or within-group differences in IVD T2-times
20 persisted after controlling for potential false-positives.

21

22 ADC did not differ between groups over time (Table 3). Although, L5-S1 ADC decreased 8.4%
23 in the control group between baseline and 3-month follow-up, yet this effect was no longer
24 significant after adjusting P-values for potential false-positives (Table 3). No within-group
25 differences were observed for the exercise group (Table 3).

1

2 No group by time effects were observed for average lumbar IVD volume or height, although
3 average lumbar IVD height increased 1.3% after three months of control (Table 4). L1-L2 IVD
4 volume differed between groups over time (net mean percent difference after six months
5 exercise compared to control: -7.2%; Supplementary Table 2). L1-L2 IVD volume significantly
6 increased 5.2% within the control group between baseline and 6-month follow-up. L5-S1 IVD
7 height also increased within-group after three months of control (+1.6%). Notably, none of
8 these significant effects persisted after adjusting for potential false-positives.

9

10 Average and individual IVD height expansion after short-duration lying did not differ between
11 groups over time (Table 5). Within the exercise group only, IVD height expansion was 1.1
12 times less at L3-L4 after six months. At three months, IVD height expansion was also 1.1 and
13 0.8 times less for the exercise (L4-L5 only) and control (L1-L2 only) groups, respectively.
14 These effects were no longer significant after adjusting for potential false-positives.

1 **DISCUSSION**

2

3 To our knowledge, this was the first RCT to examine the effects of exercise training on the
4 IVD. Prior in vitro, animal and human cross-sectional studies suggested a beneficial effect of
5 exercise on various IVD markers.[7] We recruited sedentary patients with NSCLBP more
6 likely to increase physical activity levels and show IVD changes. Our intervention followed
7 previously recommended exercises for intradiscal pressure and frequency capable of
8 modulating IVD tissues.[7] Despite these careful methodological considerations, we could not
9 measure significant beneficial modulation of IVD with exercise when compared to control.
10 Specifically, the intervention did not increase IVD T2-time, apparent diffusion coefficient or
11 rate of IVD expansion in short-duration lying, which did not confirm our hypothesis.

12

13 There were significant changes in the IVD, albeit these effects did not persist after adjustment
14 of P-values for potential false positives. For example, we measured shorter IVD T2-times with
15 exercise at 6 months. The prevailing interpretation is for a reduction in IVD water and
16 glycosaminoglycan content[15], a detrimental effect. Other authors have argued that a shorter
17 T2-time might reflect increased binding of water to the collagen matrix[31, 32] which would
18 indicate a beneficial effect. The lower apparent diffusion coefficient in the control group at
19 L5S1 at 3 months may represent reduced IVD free water movement, a detrimental change (ref
20 needed).[33, 34]

21

22 The control group had higher average lumbar IVD height at 3 months and larger L1/2 IVD
23 volume at 6 months. We had controlled for time-of-day effects on the spine[35] by performing
24 all scanning after midday. This standardization allowed to attribute variation in IVD size to

1 intrinsic IVD changes; but again, the effect did not remain significant after adjusting for
2 potential false positives.

3
4 Interestingly, lumbar IVD expansion with short-term lying decreased over the course of the
5 study from 2.2% to -0.1% in the exercise group at L3/4 at 6 months and from 3.1% to 0.5% in
6 the control group at L1/2 at 3 months, despite standardised duration of lying between scans.
7 Healthier lumbar IVDs with lower degeneration grade expand less in acute lying,[22] thus this
8 may present a beneficial finding. Again, the effect did not remain significant after adjusting for
9 potential false positives.

10
11 Whilst we are unaware of previous prospective studies, these findings conflict somewhat with
12 previous cross-sectional studies that showed long-term exposure to running/jogging[16] or
13 vigorous physical activity[36] was associated with better IVD composition markers. Notably,
14 these studies only included people with long-term exposure to physical activity loading the
15 IVD. These cross-sectional studies may therefore suffer survivorship bias (i.e. that people with
16 adverse IVD effects of exercise dropped the activity and were not captured by a cross-sectional
17 design). Alternatively, this may suggest that the six-month intervention in the current study
18 was of insufficient duration to elicit beneficial IVD adaptations. Adaptations of bone density,
19 muscle size and tendon cross-sectional area with exercise take, 9-12 months,[5] three
20 weeks[37] and 3-4 months,[21] respectively, before they are detectable. The timeframe after
21 which IVD are expected to respond to exercise is not clear. Sivan and colleagues have been
22 frequently cited as evidence that the IVD is unlikely to ever respond to loading within the
23 human lifespan, given that half-lives for the turnover of collagen (~95 years)[38] and aggrecan
24 (~22 years)[39] are quite long. However, the half-life for the turnover of the adult human femur
25 collagen is approximately 16-22 years (3-4% per year) in women and 22-45 years (1.5-3% per

1 year) in men.[40] Yet, measurable increases in human femur bone mineral density were
2 reported after 9 months of exercise.[5] The minimum duration of exercise required to elicit
3 IVD adaptations remains unknown and our study suggest it may be longer than 6 months.

4

5 In future work, it would be appropriate to consider different exercise programs that may load
6 the IVD in different ways. As highlighted in a prior literature review,[7] loading of the IVD
7 needs to be dynamic to elicit an anabolic response. The prior review of the literature suggested
8 that loading should be applied in an axial compressive manner and the magnitude of loading
9 required likely falls within those generated during walking and jogging.[7] The duration of
10 loading required to elicit an anabolic response from the IVD is unclear, with one review
11 suggesting 8 hours per day.[8] We are sceptical that this extensive duration of loading is
12 required, however, the minimum required duration is not yet clear. Overall, a potential next
13 attempt for an exercise training protocol to elicit an anabolic response in the IVD could be a
14 progressive walking/running protocol.

