THE RELATIONSHIP BETWEEN BACK PAIN AND THE MORPHOLOGY AND FUNCTION OF THE LUMBAR MULTIFIDUS MUSCLE IN INDIVIDUALS WITH AND WITHOUT LOW BACK PAIN

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The relationship between back pain and the morphology and function of the lumbar multifidus muscle in individuals with and without low back pain

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CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it produces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

_____ (Sign)

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DEDICATION

I would like to dedicate this PhD thesis to The Almighty God for His blessings and mercy throughout the course of this study and to my Parents for their prayers and support.

ABSTRACT

Background: Lumbar multifidus muscle (LMM) is thought to be highly related to chronic low back pain (CLBP), as it serves as a spinal stabilizer. Many people with CLBP are characterized by LMM atrophy and/or intramuscular fatty infiltration on magnetic resonance images, decreased percent thickness change during contraction under ultrasound imaging, or compromised LMM proprioception, which may indicate suboptimal LMM function in these individuals. While many factors (e.g., demographics, psychological variables, insomnia, and spinal phenotypes) may also confound the association between LMM and clinical outcomes (pain intensity and disability) in people with CLBP, there was a paucity of research that considered these confounders in exploring the association between LMM characteristics and CLBP. Importantly, it remains unclear whether aberrant changes in LMM characteristics are the cause or consequence of CLBP. If LMM dysfunction is related to the development or maintenance of CLBP, the improvements of LMM morphometry or function following interventions (especially motor control exercise) would be associated with the corresponding changes in pain or disability in these people.

Objectives: The aims of this work were to: (1) summarize the evidence regarding the effectiveness of motor control exercise (MCE) in modifying LMM morphometry and reducing pain and the temporal associations between post-MCE changes in LMM and the clinical outcomes in people with low back pain (LBP); (2) determine whether LMM proprioception differed between people with and without CLBP at different age ranges that had never been investigated in prior research; (3) quantify the associations between LMM morphometry and function with pain intensity and disability in people with CLBP after controlling for confounders such as demographics, psychological factors, sleep disturbances and spinal phenotypes at baseline; and (4) identify baseline factors that could predict pain

intensity and LBP-related disability in individuals with and without non-specific CLBP at the 2-year follow up.

Methods: To achieve objective #1, a systematic review was conducted to comprehensively summarize the relevant evidence. For objectives #2, 3, and 4, a 2-year prospective study was conducted. At baseline, participants with CLBP (n=70) were recruited from a tertiary referral centre for spinal pathologies and asymptomatic individuals (n=67) were recruited from a university campus. All participants completed a battery of questionnaires, performed some physical tests (including lumbar proprioception and reposition tests, ultrasonography to evaluate LMM thickness and stiffness) and underwent lumbar magnetic resonance imaging to evaluate spinal phenotypes, LMM total cross-sectional area or volume and LMM percent lean muscle volume. All participants also provided their pain intensity and LBP-related disability levels every 6 months through online questionnaires. At the 2-year follow-up, participants [CLBP (n=43), asymptomatic (n=41)] repeated questionnaires, physical tests and medical imaging.

Results: The systematic review found that MCE can change LMM dimensions in people CLBP. However, these changes were unrelated to the corresponding improvements in clinical outcomes (pain intensity and LBP-related disability). The baseline data of the prospective study found that compared to young people with CLBP (18 to 44 years), young people with CLBP and middle-aged (45-65 years) people with or without CLBP demonstrated inferior lumbar proprioceptive reweighting capability, indicating that CLBP compromised young people's lumbar proprioceptive reweighting capacity, but age-related deterioration in central and peripheral processing of lumbar proprioceptive signals become more dominant from middle-age onward. The B-mode ultrasonography found that people with CLBP had significantly smaller percent thickness changes of LMM at the L4/5 level than asymptomatic controls. However, the percent thickness change of LMM at the L4/5 level was unrelated to

LBP intensity or LBP-related disability in individuals with CLBP after adjusting for other self-reported factors. In particular, fear-avoidance belief questionnaire work subscale scores and insomnia severity index scores together explained 24% of LBP intensity in people with CLBP, while fear-avoidance belief questionnaire total scores alone explained 34% of variance of LBP-related disability in people with CLBP. The lumbar magnetic resonance imaging found that although people with CLBP had significantly more fatty infiltration in LMM, their LMM morphometric parameters were unrelated to LBP intensity or LBP-related disability after considering demographics, psychological factors, insomnia, and spinal phenotypes. The baseline data did not predict the pain intensity or LBP-related disability at follow-up time points (6 months, 12 months). The follow-up study at 2 years revealed that baseline fear-avoidance beliefs –Work scores predicted pain intensity at 2 years in people with CLBP, while baseline pain-catastrophizing scale-helplessness and insomnia predicted LBP-related disability (Roland-Morris Disability score) at 2 years in people with CLBP. The temporal changes in LMM characteristics over the two year-period were unrelated to clinical outcomes at the 2-year follow-up. Because none of the asymptomatic participants developed CLBP at the 2-year follow-up, it was impossible to determine whether baseline LMM characteristics or other factors could predict the development of CLBP.

Conclusion: Although it is believed that intramuscular fatty infiltration in LMM is higher in people with CLBP as compared to healthy people, which might be related to clinical outcomes, my systematic review has found that any post-MCE changes in LMM characteristics were unrelated to CLBP improvements. My empirical study is the first prospective study to comprehensively investigate the relative influences of LMM characteristics on LBP and LBP-related disability at different time points in people with and without CLBP after considering spinal phenotypes, demographic data, and psychosocial factors. The study revealed that aberrant changes in morphometry or function LMM at a

given time point were unrelated to the clinical outcomes (LBP intensity and LBP-related disability) after considering spinal phenotypes, psychological factors, and insomnia. Further, baseline LMM characteristics in people with CLBP did not predict their clinical outcomes at the 2-year follow-up. Instead, baseline fear-avoidance belief scores predict recurrent pain intensity, while baseline pain catastrophizing and insomnia predict LBP-related disability in individuals with CLBP at the 2-year follow-up. Taken together, my findings suggest that the LMM morphometry or function, as well as spinal phenotypes appeared to be less relevant to LBP intensity or LBP-related disability after considering various psychosocial factors. Clinicians should use validated screening tools to identify people with CLBP with strong fear-avoidance beliefs, pain catastrophizing and sleep disorders so that appropriate treatments (e.g., cognitive behavioural therapy for sleep or pain) can be administered timely. Although the current findings do not support LMM to play a crucial role in clinical symptoms or disability in people with CLBP, it is possible that a subgroup of people with more severe deterioration in LMM morphometry or function may predict long-term clinical outcomes in individuals with and without CLBP. Future large-scale prospective studies with long-term follow-ups and subgroup analyses are warranted to clarify this association.

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PhD related articles:

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1. **Pinto SM**, Cheung JPY, Samartzis D, Karppinen J, Zheng YP, Pang MYC, Wong AYL. (2022). Are Morphometric and Biomechanical Characteristics of Lumbar Multifidus Related to Pain Intensity or Disability in People with Chronic Low Back Pain After Considering Psychological Factors or Insomnia? Frontiers in Psychiatry
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Non-PhD related articles

1. Chang JR, Cheung YK, Sharma S, Li SX, Tao RRY, Lee JLC, Sun ER, **Pinto SM**, Zhou Z, Fong H, Chan WWY, Zheng K, Dino S, Fu SN, Wong AYL. Comparative effectiveness of non-pharmacological interventions on sleep in individuals with

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3. Zhou Z, Hui ES, Kranz GS, Chang JR, Luca KD, **Pinto SM**, Chan WWY, Yau SY, Chau BKH, Samartzis D, Jensen MP, Wong AYL. Potential mechanisms underlying the accelerated cognitive decline in people with chronic low back pain: A scoping review. Ageing Research Reviews 2022.
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5. Chang JR, Wang X, Lin G, Samartzis D, **Pinto SM**, Wong AYL. Are changes in sleep quality/quantity or baseline sleep parameters related to changes in clinical outcomes in patients with non-specific chronic low back pain? A systematic review. Clinical Journal of Pain 2021;38: 292-307.
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4. **Pinto SM**, Zheng YP, Pang MYC, Cheung JPY, Karppinen J, Samartzis D, Wong AYL. Factors affecting Pain and Disability in People with Chronic Low Back Pain

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5. **Pinto SM**, Zheng YP, Pang MYC, Cheung JPY, Karppinen J, Samartzis D, Wong AYL. The impact of lumbar multifidus features, psychosocial factors, and sleep problems on clinical outcomes of individuals with chronic low back pain.

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6. **Pinto SM**, Zheng YP, Pang MYC, Cheung JPY, Karppinen J, Samartzis D, Wong AYL. Do individuals with chronic low back pain have different morphometry/function

of lumbar multifidus and spinal degenerative changes as compared to asymptomatic individuals?

Conference: 2021 Back & Neck Pain Forum. Global Virtual Conference.

7. **Pinto SM**, Wong AYL, Zheng YP, Pang MYC, Cheung JPY, Karppinen J, Samartzis D. Deficits in proprioceptive reweighting in middle-aged people with chronic low back pain and asymptomatic people: a cross-sectional study. *Conference*: International Society for the Study of the Lumbar Spine Virtual Annual Meeting 2021.
8. **Pinto SM**, Boghra S, Macedo L, Zheng YP, Pang MYC, Cheung JPY, Karppinen J, Samartzis D, Wong AYL. The effectiveness of motor control exercise in improving lumbar multifidus muscles morphology in patients with low back pain - a systematic review.