15

16 Damaged or degenerated IVD, such as those associated with NSCLBP,[41] may not respond
17 to loading patterns as otherwise healthy IVD would. Cells from healthy IVDs upregulated
18 anabolic extracellular matrix genes following two hours of cyclical exposure to hydrostatic
19 pressure of 0.8-1.7 megapascal at 0.5 Hz.[20] This was not the case for cells from degenerated
20 IVDs.[20] In our study, the IVDs of patients with NSCLBP may have require different stimuli
21 to display an anabolic response. Examining the efficacy of exercise on IVD in non-patient
22 populations, including normal participants, is warranted.

23

24 Finally, alternate markers of IVD 'health' could be considered in the future research. For
25 example, the T2-time reflects the glycosaminoglycan and water content of the IVD and the

1 interaction of water with collagens.[15, 31, 32] T2-time therefore reflects the end-points of a
2 number of physiological and cellular pathways. Assessing earlier degeneration markers, such
3 as IVD nutrition using diffusion of small solutes into the IVD via studies[42] of diffusion rates
4 of low molecular weights contrast agents (e.g. Gadodiamide or Gadoteridol) into the IVD may
5 be more promising. An additional approach may be to assess other IVD markers, such as
6 T1rho,[43] even if the utility of this measure versus existing approaches such as T2-time is not
7 yet clear. Sodium spectroscopy may have utility for quantifying proteoglycan content in the
8 IVD[44] and sequence protocols that can readily be implemented in living patient collectives
9 are still to be developed.

10

11 The strengths of the current study include its prospective randomised design and the blinded
12 nature of MRI data collection and analyses. Limitations of this study include that we did not
13 have a non-intervention control group without any kind of treatment, and may have increased
14 the likelihood of finding a between-group difference, such as if the intervention reduced the
15 rate of age related decline rather than necessarily cause improvements versus baseline. This is
16 common of studies of exercise and bone.[4, 5] For ethical reasons, we considered it important
17 to have a control group which received treatment, albeit one designed to not load the IVDs.
18 The sample size, while sufficiently powering the trial for the primary repeated measures
19 analysis to detect an ~2% difference in IVD T2-time change, will not have been sufficient for
20 smaller effect sizes. It is open whether the effect of the exercise as implemented in the current
21 study on IVD T2 relaxation time is smaller than 2%. Another potential limitation is that despite
22 adopting an intent-to-treat approach for primary analyses to account for drop-outs, the study
23 may still have been underpowered. Nonetheless, publishing these results follow strong
24 recommendations by The Lancet and other scientific media outlets[45] to publish studies with
25 negative results, permitted that the trial, such as the current study, was pre-registered, to combat

1 publication bias and erroneous meta-analyses of current literature. Whilst we requested that
2 patients completed exercise diaries for their home exercise program, poor adherence and
3 inconsistent reporting of this practice limited our capacity to comment on this adherence and
4 consider this as a factor in analyses. The experimental intervention was, superficially, less
5 adhered to than in control (60% versus 77%). We intentionally set a high expectation for
6 number of treatment sessions for the experimental intervention, communicated this during
7 participant screening and included this in the exclusion criteria, to increase the amount of
8 exercise participants in the intervention group completed. The minimum required number of
9 exercise sessions per week to have an effect on the IVD is, unlike guidelines for exercise for
10 muscle[46] and bone,[47] not known. Nonetheless, a per-protocol analysis did not yield
11 different overall findings to the intent-to-treat analysis presented in this paper. Furthermore,
12 the number of comparisons made in the current study should be noted. To account for this, we
13 implemented and presented the outcomes of these analysis with and without adjustment for
14 multiple comparisons.

15

16 **CONCLUSION**

17

18 The effects of exercise on the IVD were tested in this first RCT. Exercises specifically designed
19 to beneficially modulate IVD did not significantly improve IVD MRI markers compared to
20 control or to its own baseline in a small group of patients with NSCLBP. Specifically, the
21 intervention in the current study did not statistically improve IVD composition (T2-times),
22 water diffusion speed within the IVD (ADC) or impact IVD expansion in acute lying, when
23 compared to control. This study provides a foundation for future human trials seeking to
24 establish whether various forms and durations of exercise therapeutically modulate the IVD in
25 different populations.

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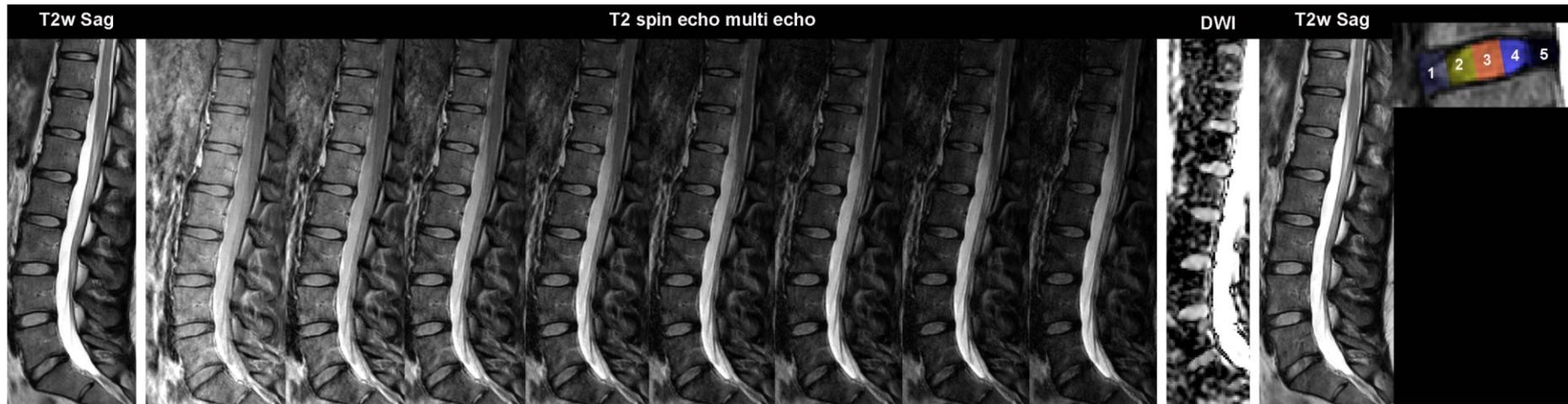
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Figure 1. Magnetic resonance techniques and sequences applied in this study.



A T2-weighted sagittal (T2w Sag) scan was performed immediately after pilot scanning. This was followed by a spin echo multi echo sequence for the assessment of intervertebral disc T2-relaxation time (the eight images shown for this sequence show the repeated echos [at 15.75, 36.75, 57.75, 78.75, 99.75, 120.75, 141.75 and 162.75ms] at the same anatomical position. Decay of image intensity across echos is used to calculate T2-time; see *Methods*). A diffusion weighted imaging (DWI) scan was performed to calculate the apparent diffusion coefficient of the intervertebral disc. Finally, a repeat T2w Sag scan was performed to assess the rate of intervertebral disc expansion in lying. The inset shows the division of the intervertebral disc into five subregions after tracing.

Figure 2. CONSORT diagram.

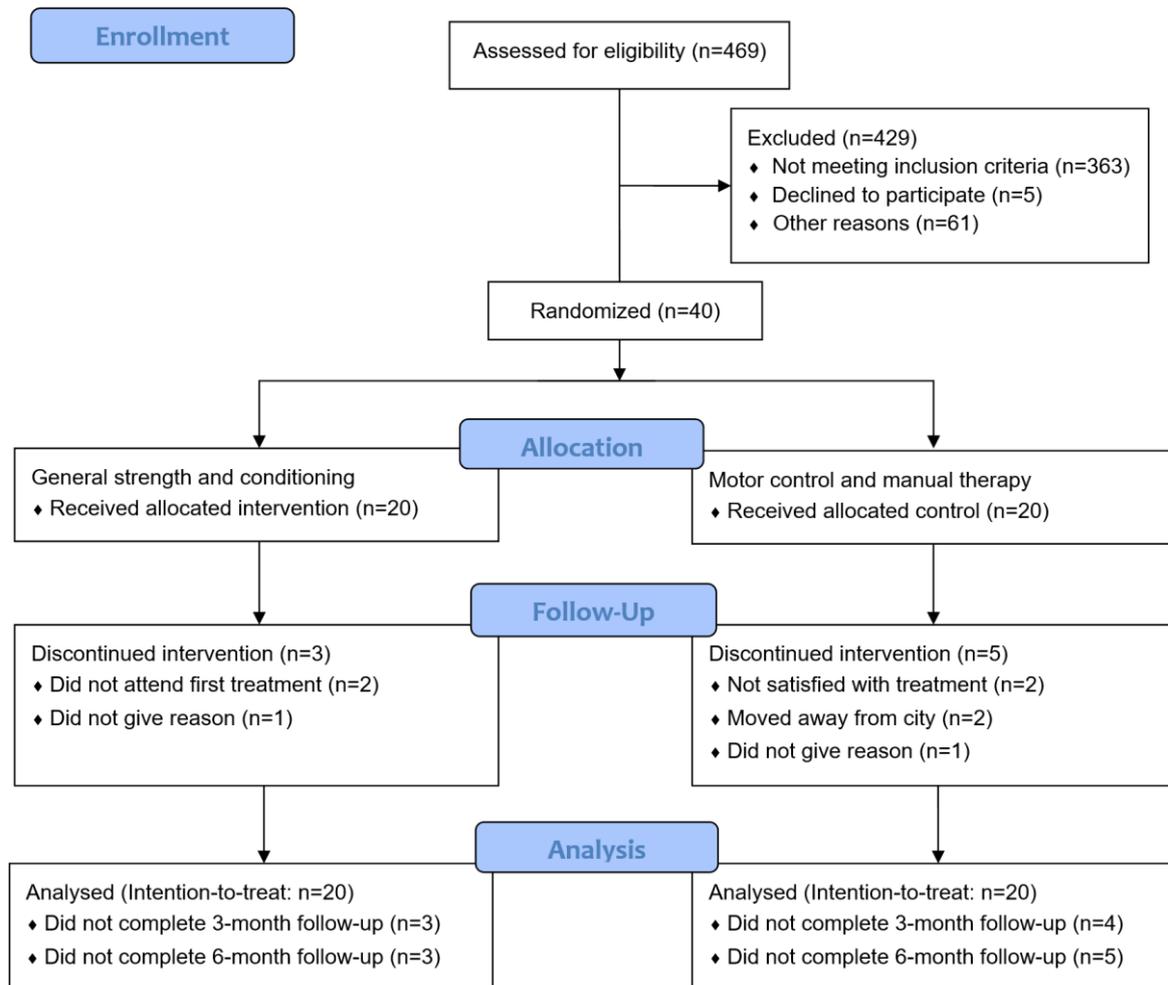
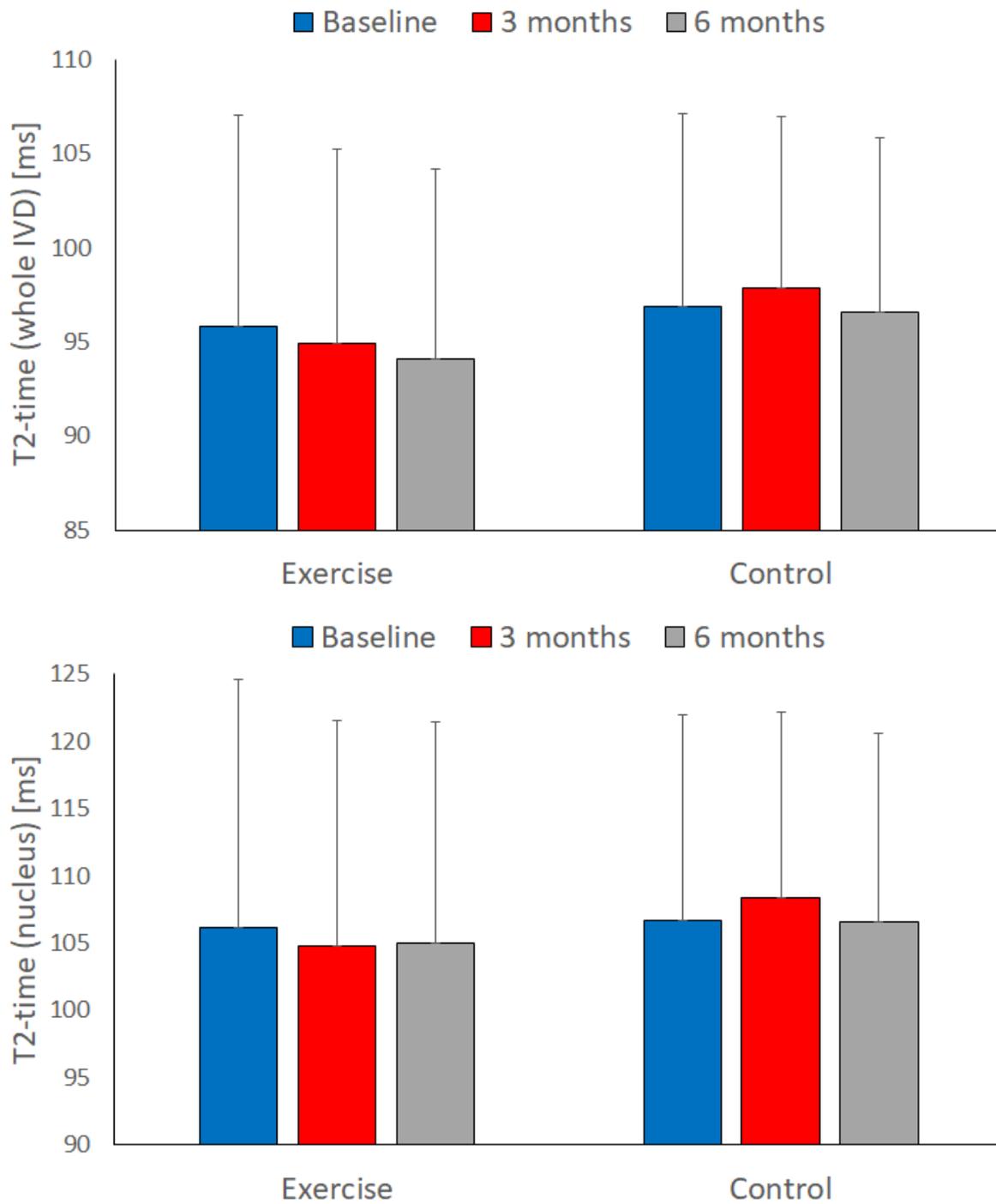