   Conference: International Society for the Study of the Lumbar Spine Virtual Annual Meeting 2021.
9. **Pinto SM**, Cheung JPY, Zheng YP, Pang MYC, Karppinen J, Samartzis D, Wong AYL. Do both morphometric and mechanical characteristics of the lumbar multifidus in people with chronic low back pain differ from those of asymptomatic counterparts?

   Conference: International Society for the Study of the Lumbar Spine Virtual Annual Meeting 2021.
10. **Pinto SM**, Wong AYL, Zheng YP, Cheung JPY, Karppinen J, Samartzis D. Altered proprioception reweighting in middle-aged people with chronic low back pain.

    Conference: Spineweek 2020, Melbourne, Australia 2020.
11. **Pinto SM**, Boghra S, Macedo L, Zheng YP, Pang MYC,Cheung JPY, Karppinen J,, Samartzis D, Wong AYL. The effectiveness of physiotherapy interventions in

improving morphology of lumbar multifidus muscles in patients with low back pain - A systematic review.

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12. **Pinto SM**, Boghra S, Macedo L, Zheng YP, Pang MYC, Cheung JPY, Karppinen J,, Samartzis D, Wong AYL. A systematic review on the effectiveness of motor control exercise in improving morphology of lumbar multifidus muscles in patients with low back pain.

    Conference: 40th Annual Congress of The Hong Kong Orthopaedic Association, Hong Kong, 2020

13. **Pinto SM**, WongAYL, Pang MYC, Zheng YP, Cheung JPY, Karppinen J, Samartzis D. Comparison of proprioceptive reweighting in middle-aged patients with chronic low back pain and healthy people: A cross-sectional study

    Conference: 40th Annual Congress of The Hong Kong Orthopaedic Association, Hong Kong, 2020

Non-PhD related conferences

1. Cheung PTY, Ng PMW, Ho JKJ, Chan GCY, **Pinto SM**, Chan WWY, Al Zoubi F, Zheng YP, De Carvalho D, Wong AYL. Intra- and inter-rater reliability of novel examiners in using shear wave elastography and myotonometry to measure erector spinae stiffness.

   Conference: World Physiotherapy-Asia Western Pacific Regional Congress with HKPA Conference 2022. Hong Kong

2. Zhou DZX, de Luca K, Hui ES, Chang JR, **Pinto SM**, Chan WWY, Chau B, Kranz GS, Yau SSY, Samartzis D, Wong AYL. A state-of-the-art review on potential mechanisms underlying poor cognitive performance in people with chronic low back pain.

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3. Cheung PTY, Ng PMW, Ho JKJ, Chan GCY, **Pinto SM**, Chan WWY, Al Zoubi F, Zheng YP, De Carvalho D, Wong AYL. Within- and between-day intra- and inter-rater reliability of using myotonometer and shear wave elastography to assess paraspinal muscle stiffness.

   Conference: 12th Pan-Pacific Conference on Rehabilitation (PPCR 2021), Hong Kong

4. Ng TKY, Kwok CKC, Ngan GYK, Wong GYK, Wong HKH, Al Zoubi F, Tomkins-Lane C, Yau SK, Samartzis D, **Pinto SM**, Fu SN, Li H, Wong AYL. Changes in physical activity during COVID-19 pandemic in people with and without chronic diseases.

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LIST OF ABBREVIATIONS

%	Percent
B- mode	Brightness mode
C	Celsius
C2	Second cervical vertebra
CLBP	Chronic low back pain
CSA	Cross-sectional
E	Young's modulus
Eg	Example
FJD	Facet joint degeneration
FT	Facet Tropism
G	Shear elastic modulus
HIZ	High intensity zone
ICC	Intraclass correlation coefficient
IVD	Intervertebral disc degeneration
L1	First lumbar vertebra
L2	Second lumbar vertebra
L3	Third lumbar vertebra
L4	Fourth lumbar vertebra
L5	Fifth lumbar vertebra
LBP	Low back pain
LMM	Lumbar multifidus muscle
MC	Modic changes
MCE	Motor control exercise
MHz	Megahertz

MRI	Magnetic resonance imaging
p	Significant level
r	Correlation value
R^2	Coefficient of determination
S1	First sacral vertebra
SN	Schmorl's nodes
ρ	Spearman rho correlation
SSI	Supersonic shear imaging
T1	Longitudinal relaxation time
T2	Transverse relaxation time
μ	Shear modulus
USI	Ultrasound imaging
v	Shear wave speed
ρ	Muscle mass density

Chapter 1. INTRODUCTION

Low back pain (LBP) is the leading cause of disability globally, affecting around 80% of people at least once in their lifetime [1, 2]. Due to the high prevalence, the cost of LBP is expected to increase enormously in the future [2]. The high prevalence of LBP is associated with high medical expenses. The estimated direct and indirect cost of LBP is around US$90 billion annually in USA alone [3]. Similarly, the annual cost of chronic LBP in Japan is $10 billion [4].

Although LBP is prevalent, the causes of LBP are largely unknown [5]. Approximately 90% of people with LBP do not have a definitive diagnosis and are labelled as non-specific LBP [5]. While the pain symptoms of most people with LBP resolve spontaneously within the first two weeks, up to 20% of people with LBP may experience persistent pain and are diagnosed with chronic LBP [5]. Importantly, many people with chronic LBP experience both physical and psychological problems, which impose the greatest medical and socioeconomic burden to the society [3, 5].

While the causes of LBP remain largely unknown [5], it is believed that many causes of LBP are related to altered spinal biomechanics [6]. According to Panjabi, the spine is an unstable structure that relies on passive, active and neural subsystems to maintain its stability [7]. The passive subsystem includes many passive structures (e.g., osteoligamentous tissues, vertebrae, intervertebral discs), while the active subsystem mainly includes muscles [8]. The neural subsystem comprises the nervous system that controls and coordinates muscle contraction to maintain spinal stability. The malfunction of any of the three subsystems will greatly compromise the spinal stability and lead to aberrant spinal biomechanics, which may lead to LBP if the malfunction persists [7, 8].

Some preliminary results have substantiated those changes in passive structures are related to LBP. Multiple studies have suggested the presence of intervertebral disc (IVD) degeneration [9], facet joint degeneration [10], Modic changes [11], endplate disruption are related to LBP. Although some evidence supports the correlation between passive structural changes and LBP, the presence of such changes may not necessarily be related to clinical LBP. One systematic review of 33 studies including 3310 patients reported that the prevalence of disc bulge as seen on MRI among asymptomatic people is 30% for people in 20 years old, 60% for people over 50 years old, and 84% for people over 80 years old [12].

In addition to the presence of passive structural changes and LBP, recent research has suggested that degeneration and decreased control of lumbar multifidus muscle (LMM) may be related to LBP [13]. Lumbar multifidus is the deepest paraspinal muscle that is deemed to be the major spinal stabilizer. This muscle comprises both superficial and deep fibres running diagonally from posterior surface of the sacrum, posterior superior iliac spine, mamillary processes of lumbar vertebrae, sacroiliac ligaments and aponeurosis of erector spinae to spinous processes of vertebrae located two to four segments superior to the origin [14]. The superficial muscle fibres span three joint levels, while deep fibres of multifidus only connect two adjacent segments. In an in vitro study Wilke et al [15] estimated that LMM provides approximately two-thirds of lumbar spinal stability due to its high proportion of type 1 fibers, short muscle fibers and close proximity to spinous processes. People with LBP have been reported to be characterized by degenerative changes (i.e., increased intramuscular fatty infiltration) in LMM [16]. People with acute or chronic LBP also demonstrate morphometric [e.g., decreased cross-sectional area (CSA) [17, 18] and resting muscle thickness] as measured by ultrasonography [19], and increased fatty infiltration in magnetic resonance images [20, 21] and functional changes (e.g., decreased percentage thickness change during

contraction) as measured by ultrasonography [19, 22], altered proprioception [23] and increased muscle stiffness [24] in LMM.

While multiple cross-sectional studies have reported the presence of single morphological or functional change in LMM in people with LBP [19, 25, 26], there is a paucity of research to investigate if one or more baseline or changes in morphology or functional changes are related to future LBP [27, 28]. One cross-sectional study involving 401 individuals, using magnetic resonance imaging (MRI) found a significant positive association between fatty infiltration of LMM and LBP among people at 40 years old, but not in people aged between 45 and 49 years.[25] Additionally, the presence of fatty infiltration did not predict future development of LBP at the 4- and 9-year follow-ups. However, this study did not account for psychosocial factors and the method used to quantify fatty infiltration differed from other studies. Another study using ultrasound imaging found that 17 people with LBP displayed a smaller CSA and percent thickness contraction in LMM as compared to 17 asymptomatic controls [26]. However, this study was limited by the small sample size.