Figure 3. Average lumbar IVD T2-time with exercise compared to control.



Top panel: Whole intervertebral disc (IVD). Bottom panel: Central IVD (nucleus pulposus) subregion. Values are mean (standard deviation). No significant changes were observed.

Table 1. Baseline demographic and intervertebral disc (IVD) morphological data.

	Exercise	Control
Age, years	35 (5)	35 (4)
Female, n (%)	10 (50)	9 (45)
Height, cm	172.5 (9.1)	169.6 (7.7)
Weight, kg	76.9 (16.8)	77.8 (13.5)
Body mass index, kg/m ²	25.4 (4.2)	27.1 (4.9)
Pain, 0-100 VAS	41 (18)	49 (19)
Disability, % on Oswestry index	24.5 (12.1)	23.4 (8.5)
Average lumbar IVD Pfirrmann grade	2.3(0.5)	2.3(0.5)
Lordosis angle, degrees	33.5 (9.0)	32.0 (7.5)

Data are mean(SD) except for number of females. N=20 in each group. IVD: intervertebral

disc. Pfirrmann grade averaged from all lumbar discs.

Table 2. T2-relaxation time of the intervertebral disc (IVD) and its subregions.

	Baseline and within-group difference						Group x time effect P-value
	Exercise			Control			
	n	Mean (SD)	P-value	n	Mean (SD)	P-value	
Total IVD, ms							
Baseline	20	95.8 (11.3)	-	20	96.9 (10.3)	-	0.549
Δ 3-month	17	-0.9 (5.2)	0.480	16	1.0 (4.6)	0.399	
Δ 6-month	17	-1.7 (4.7)	0.150	15	-0.3 (5.4)	0.812	
IVD anterior annulus, ms							
Baseline	20	79.8 (8.3)	-	20	81.0 (7.5)	-	0.669
Δ 3-month	17	0.6 (5.7)	0.665	16	-0.3 (6.0)	0.842	
Δ 6-month	17	-0.9 (8.0)	0.659	15	0.4 (6.4)	0.832	
IVD anterior nucleus, ms							
Baseline	20	93.4 (12.0)	-	20	94.7 (11.6)	-	0.349
Δ 3-month	17	-1.5 (5.4)	0.254	16	1.4 (5.7)	0.351	
Δ 6-month	17	-1.4 (5.2)	0.285	15	0.3 (7.4)	0.863	
IVD centre nucleus, ms							
Baseline	20	106.2 (18.4)	-	20	106.7 (15.3)	-	0.375
Δ 3-month	17	-1.4 (7.8)	0.455	16	1.7 (5.5)	0.220	
Δ 6-month	17	-1.1 (6.8)	0.496	15	-0.1 (6.7)	0.969	
IVD posterior nucleus, ms							
Baseline	20	101.0 (14.9)	-	20	101.5 (14.5)	-	0.392
Δ 3-month	17	-1.3 (7.1)	0.423	16	1.6 (5.6)	0.273	
Δ 6-month	17	-1.4 (6.4)	0.379	15	0.1 (6.1)	0.966	
IVD posterior annulus, ms							
Baseline	20	85.1 (8.0)	-	20	86.6 (9.6)	-	0.537
Δ 3-month	17	0.5 (8.6)	0.818	16	-2.7 (9.9)	0.292	
Δ 6-month	17	-2.4 (4.4)	0.028	15	-3.2 (7.5)	0.111	

Data are mean(SD) at baseline and mean(SD) change at 3- and 6-months. Raw (unadjusted) P-values shown. Bold: $p \leq 0.05$ before adjustment for multiple comparisons using the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives. See Supplemental Table 1 for individual vertebral level data.

Table 3. Apparent diffusion coefficient in the intervertebral discs.

	Baseline and within-group difference						Group x time effect P-value
	Exercise			Control			
	n	Mean (SD)	P-value	n	Mean (SD)	P-value	
AvLx, mm²/s							
Baseline	20	768.2 (83.1)	-	20	765.7 (104.6)	-	0.825
Δ 3-month	17	1.3 (99.7)	0.959	16	-7.1 (76.9)	0.714	
Δ 6-month	17	-20.5 (74.3)	0.278	15	-7.9 (81.1)	0.708	
L1-L2, mm²/s							
Baseline	20	819.6 (131.3)	-	20	826.9 (160.5)	-	0.678
Δ 3-month	17	-27.9 (172.5)	0.511	16	7.5 (127.8)	0.816	
Δ 6-month	17	-8.7 (94.8)	0.716	15	20.4 (126.5)	0.536	
L2-L3, mm²/s							
Baseline	20	807.3 (102.3)	-	20	802.6 (141.7)	-	0.594
Δ 3-month	17	-7.2 (119.8)	0.805	16	31.9 (115.2)	0.277	
Δ 6-month	17	-17.9 (94.8)	0.456	15	9.8 (110.3)	0.734	
L3-L4, mm²/s							
Baseline	20	839.7 (106.1)	-	20	784.2 (178.1)	-	0.853
Δ 3-month	17	8.5 (132.8)	0.795	16	-11.8 (112.4)	0.678	
Δ 6-month	17	-41.8 (102.9)	0.114	15	-37.1 (117.5)	0.231	
L4-L5, mm²/s							
Baseline	20	749.8 (171.5)	-	20	726.6 (151)	-	0.359
Δ 3-month	17	50.0 (141.4)	0.155	16	-2.6 (123.2)	0.932	
Δ 6-month	17	-6.2 (149.6)	0.869	15	-1.2 (147.4)	0.976	
L5-S1, mm²/s							
Baseline	20	624.9 (162.6)	-	20	688.3 (104.8)	-	0.664
Δ 3-month	17	-11.8 (172.7)	0.781	16	-57.5 (95.5)	0.023	
Δ 6-month	17	-19.3 (121.2)	0.529	15	-29.6 (101.8)	0.269	

Data are mean(SD) at baseline and mean(SD) change at 3- and 6-months. AvLx: Average of lumbar levels. Raw (unadjusted) P-values shown.

Bold: $p \leq 0.05$ before adjustment for multiple comparisons using the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives.

Table 4. Volume and height of the lumbar intervertebral discs (averaged between levels).

	Baseline and within-group difference						Group x time effect P-value
	Exercise			Control			
	n	Mean (SD)	P-value	n	Mean (SD)	P-value	
Intervertebral disc volume, cm³							
Baseline	20	8.6 (1.9)	-	20	8.7 (2.9)	-	0.256
Δ 3-month	17	-0.1 (0.6)	0.505	16	0.3 (0.7)	0.138	
Δ 6-month	17	0.0 (0.6)	0.843	15	0.3 (0.6)	0.084	
Intervertebral disc height, mm							
Baseline	20	8.1 (0.8)	-	20	8.0 (0.8)	-	0.054
Δ 3-month	17	-0.1 (0.3)	0.158	16	0.1 (0.2)	0.035	
Δ 6-month	17	0.0 (0.2)	0.934	15	0.1 (0.2)	0.148	

Data are mean(SD) at baseline and mean(SD) change at 3- and 6-months. Raw (unadjusted) P-values shown. Bold: $p \leq 0.05$ before adjustment for multiple comparisons using the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives. See Supplemental Table 2 for individual vertebral level data.

Table 5. Expansion of intervertebral disc height in short-duration lying.

	Baseline and within-group difference						Group x time effect P-value
	Exercise			Control			
	n	Mean (SD)	P-value	n	Mean (SD)	P-value	
AvLx, %							
Baseline	20	1.7 (2.6)	-	20	2.0 (2.8)	-	0.710
3-month	17	0.5 (2.2)	0.120	16	0.4 (2.9)	0.076	
6-month	17	0.3 (3.5)	0.157	15	1.5 (3.4)	0.564	
L1-L2, %							
Baseline	20	1.0 (4.0)	-	20	3.1 (3.7)	-	0.384
3-month	17	0.7 (2.7)	0.760	16	0.5 (4.2)	0.045	
6-month	17	0.0 (3.9)	0.443	15	1.7 (4.6)	0.296	
L2-L3, %							
Baseline	20	1.6 (3.3)	-	20	2.0 (3.6)	-	0.728
3-month	17	0.2 (3.8)	0.242	16	0.4 (2.9)	0.128	
6-month	17	0.8 (3.2)	0.457	15	2.2 (3.5)	0.866	
L3-L4, %							
Baseline	20	2.2 (2.7)	-	20	2.7 (3.7)	-	0.925
3-month	17	1.4 (2.9)	0.392	16	1.8 (4.8)	0.495	
6-month	17	-0.1 (3.3)	0.020	15	1.0 (4.5)	0.186	
L4-L5, %							
Baseline	20	2.5 (3.3)	-	20	1.2 (3.8)	-	0.429
3-month	17	-0.2 (2.4)	0.008	16	-0.1 (4.2)	0.285	
6-month	17	0.9 (4.8)	0.246	15	1.6 (3.6)	0.676	
L5-S1, %							
Baseline	20	1.6 (5.8)	-	20	2.2 (6.0)	-	0.857
3-month	17	0.4 (5.8)	0.550	16	0.3 (4.2)	0.265	
6-month	17	-0.2 (5.7)	0.349	15	1.1 (5.8)	0.590	

Data are mean(SD) percentage increase in disc height at baseline and, in contrast to other tables, data at 3- and 6-months are also absolute

mean(SD). AvLx: Average of lumbar levels. Raw (unadjusted) P-values shown. Bold: $p \leq 0.05$ before adjustment for multiple comparisons using

the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives.

Supplementary Table 1. T2-relaxation time of the individual lumbar intervertebral disc (IVD) and its subregions.

	Baseline and within-group difference						Group x time effect P-value
	Exercise			Control			
	n	Mean (SD)	P-value	n	Mean (SD)	P-value	
L1-L2 Total IVD, ms							
Baseline	20	100.6(15.9)	-	20	100.2(12.6)	-	0.394
Δ 3-month	17	-2.4 (10.8)	0.367	16	0.4 (6.7)	0.798	
Δ 6-month	17	-4.8 (10.3)	0.060	15	-0.9 (5.9)	0.554	
L1-L2 IVD anterior annulus, ms							
Baseline	20	77.6(12.9)	-	20	78.7(13.2)	-	0.732
Δ 3-month	17	3.6 (17)	0.394	16	0.5 (16.1)	0.893	
Δ 6-month	17	7.9 (50)	0.517	15	-1.2 (10.5)	0.665	
L1-L2 IVD anterior nucleus, ms							
Baseline	20	92.1(16.7)	-	20	96.3(17.3)	-	0.979
Δ 3-month	17	-2.2 (7.6)	0.234	16	-1.6 (10.1)	0.522	
Δ 6-month	17	-3.5 (13.6)	0.291	15	-2.7 (10.7)	0.33	
L1-L2 IVD centre nucleus, ms							
Baseline	20	110.4(27.2)	-	20	108.4(19.2)	-	0.203
Δ 3-month	17	-4.7 (13.6)	0.163	16	1.2 (7.6)	0.531	
Δ 6-month	17	-5.6 (15.3)	0.141	15	1.3 (6.3)	0.419	
L1-L2 IVD posterior nucleus, ms							
Baseline	20	113.5(21.8)	-	20	111.8(16.9)	-	0.141
Δ 3-month	17	-4.6 (12.3)	0.133	16	1.8 (8.3)	0.383	
Δ 6-month	17	-5.9 (12.8)	0.064	15	0.3 (8)	0.874	
L1-L2 IVD posterior annulus, ms							
Baseline	20	93.2(14.0)	-	20	91.8(11.5)	-	0.340
Δ 3-month	17	-0.4 (19.9)	0.932	16	-1.5 (13.4)	0.655	
Δ 6-month	17	-8.6 (7.3)	0.00003	15	-4.5 (9.9)	0.087	
L2-L3 Total IVD, ms							
Baseline	20	98.5(16.1)	-	20	104.0(13.7)	-	0.151
Δ 3-month	17	-3.1 (6.9)	0.071	16	1.2 (7.9)	0.556	
Δ 6-month	17	-1.6 (8.6)	0.458	15	-0.2 (6.4)	0.926	