Although it is generally believed that morphometry changes in LMM (e.g., increased fatty infiltration) indicate altered muscle function (e.g., poorer muscle contraction), this hypothesis has never been tested. Similarly, if the presence of LMM atrophy indicates a dysfunction in LMM for maintaining spinal stability, the passive spinal structures adjacent to the atrophied LMM should be more likely to display degenerative changes. While recent research involving 16 males and 19 females with chronic LBP showed that there was a small correlation between LMM fatty infiltration and disc degeneration [29], the study was limited by small sample size. Likewise, a recent cross-sectional study demonstrated that increased fatty infiltration of LMM and erector spinae were related to severe lumbar IVD degeneration [30]. However, the causal relationship between paraspinal muscle morphometric change and

disc degeneration remains unclear. In addition, psychosocial features can contribute to the pain experience.

In the Mature Organism Model, Louis Gifford explains how the brain, body tissues, and external environment interact to elicit pain responses in the human body. According to Gifford's model, the brain functions as a 'scrutinizing center'. The brain evaluates the 'signal' provided by the body's tissues. Brain modulation is influenced by environmental factors, pain beliefs, and past experiences. In this situation, fear of pain or further damage can sensitize the brain and increase the perception of pain. Once the pain is modulated, the brain chooses an action or 'output', which can be altered physiology or altered behaviour [31]. Furthermore, according to The Common Sense Model for pain, the theory holds that how individuals perceive their illness/pain impacts their attempts to cope with it, thereby affecting their health outcomes, such as their functioning level, psychological distress and sense of well-being. According to The Common Sense Model for pain, the theory holds that how individuals perceive their illness/pain impacts their attempts to cope with it, thereby affecting their health outcomes, such as their functioning level, psychological distress and sense of well-being [32]. As indicated by The Common Sense Model, cognitive illness is represented by five dimensions: 1) identity- consists about the belief how the condition is identified, which experiences are manifestations of the illness and which ones are not, along with how those experiences are labelled; 2) timeline - consists about beliefs related to the duration of illness/pain, when it started and when it will end; 3) consequences - consists about beliefs regarding the impact of illness/pain on the life; 4) cause – consists about beliefs regarding the reasons why the illness/pain developed and how its symptoms manifested; 5) control- consists about a person's perception of how much he/she can manage/control the illness/pain and its symptoms, and representations of how that can be done [32]. Studies have shown that psychological factors e.g., anxiety, depression, pain catastrophizing, fear-avoidance beliefs,

etc are related to pain intensity and disability in people with CLBP [33-38]. Additionally, insomnia has been reported in people with CLBP [39]. To date, no study has investigated the correlation among all the changes in LMM morphology, function, MRI phenotypes and psychological factors and pain intensity and/disability in people with CLBP.

1.2 DISSERTATION OBJECTIVES

Given the above, the proposed project aims to determine: (1) the interrelations among morphological, mechanical and functional characteristics of LMM; (2) whether baseline LMM characteristics can predict future LBP intensity after accounting for other confounding factors; and (3) whether temporal changes in some LMM characteristics are associated with the respective LBP outcomes after accounting for various spinal degenerative features and psychosocial confounders.

This Dissertation includes 8 chapters. the contents of Chapter 3, 4 and 5 have been published in separate peer-review journals.

Chapter 2 presents literature review on the anatomy of LMM, various technologies for quantifying morphometry, mechanical properties and functions of LMM.

Chapter 3 is a systematic review to summarize evidence regarding whether morphometry of LMM can be altered by motor control exercises and whether improved morphometry of LMM is related to the improved LBP symptoms or LBP-related disability.

Chapter 4 presents the differences in proprioception between people with and without CLBP.

Chapter 5 presents whether baseline morphometric and biomechanical characteristics of LMM are related to pain intensity/disability in people with chronic low back pain after considering psychological factors or insomnia.

Chapter 6 presents whether baseline LMM characteristics, and spinal phenotypes differ between people with and without CLBP and the interrelationships between fear-avoidance

beliefs, insomnia, LMM parameters or other spinal phenotypes and pain intensity/disability) in people with CLBP.

Chapter 7 presents whether baseline LMM characteristics can predict future LBP intensity/disability in people with CLBP after controlling for baseline spinal phenotypes, psychological factors and insomnia.

Chapter 8 provides an integrated discussion and conclusion.

Chapter 2. LITERATURE REVIEW

In this chapter, it will cover some basic information regarding the lumbar multifidus muscles (LMM), the changes in back muscle function (e.g., contraction, proprioception, and reposition sense) in people with LBP. various technologies in quantifying the morphometry of LMM, and grading methods for various MRI phenotypes.

2.1 Lumbar multifidus

2.1.1 Anatomy and function of lumbar multifidus

Multifidus muscle is a thin and long series of muscles that runs deep through the entire spine from sacrum to second cervical vertebra (C2) (Figure 2.1) [14]. It comprises two layers (superficial and deep) of muscles attaching to either sides of the spine and is the thickest at the lumbar spine [40]. Multifidus muscle originates from the posterior surface of the sacrum, posterior superior iliac spine, mammillary processes of lumbar vertebrae, transverse processes of the thoracic vertebrae and articular processes of the cervical vertebrae from C4-C7 and inserts at the spinous processes of the vertebrae located two-four segments above the origin [14]. Multifidus muscles at the lumbar region between first lumbar vertebra (L1) and first sacrum vertebra (S1) levels are named LMM (Figure 2.2).

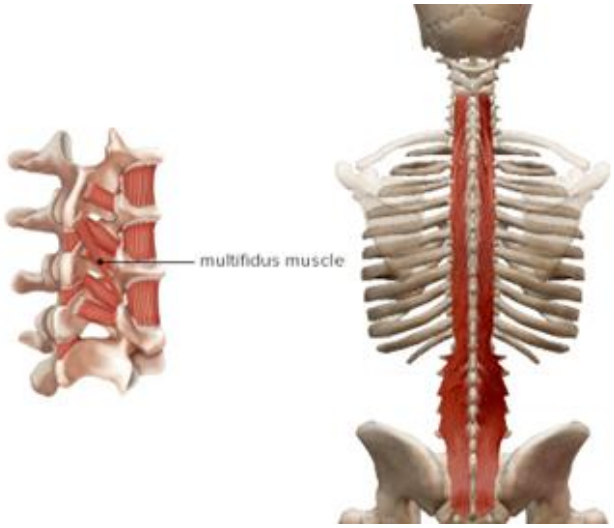

Figure 2. 1 Anatomy of Multifidus [Foundationalconcepts.com]

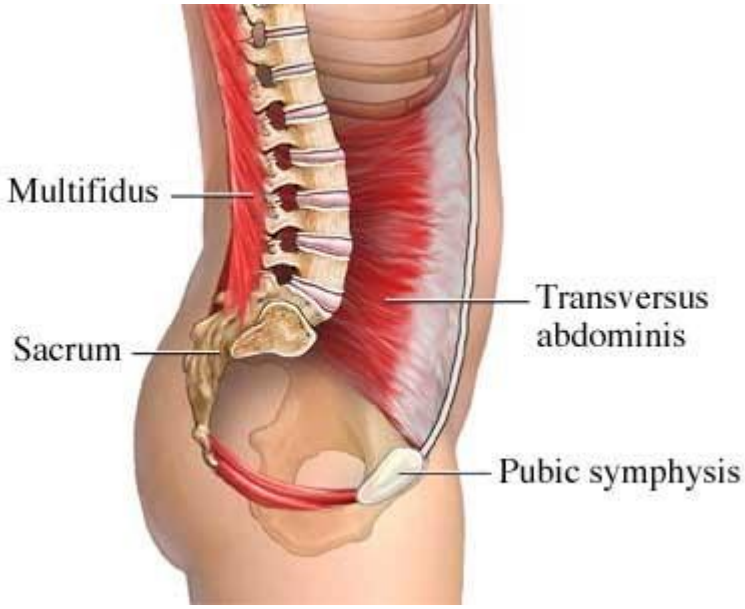

Figure 2. 2 Lumbar Multifidus Muscle [Foundationalconcepts.com]

The functions of LMM are related to its structural properties. Human studies have reported that when LMM are recruited bilaterally, they cause extension of the lumbar spine. When they are recruited unilaterally, they laterally flex and contralaterally rotate the spine [14]. Although LMM contains both type I (slow twitch and fatigue-resistant muscle) and type II (fast twitch and less fatigue-resistant) muscle fibres [41], approximately 62% of muscle fibres in LMM are type I muscle fibres [42]. The presence of a high proportion of type I fibres in LMM support its role as an anti-gravity muscle to contract for a prolonged period without fatigue. Further, as LMM has large cross-sectional area (CSA) and short muscle fibres along the lumbar spine [43], it provides good intersegmental control and stability.

While the most important function of the LMM is thought to provide intersegmental control of the spine, control lumbar lordosis and withstand the compressive loading of the lumbar spine [40, 44], it has been reported that muscle spindles in the LMM provides proprioception of the lower back [44, 45]. The loss of proprioception has been reported to be associated with LBP [46, 47]. O'Sullivan et al reported that compared to a control group, people with lumbar segmental instability had deficiency in lumbar proprioception awareness [48].