L2-L3 IVD anterior annulus, ms							
Baseline	20	83.9(28.8)	-	20	81.2(11.4)	-	0.148
Δ 3-month	17	-5 (27.8)	0.463	16	-3.9 (7.6)	0.049	
Δ 6-month	17	-7 (26.5)	0.284	15	-0.6 (9.9)	0.819	
L2-L3 IVD anterior nucleus, ms							
Baseline	20	94.3(18.5)	-	20	96.9(16.5)	-	0.188
Δ 3-month	17	-3.1 (8.3)	0.137	16	3 (11.6)	0.304	
Δ 6-month	17	-1.4 (9)	0.516	15	2.2 (7.7)	0.272	
L2-L3 IVD centre nucleus, ms							
Baseline	20	108.5(24.1)	-	20	118.0(21.3)	-	0.079
Δ 3-month	17	-2.1 (7.7)	0.263	16	2.7 (10.2)	0.298	
Δ 6-month	17	-0.1 (10.6)	0.984	15	-1.2 (8.6)	0.592	
L2-L3 IVD posterior nucleus, ms							
Baseline	20	106.5(20.2)	-	20	115.5(21.8)	-	0.021
Δ 3-month	17	-4.1 (7.2)	0.024	16	1.8 (7.1)	0.311	
Δ 6-month	17	-0.6 (10.2)	0.801	15	0.1 (5.9)	0.932	
L2-L3 IVD posterior annulus, ms							
Baseline	20	86.7(14.3)	-	20	88.2(13.8)	-	0.850
Δ 3-month	17	-2.6 (11.3)	0.359	16	-3.5 (13.5)	0.31	
Δ 6-month	17	-2.3 (10.9)	0.397	15	-4.7 (12.9)	0.167	
L3-L4 Total IVD, ms							
Baseline	20	101.6(14.0)	-	20	98.2(19.8)	-	0.839
Δ 3-month	17	0 (6.6)	0.997	16	-0.8 (9.6)	0.742	
Δ 6-month	17	0.4 (7)	0.801	15	-1.2 (8.2)	0.590	
L3-L4 IVD anterior annulus, ms							
Baseline	20	79.5(7.7)	-	20	82.9(12.8)	-	0.114
Δ 3-month	17	3.2 (10.2)	0.2	16	-3.2 (11.8)	0.292	
Δ 6-month	17	1 (7.3)	0.56	15	0.9 (13)	0.781	
L3-L4 IVD anterior nucleus, ms							
Baseline	20	102.2(18.1)	-	20	95.9(23.3)	-	0.782
Δ 3-month	17	-0.9 (9.4)	0.702	16	-0.4 (8.7)	0.85	
Δ 6-month	17	1.3 (9.9)	0.595	15	-0.8 (10.7)	0.788	
L3-L4 IVD centre nucleus, ms							0.892

Baseline	20	117.3(23.9)	-	20	109.1(29.9)	-	
Δ 3-month	17	0.5 (9.4)	0.811	16	0.9 (7.9)	0.645	
Δ 6-month	17	1.8 (10.1)	0.467	15	0.7 (9.3)	0.787	
L3-L4 IVD posterior nucleus, ms							
Baseline	20	107.0(19.2)	-	20	101.4(25.8)	-	0.927
Δ 3-month	17	0.5 (10.2)	0.829	16	0.3 (12.2)	0.909	
Δ 6-month	17	0.2 (8.2)	0.902	15	-0.9 (8.9)	0.684	
L3-L4 IVD posterior annulus, ms							
Baseline	20	80.9(12.9)	-	20	85.9(14.6)	-	0.826
Δ 3-month	17	-3.6 (12.1)	0.232	16	-4.7 (16)	0.246	
Δ 6-month	17	-3.1 (9.2)	0.18	15	-5.5 (13.4)	0.122	
L4-L5 Total IVD, ms							
Baseline	20	90.3(16.0)	-	20	89.4(18.3)	-	0.287
Δ 3-month	17	-0.7 (6.3)	0.634	16	1.7 (5.1)	0.204	
Δ 6-month	17	-1.9 (7.8)	0.312	15	1.7 (5.5)	0.250	
L4-L5 IVD anterior annulus, ms							
Baseline	20	79.6(8.5)	-	20	80.5(8.6)	-	0.004
Δ 3-month	17	0.1 (8.8)	0.946	16	0.7 (9.2)	0.748	
Δ 6-month	17	-5.8 (9)	0.012	15	2.9 (7.3)	0.134	
L4-L5 IVD anterior nucleus, ms							
Baseline	20	88.9(19.3)	-	20	88.5(23.4)	-	0.113
Δ 3-month	17	-0.8 (7.5)	0.669	16	3.7 (8.4)	0.091	
Δ 6-month	17	-1.7 (7.7)	0.365	15	4 (9.5)	0.111	
L4-L5 IVD centre nucleus, ms							
Baseline	20	100.8(25.7)	-	20	98.5(29.8)	-	0.367
Δ 3-month	17	-2.1 (10.2)	0.399	16	2.2 (7.5)	0.244	
Δ 6-month	17	-1.1 (12.5)	0.722	15	0.8 (8.2)	0.714	
L4-L5 IVD posterior nucleus, ms							
Baseline	20	93.0(21.7)	-	20	89.1(22.7)	-	0.693
Δ 3-month	17	-1.2 (9.3)	0.597	16	0.9 (6.1)	0.564	
Δ 6-month	17	-0.3 (10.6)	0.895	15	0.3 (7)	0.87	
L4-L5 IVD posterior annulus, ms							
Baseline	20	77.762(12.245)	-	20	78.4(8.5)	-	0.412