2.1.2 Morphological characteristics of lumbar multifidus in people with low back pain (LBP)

LMM is more prone to degenerative changes compared with other paraspinal muscles in people with LBP.[16] Histologically, LMM in people with LBP is characterized by moth-eaten appearance in type I fibres and atrophy of type II muscle fibres [49]. Some studies have demonstrated reduction in type I and type II fibres on the affected sides as compared to the unaffected side [50]. However, contradictory findings have also been reported in some studies [51, 52]. For instance, Mattila et al [51] reported that no significant atrophy of type II muscle fibres between 41 people with IVD degeneration and 12 asymptomatic controls. Mannion et al [52] found that compared to 21 asymptomatic controls, 21 people with LBP

had higher proportion of type II fibres. However, these two studies were limited by small sample sizes.

Morphologically, degenerative changes in LMM can be seen on MRI and computed tomography (CT) scans as the reduction in CSA/atrophy of LMM and increased intramuscular fatty infiltration (i.e., replacement of muscle tissue with fat). Multiple studies have reported decreases in LMM CSA [17, 18, 53] and increases in fatty infiltration of LMM in people with LBP as compared to asymptomatic individuals.[20, 54] A systematic review also concluded that there was moderate evidence to support the atrophy of LMM in people with chronic LBP.[55] Specifically, while people with chronic LBP have 23.6% mean fat in LMM, whereas healthy individuals only have 14.5% of fat in LMM.[21]

2.1.3 Percentage thickness change

In addition to CSA, people with LBP display decreased percentage thickness change during contraction as compared to asymptomatic controls [26, 56] Muscle thickness change can be treated as a surrogate for muscle contraction. A stronger muscle contraction is associated with a greater muscle thickness change. An experimental pain study reported that LMM contraction was reduced in the presence of induced pain after hypertonic saline injection [57]. Percentage thickness change is usually measured by ultrasonography and is calculated as (contracted thickness - resting thickness)/resting thickness x 100% [58]. Likewise, another study with 34 people with and without LBP reported that the percentage thickness people with LBP was smaller than people without LBP [26]. Conversely, compared with 10 asymptomatic individuals, people with chronic LBP (n = 10) demonstrated a higher percentage thickness of LMM only at L5/S1 level but not at L4/L5 level, in standing during activation with a contralateral arm lift. Interestingly, there was no significant difference in percentage thickness change at rest, in prone and standing position, and during contralateral arm lift in prone position [56].

2.2 Reposition Sense

In addition to altered morphometry and muscle activity in LMM, people with LBP have been reported to have poorer trunk reposition sense as compared to asymptomatic individuals [59]. Reposition sense is commonly evaluated by testing lumbar repositioning accuracy to a destinated position in sitting [60], 4-point kneeling [61], and in standing [47, 62]. Some studies have reported that the lumbar repositioning accuracy was lower in people experiencing LBP than asymptomatic individuals [45, 47, 59, 62]. However, research also reported that there was no significant difference in repositioning error between people with chronic LBP and asymptomatic controls [60]. The discrepancy might be attributed to different testing methods (e.g., testing positions) and sample sizes in these studies. For instance, Gill and Callaghan [47] tested the reposition sense of 20 people with and 20 without LBP in standing and 4-point kneeling, while another study tested reposition sense in sitting.[60] Newcomer tested the trunk reposition sense of 20 people with and 20 without LBP in standing, with legs and pelvis being immobilized by a strap, which might confound the results by increasing the sensory inputs from legs and pelvis [62].

2.3 Proprioception

Apart from altered reposition sense, previous research has also suggested that people experiencing LBP display altered trunk proprioception. Proprioception is the awareness of the position and movement of the body parts, facilitated by receptors from skin, tendons, ligaments, joint capsules and muscle spindles [63]. Since proper proprioception is need for accurate trunk reposition ability, proprioceptive is commonly tested by measuring the reposition error [60]. However, the accuracy of a repositioning test relies on the concentration, attention, proprioception, and memory of an individual. Therefore, another assessment has been used to evaluate trunk proprioception.

In order to test the trunk proprioception of an individual, researchers have used a muscle vibrator to test the proprioception reweighting ability of an individual. In particular, muscle vibrators are placed at the bilateral L5/S1 LMM and bilateral triceps surae muscles. Vibrations to a muscle will create an illusion of muscle elongation. For example, vibrations to bilateral triceps surae muscles in standing will create an illusion that the body lean forward. Therefore, the individual will lean backward to prevent falling forward. Conversely, when vibration is given to bilateral LMM in standing, it will create an illusion of posterior pelvic tilt. Therefore, a person will lean forward to counterbalance the posterior pelvic tilt. By measuring the relative displacement of the body before and after vibrations to LMM and triceps surae, the relative reliance of proprioception sense of LMM or calves for balance can be estimated.

2.3.1. Proprioception and LBP

People with LBP display impaired lumbar proprioception compared with healthy people [64-67]. Compared to asymptomatic individuals, both young and older people with LBP show difficulty in reweighting proprioceptive signals from LMM and calf muscles for standing balance control when these muscles were vibrated [23].

Theoretically, muscle vibration would induce an illusion of muscle elongation. If a person relied on a particular muscle for balance control, vibration to that muscle would lead to greater body sway. Brumagne et al [23] found that both young and old people with LBP relied more on triceps surae than lumbar multifidus for balance control as compared to young asymptomatic individuals. These findings indicate that LBP and age may affect the accuracy of trunk proprioception, which leads to a shift in increased reliance on ankle proprioception for balance control. However, this study was limited by small sample size (20 young and 20 older people with and without LBP).

A prospective study involving 104 young students with and without LBP with a mean age of 19 years found that an increased reliance on triceps surae proprioception rather than paraspinal muscle proprioception for standing balance on a stable surface at baseline predicted an increased risk of developing LBP in the next two years [68]. However, since this study only recruited young university students, it remains unclear if trunk proprioception deficits in asymptomatic middle-aged people would predict LBP episodes in the future.

Although prior research has suggested that young people with LBP displayed altered proprioception, it remains unclear if similar deficits in trunk proprioception exist in older people with CLBP, which may help identify high risk people for personalized care. Further, while LMM may play an important role in trunk proprioception and people with CLBP are usually characterized by specific morphological changes, no studies have explored if altered LMM morphology, proprioception deficits and LBP are interrelated in people with CLBP.

2.4 Technologies in measuring morphometry of LMM

Multiple non-invasive imaging methods have been used to measure the morphometry/biomechanical properties of LMM. Some of them measure the active movement of muscles (e.g., brightness-mode ultrasonography), while others measure the stiffness (e.g., shear-wave elastography) or structures of LMM (e.g., MRI).

2.4.1 Ultrasound Imaging

Ultrasound is defined as sound with a frequency higher than 20,000Hz. Brightness-mode (B-mode) ultrasound imaging is widely used to assess the morphometric characteristics (CSA and dimensions) of a muscle, whereas shear-wave elastography is used to measure muscle stiffness [69, 70].

2.4.1.1 B- Mode Ultrasound Imaging (USI)

In B-mode USI, the frequency of 3.5 to15MHz is used [70]. An ultrasound wave is produced when an electric current is sent to an ultrasound probe which passes through multiple crystals

which are located in the probe. When these ultrasound waves penetrate a biological tissue, they are either absorbed, reflected or scattered. The image is formed based on the location of the reflected sound waves on the transducer, the time required for the reflection of waves and its amplitude [70]. On an ultrasound image, structures containing more fluid appear as black while those with less/no fluid appear as white, and are termed as hypoechoic (e.g., muscle) or hyperechoic (e.g., bone) respectively [70]. B-mode USI has been used to measure different trunk muscles in various populations (e.g., firefighters, soldiers, dancers, ice hockey players, people with LBP) [18, 26, 71-73]. It has also been used to investigate the effects of various interventions on trunk muscle morphometry in people with LBP [74-76]. B-mode USI is a non-invasive method to estimate muscle activation [77]. Good to excellent intra- (Interclass correlation coefficient (ICC) = 0.86–0.93) and inter-examiner (ICC = 0.86–0.90) reliability has been reported for B-mode USI in assessing resting/contracted thickness and percent thickness change in LMM [78]. Additionally, B-mode USI has shown a significant correlation (r=0.79) with electromyography for evaluating up to 30% maximum voluntary contraction of LMM [77]. There are multiple advantages to use B-mode USI. First, it is non-invasive and less expensive. Second, it can capture images or videos within a short period of time. Therefore, it allows the selection of multiple images to improve reliability [79]. Third, LMM thickness is relatively easy to measure on an ultrasound image given the clear visibility of LMM border and facet joints [80]. Nevertheless, the reliability of using USI depends on the quality of images being selected for offline measurements and the experience of the operator.

2.4.1.2 Ultrasound elastography

Ultrasound elastography is a non-invasive technique used to measure mechanical properties of tissue [70]. It evaluates the deformation of tissue caused by the external or internal force [69]. Ultrasound elastography techniques can be classified into strain imaging and shear-

wave imaging methods based on the type and method of force used to cause the deformation of tissue [70]. In the strain imaging, the tissue displacement is measured when a mechanical force is applied externally or internally, whereas shear-wave imaging uses an acoustic radiation force to generate a shear-wave (deformation of tissue) to a tissue [81]. The usage of shear-wave elastography has increased in the past decade to quantitatively measure elasticity of tissue [81].

Strain imaging is used to detect pathology in the tissue by qualitatively comparing the strain in the different regions of the same tissue [69]. It is mainly used to detect lesions in breast, thyroid, liver or prostate gland pathology [69]. Its application is mainly restricted to tissues where uniform compression can be applied and it measures relative elasticity [82]. However, as it depends on the magnitude of operator's applied compression, artefacts may produce on an image [82]. That said, strain imaging has the advantages that compression application does not require additional equipment and it has no risk of tissue heating.

Shear wave imaging on the other hand quantitatively measures elasticity of the tissue [83]. It not only identifies the site of pathology but also helps classify the type of pathology [83]. Apart from versatile application to quantify elasticity of cornea, brain, myocardium, arteries, breast, prostate, liver and thyroid gland, shear imaging can also be used to evaluate muscles by measuring load dependent, passive elasticity and changes in elasticity of a healing muscle [82]. Additionally, shear wave imaging is better than strain imaging it causes minimal defraction and attenuation of image signals. However, tissue heating may be a concern [84]. In particular, if the ultrasound probe was put on the skin for 0.1, 1 and 5 seconds, the skin temperature would increase by 18.3°C, 14.9°C, and 12.6°C, respectively, although no adverse effects have been reported.

Supersonic shear imaging (SSI) is one of the shear-wave elastography techniques which can provide 2-Dimensional image [82]. The SSI produces multiple consecutive ultrasound push beams which are transmitted in a sequence at different depths of the tissue. These push beams interfere to produce quasi-planar shear wave with a high frame frequency of 5000-6000 frames/second enabling to capture the propagation of shear wave [85]. Shear elastic modulus or Young's modulus are used to report the elasticity [86]. Since muscles are not isotropic in nature and Young's modulus calculation requires the assumption of isotropic material which cannot be fulfilled by a muscle [87]. Therefore, shear elastic modulus is the most preferred measure to report the muscle elasticity/stiffness. The shear elastic modulus can be calculated as follows:

$$E=3G=3\rho v^2$$

E is Young's modulus, G is shear elastic modulus, v is the shear wave speed and p is the muscle mass density. The shear wave speed is directly proportional to Young's modulus or shear elastic modulus, in short, higher shear elastic modulus signifies higher stiffness. SSI is a valid tool to quantitively evaluate the stiffness of the muscle not only at rest [88] but also during contraction [89]. Shear elastic modulus is correlated with the muscle activity/function, where higher shear elastic modulus represents higher muscle activity [90]. Excellent intra- (ICC=0.99) and inter-observer (ICC=0.95) reliability have been reported for using SSI to quantify the elasticity of LMM at rest and during contraction in asymptomatic individuals [91]. Masaki et al [92] reported that LMM stiffness was higher in 9 people with LBP as compared to 23 asymptomatic controls. However, Chan et al [93] found that while there was no significant difference in LMM stiffness between 12 people with and 12 without LBP in prone position (at rest), the between-group difference in LMM stiffness was significant when the stiffness was tested in other functional positions (e.g., 25º and 45º forward-stooping postures). However, these two studies were limited by small sample sizes. A recent large-

scale study found that only resting LMM stiffness (p= 0.04) but not contracted stiffness (p=0.50) was greater in 60 people with LBP as compared to 60 asymptomatic controls [24].

2.4.2 Magnetic Resonance Imaging Phenotypes

Magnetic resonance imaging (MRI) is one of the preferred imaging modalities as compared to plain radiographs because MRI is more sensitive in identifying the causes and/or structural abnormalities in people with LBP [94]. Although MRI are not recommended as a routine imaging method for people experiencing LBP because of the risk of finding false positive features,[95] it is valuable for exploring underlying problems in people with LBP in clinical research. Various lumbar MRI phenotypes (pathoanatomical and degenerative changes of the vertebral column and intervertebral discs) such as IVD degeneration, Modic changes, Schmorl's node, high-intensity zones (HIZs), facet joint degeneration and facet tropism have been attributed as causative factors for LBP [96-98]. Phenotype is defined as 'The observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment' [99].

2.4.2.1 Intervertebral disc degeneration

Lumbar IVD degenerative changes can be identified as disc herniation or disc bulge on MRI using Pfirrmann [100] or Schneiderman [101] classification. Pfirrmann's classification uses the T2-weighted sagittal MR images to estimate the signal intensity, homogeneity of disc, height of the disc, difference in the signal intensity between nucleus pulposus and annulus fibrosus on a scale from I to V (Appendix 2.1) [100]. Good to excellent intra- (0.84–0.90) and inter-observer (0.69–0.81) reliability have been reported for this classification [100]. Although Pfirrmann's classification is the most widely used grading method [102], it has a few limitations. First, the changes in signal intensity in the disc structure might be affected

due to MRI T2 processing. Second, the grading is subjective and can cause interobserver bias by underestimating or overestimating the grading [103]. Third, it cannot detect early degenerative changes.

The prevalence of lumbar disc herniation in people with LBP is 46,2% while in general population is 11.9% [104]. Studies have demonstrated a strong association between IVD degeneration and LBP [105-107]. A cross-sectional study by Livshits et al on 2,556 women (mean age of 50 years) concluded that IVD degeneration and overweight were positively correlated with LBP. However, since this study only recruited female participants, the findings could not be generalizable to the general population aged below 50 years and men [105].

2.4.2.2 Modic changes

Modic changes is defined as the changes of the vertebral endplates and can be identified as changes in the signal intensity as hypo-intense or hyper-intense signals on the endplates and vertebral bone marrow on T1 and T2 weighted MRI (Appendix 2.2) [108]. There is a high incidence of these changes in the lumbar spine regardless of the vertebral level, but most often at L4/5 and L5/S1. The point prevalence rates of Modic changes ranged from 18% to 62% in people with LBP [109, 110], while 3% to 10% in people without LBP[111]. There are three types of Modic changes type 1,2 and 3. In type 1, images appear as high signal intensity on T2 while low signal intensity on T1. Fibrovascular changes in the subchondral marrow are noted. In type 2, images appear as high signal intensity on T1 and T2 and the bone is replaced with fat. In type 3, images appear as low signal intensity on T1 and T2 and the bone is replaced with subchondral sclerosis [112, 113]. Compared to type 2, type 1 Modic change has demonstrated a significantly stronger association with LBP [114, 115]. The possible causes of Modic changes are microfractures of endplate and anaerobic bacterial infection [116].

Numerous studies have shown a correlation between Modic changes and LBP [11, 117-119]. A prospective study by Luoma et al on 24 people with LBP reported that a large type 1 Modic lesion at baseline was correlated with an accelerated degenerative process in the disc space and vertebral endplates [120]. Although a cross-sectional study reported that Modic changes are associated with IVD degeneration and LBP [11], a systematic review and meta-analysis found inconsistent results regarding the association between Modic changes and LBP, which might be attributed to low-quality of the included studies and small sample sizes in the primary studies [121].

2.4.2.3 Schmorl's node

Schmorl's node is a vertebral lesion, in which the nucleus pulposus herniates into an adjacent vertebra though the vertebral endplates. The prevalence of presence of Schmorl's nodes in people with LBP is 42.7% and in people without LBP is 11.5% [122]. It is commonly seen in thoracolumbar spine on MRI [123]. The potential causes of Schmorl's nodes are trauma, unknown causes, neoplastic lesions [124], immunological problems, and endplate degeneration [125]. Williams et al reported a positive correlation between Schmorl's nodes and lumbar IVD degeneration. However, this study only involved asymptomatic twin females [126]. Similarly, a cross-sectional study reported that Schmorl's nodes might be an important risk factor for causing IVD degeneration and LBP [124]. A cross-sectional study by Abbas et al [127] also found significant correlations between the presence of Schmorl's nodes and age, smoking, vascular disease, and IVD degeneration. The common location of Schmorl's node varied between studies. One study reported that Schmorl's nodes mostly found at L2 and L3 endplates (mean age 40.4 years). Another study found most of the Schmorl's nodes appeared at L1 and L2 endplates (mean age 62.5 years). The diverse locations of Schmorl's nodes might be ascribed to difference in ages of the people.

2.4.2.4 High Intensity Zone

High-intensity zones (HIZs) are displayed as high-intensity areas of the posterior annulus fibrosus of the disc on T2-weighted MRI [97]. The HIZ is classified based on its location in the disc, shape and signal type. Shape types are round (round or concentric), fissure (parallel to the endplate), vertical (vertical to endplate), rim (oblique to endplate) and enlarged (large round cavity) while the location in the disc includes anterior and posterior (Appendix 2.3). Signal intensity types consists of T1-weighted low-intensity (hypo-intense signal than bone marrow), T1-weighted high-intensity (hyper-intense signal than bone marrow) and T1-weighted iso-intensity (same signal than bone marrow).

The point prevalence rates of HIZs ranged from 3% to 61% in people with LBP, while that of asymptomatic individuals ranged from 2 to 3% [98]. The incidence of LBP is higher when HIZ is presented at lower lumbar levels (e.g., L4/L5 and/or L5/S1) and involves multiple disc levels [128]. A systematic review concluded that HIZ might be a risk factor for LBP [98]. Wang et al [128] reported that among 623 people with LBP, HIZ was present in at least one disc in 200 people. Thirty-three people had HIZ at multiple disc levels, while 24 displayed HIZ in adjacent discs. Although the rate of LBP in people with HIZ was higher compared to people without HIZ, there was no correlation between spatial distribution of HIZ and LBP. Because the mean age of the recruited participants was 50 years, it remains unclear if these findings are applicable to people with LBP, or people who are younger or older than 50 years. Further, the sample size of participants with LBP was small. Liu et al [129] reported that the prevalence of HIZs in 72 people with LBP was 45.8%, while that of 79 asymptomatic controls was 20.2%. Compared with people without LBP, the mean signal of HIZs was significantly brighter in people with LBP. These studies used different grading methods.