Δ 3-month	17	1.9 (11.9)	0.523	16	-1.4 (7.9)	0.473	
Δ 6-month	17	-1.6 (7.3)	0.385	15	0.2 (7.6)	0.928	
L5-S1 Total IVD, ms							
Baseline	20	87.9(16.4)	-	20	92.6(15.4)	-	0.962
Δ 3-month	17	1.8 (11.4)	0.508	16	2.4 (7.4)	0.198	
Δ 6-month	17	-0.3 (6.3)	0.826	15	-0.5 (4.8)	0.690	
L5-S1 IVD anterior annulus, ms							
Baseline	20	78.3(13.8)	-	20	81.8(10.1)	-	0.860
Δ 3-month	17	3.1 (10.3)	0.219	16	4.7 (10.4)	0.084	
Δ 6-month	17	1.5 (11.1)	0.574	15	0.9 (5.9)	0.548	
L5-S1 IVD anterior nucleus, ms							
Baseline	20	89.8(19.9)	-	20	95.8(17.5)	-	0.797
Δ 3-month	17	-0.6 (11.4)	0.832	16	1.7 (8.4)	0.414	
Δ 6-month	17	-1.4 (7.7)	0.457	15	-1 (7.1)	0.575	
L5-S1 IVD centre nucleus, ms							
Baseline	20	93.9(24.0)	-	20	99.5(24.3)	-	0.917
Δ 3-month	17	1.1 (14.5)	0.755	16	1.5 (9)	0.504	
Δ 6-month	17	-0.9 (7.2)	0.62	15	-1.5 (6.4)	0.382	
L5-S1 IVD posterior nucleus, ms							
Baseline	20	85.3(17.2)	-	20	89.3(21.1)	-	0.917
Δ 3-month	17	2.3 (11.9)	0.422	16	2.8 (7.4)	0.141	
Δ 6-month	17	-0.4 (6.8)	0.831	15	0.7 (7.8)	0.724	
L5-S1 IVD posterior annulus, ms							
Baseline	20	87.0(15.3)	-	20	89.0(16.0)	-	0.193
Δ 3-month	17	7.1 (15.9)	0.077	16	-2 (13.3)	0.559	
Δ 6-month	17	3.3 (12.8)	0.297	15	-1.5 (9.6)	0.551	

Data are mean(SD) at baseline and mean(SD) change at 3- and 6-months. Raw (unadjusted) P-values shown. Bold: $p \leq 0.05$ before adjustment for multiple comparisons using the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives.

Supplementary Table 2. Individual lumbar intervertebral discs (IVD) volume and height.

	Baseline and within-group difference						Group x time effect P-value
	Exercise			Control			
	n	Mean (SD)	P-value	n	Mean (SD)	P-value	
L1-L2 IVD volume, cm³							
Baseline	20	7.5 (1.8)	-	20	7.0 (2.6)	-	0.042
Δ 3-month	17	-0.1 (0.5)	0.486	16	0.3 (0.7)	0.085	
Δ 6-month	17	-0.2 (0.7)	0.382	15	0.4 (0.6)	0.029	
L2-L3 IVD volume, cm³							
Baseline	20	8.4 (2.0)	-	20	9.0 (3.7)	-	0.702
Δ 3-month	17	0.1 (0.7)	0.465	16	0.0 (0.9)	0.893	
Δ 6-month	17	0.0 (0.7)	0.977	15	0.1 (0.8)	0.494	
L3-L4 IVD volume, cm³							
Baseline	20	9.8 (2.4)	-	20	9.5 (3.2)	-	0.517
Δ 3-month	17	0.0 (1.0)	0.953	16	0.4 (0.9)	0.104	
Δ 6-month	17	0.0 (1.2)	0.913	15	0.3 (0.8)	0.192	
L4-L5 IVD volume, cm³							
Baseline	20	10.2 (2.7)	-	20	9.9 (2.9)	-	0.160
Δ 3-month	17	-0.5 (1.2)	0.116	16	0.2 (1.0)	0.423	
Δ 6-month	17	0.2 (1.3)	0.568	15	0.4 (1.1)	0.220	
L5-S1 IVD volume, cm³							
Baseline	20	7.4 (2.1)	-	20	7.9 (3.0)	-	0.224
Δ 3-month	17	-0.1 (0.6)	0.567	16	0.4 (0.9)	0.111	
Δ 6-month	17	0.1 (0.8)	0.492	15	0.4 (1.2)	0.240	
L1-L2 IVD height, mm							
Baseline	20	7.1 (0.7)	-	20	6.7 (0.8)	-	0.229
Δ 3-month	17	-0.1 (0.3)	0.063	16	0.0 (0.3)	0.694	
Δ 6-month	17	-0.1 (0.4)	0.125	15	0.0 (0.2)	0.910	
L2-L3 IVD height, mm							
Baseline	20	7.8 (0.7)	-	20	7.8 (1.1)	-	0.443
Δ 3-month	17	-0.1 (0.2)	0.362	16	0.0 (0.3)	0.540	
Δ 6-month	17	-0.1 (0.4)	0.260	15	0.1 (0.4)	0.513	

L3-L4 IVD height, mm							0.091
Baseline	20	8.8 (1.0)	-	20	8.2 (1.0)	-	
Δ 3-month	17	-0.1 (0.3)	0.311	16	0.2 (0.4)	0.062	
Δ 6-month	17	-0.1 (0.4)	0.525	15	0.1 (0.3)	0.082	
L4-L5 IVD height, mm							0.163
Baseline	20	9.1 (1.7)	-	20	9.0 (1.4)	-	
Δ 3-month	17	-0.1 (0.4)	0.267	16	0.1 (0.4)	0.241	
Δ 6-month	17	0.2 (1.0)	0.423	15	0.1 (0.3)	0.351	
L5-S1 IVD height, mm							0.144
Baseline	20	7.8 (1.7)	-	20	8.3 (1.4)	-	
Δ 3-month	17	-0.1 (0.4)	0.511	16	0.1 (0.3)	0.039	
Δ 6-month	17	0.1 (0.6)	0.521	15	0.1 (0.3)	0.350	

Data are mean(SD) at baseline and mean(SD) change at 3- and 6-months. Raw (unadjusted) P-values shown. Bold: $p \leq 0.05$ before adjustment for multiple comparisons using the false discovery rate method. No P-values were statistically significant after adjustment via the false discovery rate method to reduce the risk of false-positives.