2.4.2.5 Facet joint degeneration

As the cartilage in the facet joint degenerates due to external loading, the space between the two surfaces decreases and may result in the development of bone spurs, called osteophytes. Although facet joint degeneration is thought to be a normal aging process, it may sometime cause pain, stiffness and decreased range of motion in the spine [130]. The prevalence of facet joint degeneration in people with CLBP is 15 to 41% [131] and 35% [131]in asymptomatic individuals. Facet joint degeneration is the highest at L4/L5 and L5/S1 [130]. The severity of facet joint degeneration on MRI or CT images are usually graded by 4-point scale developed by Weishaupt et al (Appendix 2.4) [132]. The grading of degeneration is based on the facet joint space, hypertrophy of articular process, relative size of osteophytes, and subarticular bone erosions or subchondral cysts. The grades range from 0 to 3. A higher number indicates more severe degeneration [102]. Prior research has shown moderate to high inter-rater agreement on the grading [132]. In addition to osteophyte, facet joint tropism may also indicate abnormality of facet joint. Facet joint tropism is defined as an asymmetry between the orientation of left and right facet joint. Tropism is noted if the difference between the right and left facet joints angle on the coronal plane is equal to or greater than 8º [133]. The prevalence of Facet tropism in lumbar spine is 44.6% [134]in people with LBP and 46.3% [135]in community-based populations.

A cross-sectional study by Kalichman et al found no association between facet degeneration and LBP [10]. A recent study found that facet tropism at the L2/3 level is correlated with LBP [136]. Surprisingly, there was no correlation between facet tropism at the L3/4, L4/5 and L5/S1 and LBP [136]. While the negative results might be attributed to fact that facet joint degeneration is unrelated to LBP. However, it may be possible that different scales used different grading system to quantify facet joint degeneration. Further, since many studies did

not consider both facet joint degeneration and facet tropism simultaneously, they might have overlooked some facet joint degeneration or abnormality.

Chapter 3. Does motor control exercise restore normal morphology of lumbar multifidus muscle in people with low back pain? – A systematic review

3.1 INTRODUCTION

Low back pain (LBP), defined as pain or discomfort between the twelfth ribs and buttocks [137, 138], is the leading cause of disability worldwide [1]. It affects up to 84% of people at least once in their lifetime. The prevalence of LBP is anticipated to increase with an aging global population [2]. Since LBP can lead to tremendous medical burdens and work disability, the overall cost of LBP expected to increase over time [2]. Although LBP is ubiquitous, approximately 85% of LBP cases have unclear etiology [5]. Biomechanical research suggests that the occurrence/maintenance of LBP may be related to the suboptimal motor control of deep trunk muscles [139]. Specifically, lumbar multifidus muscle (LMM) is a major paraspinal muscle that provides intersegmental control of the spine [7, 40, 140] and withstands the compressive loading of the lumbar spine [141]. Therefore, structural/functional deficits of LMM may be related to the onset or maintenance of chronic LBP (CLBP).

Compared to asymptomatic individuals, some people with acute or CLBP demonstrate morphometric and/or functional changes in LMM (e.g., reduced cross-sectional area (CSA)

[17, 53, 54, 142, 143], increased intramuscular fatty infiltration [20, 21, 54, 144], decreased resting thickness [145], and percentage thickness changes during maximum voluntary isometric contraction [145] or contralateral arm lift) [146, 147]. However, no significant relation between CSA/fatty infiltration of LMM and LBP has also been reported [148]. Although LMM atrophy may be specific to the location and the side of symptoms [149], prolonged immobilization may also result in general LMM atrophy [141]. Given the close association between LMM and LBP, one rehabilitation approach is to improve the function and morphology of LMM. Of various physiotherapy interventions, motor control exercise (MCE) is thought to be able to restore LMM morphology and function in people with LBP [75, 138]. Multiple studies have investigated the effectiveness of MCE in restoring normal LMM morphometry [150, 151] or decreasing LBP among people with CLBP [74, 76, 152, 153]. Some found that MCE increased LMM sizes in these people [74, 138, 154]. Although a recent Cochrane review found low- to moderate-quality evidence to support MCE in inducing clinically meaningful pain reduction in people experiencing CLBP as compared to different kinds of controls including sham intervention and education [155], no review has summarized the effectiveness of MCE in concomitantly restoring LMM morphology and reducing LBP. Further, temporal relations between post-MCE changes in LMM morphology (changes induced by the treatment) and changes in pain intensity/LBP-related disability among people with LBP have not been summarized. Therefore, this systematic review aimed to summarize the evidence regarding: (1) the effectiveness of MCE in restoring normal LMM morphometry and decreasing LBP; and (2) whether the post-treatment changes in morphology were associated with changes in pain and/or function of people with LBP.

3.2 METHODS

3.2.1 Identification and selection

This review conforms to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines and is registered with PROSPERO (CRD42019120978).[156] A systematic search was conducted in CINAHL, MEDLINE, Cochrane Central Register of Controlled Trials, the Physiotherapy Evidence Database (PEDro), EMBASE and SPORTDiscus) from inception to 30 September 2020. Non-English publications were excluded. The search keywords and Medical Subject Headings included were related to LBP, lumbar multifidus, physiotherapy, or rehabilitation (Appendix 3.1). Studies were included if they: (1) were randomized controlled trials (RCTs); (2) involved people with LBP regardless of chronicity; and (3) compared effects of MCE with another intervention/control groups(s) on at least one morphological/morphometric change of LMM (e.g., CSA, resting/contracted thickness, percent thickness change during contraction, intramuscular fatty infiltration) (see Appendix 3.2 for details). Studies involving surgical interventions or cross-sectional comparisons between asymptomatic and symptomatic individuals, review articles, conference proceedings, theses, animal studies and grey literature were excluded. The reference lists of systematic reviews related to LMM morphology/morphometry were reviewed to identify relevant primary studies. The reference lists of the included studies were tracked backward, while forward citation tracing was performed using Web of Science. The corresponding authors of the included studies were contacted to identify additional relevant publications.

Two reviewers (SMP and SBB) independently screened the titles and abstracts based on the selection criteria. Potential full-text articles were retrieved and reviewed. Disagreements in the study inclusion at each stage were resolved by discussion. Any unresolved disagreements were decided by a third reviewer (AW). The inter-rater agreement at each screening stage was analyzed by Kappa coefficients (κ). The agreement was interpreted as none to slight

(κ=0.01-0.20), fair (κ=0.21-0.40), moderate (κ=0.41-0.60), good agreement (κ=0.61-0.80), or almost perfect (κ=0.81-1.00) [157].

3.2.2 Data extraction

The two reviewers independently extracted authors' names, year of publication, case definition, sample size, participants' characteristics, intervention details, outcome measures, measurement methods, attrition rate, and pre- and post-treatment results using a standardized extraction form. The primary outcome measures included LMM morphometry (e.g., resting, and contracted LMM thickness, percent thickness change during contraction, volume, CSA, and intramuscular fatty infiltration, etc.) and pain. The LMM morphometric data (e.g., CSA, volume, resting thickness, contracted thickness, percent thickness changes) at each lumber level on both sides were extracted from each included study, whenever possible. Percent thickness change was calculated from [(thickness contracted – thickness rest)/thickness rest x 100] [79]. Greater percent LMM thickness change during contraction as measured by ultrasonography was thought to be an indirect measure for LMM contraction [158, 159]. The LMM CSA was commonly used to estimate the muscle atrophy/weakness [160]. Increased muscle CSA signified muscle hypertrophy [161, 162]. Secondary outcome measures included correlations between changes in LMM morphology and LBP intensity/LBP-related disability.

3.2.3 Risk of bias assessment

The two reviewers (SMP and SBB) independently assessed the Risk of Bias (RoB) using the Cochrane collaboration RoB Tool (RoB 2.0) [163]. Any disagreements regarding the scores were resolved by the third reviewer (AW). Each item was scored as low, some concern, or high risk of bias according to the Cochrane handbook descriptions.

3.2.4 The GRADE approach

The two authors (SMP and SBB) independently assessed the quality of evidence of the primary outcomes using the GRADE as per GRADE handbook of grading quality of

evidence and strength of recommendations. The assessment was based on the study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations [164]. The quality of evidence was rated at four levels: high, moderate, low, and very low. GRADE was assessed using http://gradepro.org.

3.2.5 Data synthesis

A meta-analysis was planned to pool relevant data from the included studies. However, given the high clinical heterogeneity among studies (i.e., different muscle measurement methods, such as ultrasonography, computerized tomography (CT) or magnetic resonance imaging, and diverse treatments) a qualitative analysis was conducted.

Since some included studies did not report within- or between-group treatment effects, secondary-analyses were conducted using Review Manager (RevMan 5.3) to compare within- and between-group differences, as well as the corresponding mean differences (MD) and 95% confidence intervals (CI) in primary outcomes using methods (i.e., calculating mean change in each group by subtracting post-intervention mean from baseline mean or calculating mean differences between two groups using post-intervention measurements) recommended in the Cochrane handbook for Systematic Reviews of Intervention [165]. To facilitate the comparisons of LMM volume, CSA and pain intensity among studies, the measurement unit in cm^3, cm^2 and cm were converted into mm^3, mm^2 and mm, respectively. Minimal clinically important difference (MCID) for pain, which means the smallest change in pain that a patient considers clinically meaningful, was set at 20mm on visual analogue scale (VAS) [166]. Minimal detectable change at 95% confidence (MDC_{95}) was used to indicate the post-treatment change in scores that exceeded the measurement error (i.e., true change). For people with LBP, the MDC_{95} for LMM CSA, resting and contracted thickness were $100mm^2$ [167], 3.6mm [79], and 1.8mm [79], respectively. The MDC_{95} for percent thickness change during contraction was 15.7% [79].

3.3 RESULTS

3.3.1 Study selection

The search yielded 4,114 citations. Nine RCTs were included from 41 screened full-text articles (Figure 3.1). The 2 reviewers demonstrated good agreements in selecting relevant papers at the first (κ=0.68) and second stages of screening (κ=0.76) (Appendix 3.3).

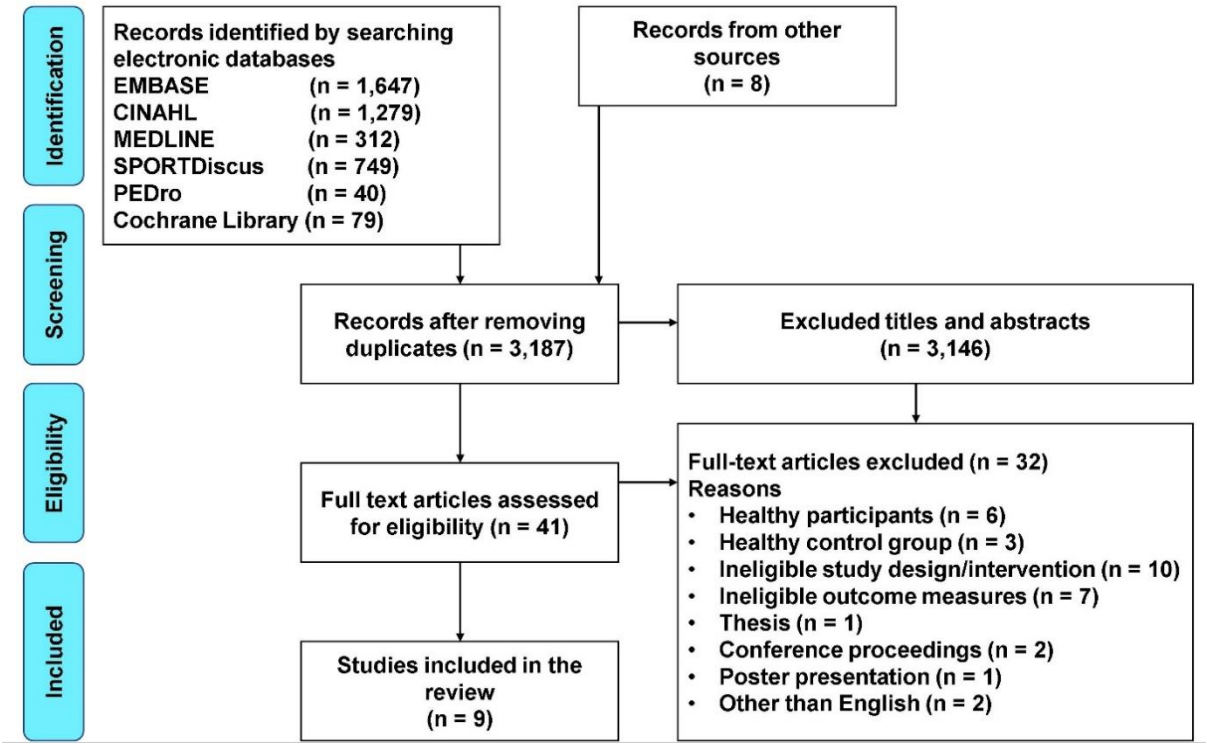

Figure 3. 1 A flow diagram of the literature search

3.3.2 Characteristics of the included studies

The 9 included RCTs were published between 1996 and 2020, involving 451 participants (410 chronic, 41 acute LBP). The mean ages of participants ranged from 31 [168] to 50.8 [169] years. The effectiveness of MCE (focusing on the activation of deep trunk muscles in different positions) [74-76, 138, 168-172] in restoring normal LMM morphology or decreasing LBP were compared with McKenzie exercise [76], general exercise [74, 138], general physiotherapy (e.g., transcutaneous electrical nerve stimulation (TENS), therapeutic ultrasound therapy, infra-red radiation, and traction) [138, 169-171], massage [169], high-load lifting exercise [75], general strengthening plus aerobic exercises[172] and analgesics,[168, 169] (Appendix 3.4). The number of MCE sessions ranged from 12 to 36. Table 3.1 summarizes the characteristics of these studies. These RCTs had either 2 [74-76, 138, 168, 171, 172], 3 [170], or 4 treatment arms.[169] Five studies involved a combination of one or two treatments with MCE in at least one arm [138, 168-170, 172] (e.g., MCE plus massage [169], MCE plus TENS [169], MCE plus general physiotherapy [138, 170], MCE plus manual therapy [172] and MCE plus analgesics [168, 169]).

Ultrasonography [74-76, 138, 168, 169], CT-scans [170, 171] or magnetic resonance imaging [172] were used to image LMM morphology in the included studies. Most studies measured bilateral CSA [138, 168, 172], resting thickness [74-76, 138], and contracted thickness [76, 169] from ultrasound and magnetic resonance images. Other studies measured CSA from CT images [170, 171]. Although the current study aimed to extract morphometric data from each vertebral level, only one included study reported the CSA of LMM from each of the 5 lumbar

levels (L1 to L5) [172]. Similarly, only 1 included study reported the LMM volume of each lumbar level from L1 to L5 [172]. Although LMM morphometry on the painful side might differ from non-painful side [26, 54], most of the included studies did not specify the side of measurements. These studies reported the post-treatment morphometric changes in LMM in terms of percentage or actual dimensions. Given the diverse treatment combinations and LMM morphometry measurement methods in the included studies, the planned meta-analysis was not conducted.

Table 3. 1 Characteristics of included studies.

Publications	Case definition	Age (mean ± SD); sample/Sex	Treatment (Frequency, duration, and duration/session)	Outcome measures	LMM parameters	Measurement Method	Measurement time points
Akbari et al, 2008 [74]	Chronic LBP >3 months	MCE: 39.6 ± 3.5 yrs; n = 25 GE: 40 ± 3.6 yrs; n = 24	8 wks, 2x/wk, 30 mins	Pain VAS BPS.	LMM resting thickness (L4-5)	USG	Baseline, 8 wks
Berglund et al, 2017 [75]	Chronic LBP >3 months	MCE: 43.3 ± 10.3 yrs; M/F = 13/20 HLL: 42.3 ± 9.8 yrs; M/F = 15/17	12 sessions over 2 months.	Pain VAS	LMM resting thickness on both sides of L5 vertebra	USG	Baseline, 2 months
Hides et al, 1996 [168]	Acute LBP <3 weeks	MCE + analgesics: 30.9 ± 6.5 yrs; M/F = 8/13. Analgesics: 31 ± 7.9 yrs; M/F = 10/10	4 wks and 10 wk	MPQ; pain VAS; daily pain diaries. RMDQ; lumbar ROM; habitual activity levels	LMM CSA (L2 to S1)	USG	Baseline, 1, 2, 3, 4 and 10 wks
Hosseinifar et al, 2013 [76]	Chronic LBP >3 months	MCE: 40.1 ± 10.8 yrs; n = 15 McKenzie: 36.6 ± 8.2 yrs; n = 15	6wks, 3x/wk, 60 mins	Pain VAS; FRIQ	Rt & Lt LMM resting & contracted thickness (L4-5)	USG	Baseline, 6 wks
Kehinde et al, 2014 [169]	Chronic LBP (Unclear definition)	MCE: 45.84 ± 9.95 yrs; n = 31 MCE + TENS: 45.84 ± 9.95 yrs; n = 31 MCE + massage: 44.57 ± 11.82	8 wks, 2x/wk		LMM contracted thickness (L4-5)	USG	Baseline, 8 wks

		yrs; n = 30 Analgesics: 50.83 ± 13.03 yrs; n = 30					
Kim and Kim, 2013 [170]	Chronic LBP 3 months	GPT: 39.6 ± 6.2yrs; n = 10 GPT + MCE using sling: 39.9 ± 5.8 yrs; n = 10 GPT + MCE using sling + pushups: 40.5 ± 5.4 yrs; n = 10	6 wks,3x/wk,30 minutes.	ODI, surface electromyo graphic	LMM CSA on both sides (level was not reported)	CT	Baseline, 2,4, and 6 wks
Lee et al, 2011 [171]	Chronic LBP (Unclear definition)	MCE with a gymnastic ball: 32.7 ± 5.9 yrs; n = 17 GPT: 33.1 ± 5.7 yrs; n = 16	12 wks, 3x/wk, 45 mins	Pain VAS	LMM CSA (L4-5)	CT	Baseline,12 wks
Nabavi et al, 2018 [138]	Chronic LBP >12 weeks	MCE + GPT: 40.8 ± 8.2 yrs; n = 20 GE + GPT: 34.1 ± 10.8 yrs; n = 21 Noted: GPT = US, TENS, IRR	4wks, 3x/wk	Pain VAS	LMM resting thickness. (Rt & Lt) at L5 LMM CSA (Rt& Lt) at L5	USG	Baseline, 4 wks
Tagliaferri et al, 2020 [172]	Chronic LBP >3 months	MCE + Manual therapy: 34.6 ± 7.2 yrs; n = 20 GSA: 34.8 ± 4.9 yrs; n = 20	MCE + Manual therapy: 1-3 months, 10 sessions, 30 mins;4-6 months, 2x30 mins session GSA: 1-3 months,2x/wk, 60 mins 4-6 months, 1-2x/wk, 60 mins. 1-6	Pain VAS, ODI, SF-36, isometric trunk extension, isometric trunk flexion, 1-RM leg press, leg press endurance,	LMM volume (L1-L5)	MRI	Baseline, 3 months, and 6 months

		months,3x/wk, 20-40min	peak oxygen consumption

Abbreviations: BPS, back performance scale; CSA, cross-sectional area; CT, computed tomography; FRIQ, functional rating index questionnaire; GE, general exercises; GPT, general physiotherapy; GSA, general strengthening and aerobic exercises; HLL, high load lifting; IRR, infrared radiation; LBP, low back pain; LMM, lumbar multifidus muscle; Lt, left; MCE, motor control exercise; M/F, male/female; mins, minutes; MPQ, McGill pain questionnaire; MRI, magnetic resonance imaging ODI, Oswestry disability index; RMDQ, Roland Morris Disability questionnaire; ROM, range of motion; Rt, right; SF-36, 36-Item short-form health survey, US, ultrasound therapy; USG, ultrasonography; VAS, visual analogue scale; wk, weeks; x/wk, times per week; yrs, years; 1-RM, one-repetition maximum

3.3.3 Risk of bias

Risk of bias assessment for individual trials is presented in Figure 3.2. Nine studies [74-76, 138, 150, 168-170, 172] were considered to have a high risk of bias.

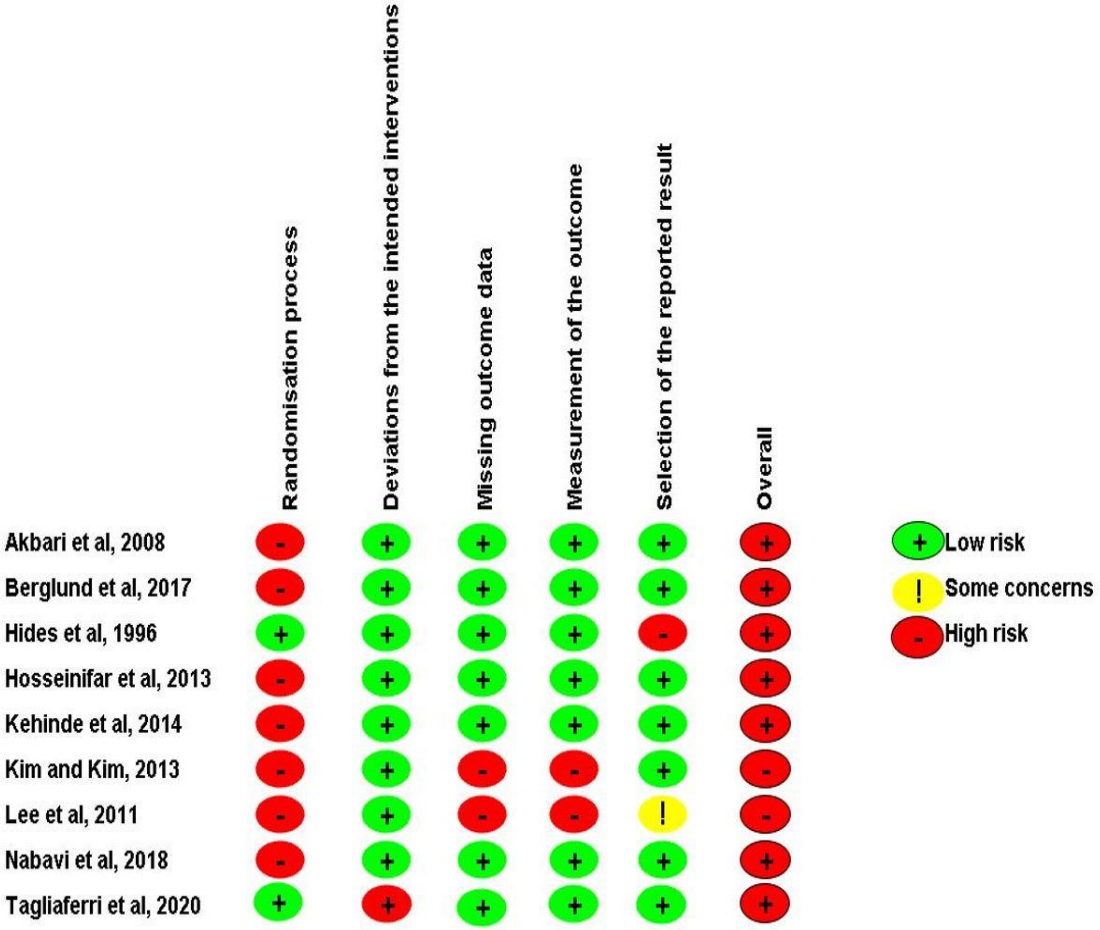

Figure 3. 2 Risk of bias assessment according to Cochrane Collaboration's tool (RoB 2.0) for randomized controlled trial.

3.3.4 Effects of MCE on LMM morphology

The quality of evidence is presented in Appendix 3.5 and details of the effectiveness of MCE in restoring normal LMM morphology are presented in Table 3.2 and 3.3.

Table 3. 2 Effect of motor control exercise on the morphometry of lumbar multifidus muscle.

Publications	Interventions	Durations	Within-group change in morphology	Between-group differences (MD (95% CI) s
LMM volume				
Tagliaferri et al, 2020 [172]	Gp1: MCE + manual therapy Gp2: GSC MRI – L1-L5	Gp1: 3 months:10 sessions, 30 mins. 4-6 months 2x/wk, 30 mins. Gp2: 3 months: 2x/wk, 60 mins 4-6 months: 1-2x/wk, 60 mins. 6months: 3x/wk, 20-40min	Changes from baseline to 3 months (L1-L5 volume) Gp1 mean changes (95% CI): at 3 months = -200mm^3 (-700 to 300mm^3), (p = 0.477) Gp2 mean changes (95% CI): at 3 months = 400mm^3 (-100 to 1000mm^3), (p = 0.102) No significant increase in LMM volume from L1-L5 in both the groups at 3 months Changes from baseline to 6 months (L1-L5 volume) Gp1 mean changes (95% CI): at 6 months = 200mm^3 (-300 to 700mm^3), (p = 0.463) Gp2 mean changes (95% CI): at 6 months = 800mm^3 (300 to 1300mm^3), (p = 0.003) Only Grp 2 demonstrated significant increases in LMM volume from L1-L5 at 6 months.	Between-group analysis (Gp2-Gp1) At 3 months MD (95% CI) = 600mm^3 (-100 to 1,400mm^3), (p = 0.096) At 6 months MD (95% CI) = 600mm^3 (-100 to 1,400mm^3), (p = 0.116) No significant between-group differences in LMM volume at 3 and 6 months.
LMM CSA				
Hides et al, 1996 [168]	Gp1: MCE + drugs Gp2: Drugs only	4 wks and 10wks	The difference between the sides at the most affected vertebral level was expressed as a percentage of CSA for the unaffected side at that level.	Significantly greater post-treatment increases in LMM CSA on the painful side in Gp1 than Gp2 at 4th week FU (p = 0.0001) Since percentage changes in CSA were reported,

	USG - L2-S1		Gp1: at 4th wk = 0.71 ± 2.49%, at 10th wk = 0.24 ± 3.29% Gp2: at 4th wk = 16.84 ± 9.26%; at 10th wk =14.02 ± 6.31% Since percentage changes in CSA were reported, MDC_{95} could not be used for comparisons	MDC_{95} could not be used for comparisons.
Kim and Kim 2013 [170]	Gp1: GPT Gp2: MCE using sling + GPT. Gp3: MCE using sling + GPT + pushups. CT scan (level was not reported)	6 wks, 3x/wk, 30 mins	Change from baseline to 6 wks. Gp1 mean change: Rt LMM = -0.2 ± 0.5mm², Lt LMM = 0.2 ± 0.5mm² (p > 0.05) Gp2 mean change: Rt LMM = 11.2 ± 3.2mm², Lt LMM = 11.5 ± 3.8mm² ($p < 0.01$). Gp3 mean change: Rt LMM = 7.0 ± 2.1mm², Lt LMM = 7.5 ± 2.0mm² ($p < 0.01$). Significant increase in LMM CSA in Gp2 and Gp3 Changes in all groups did not exceed MDC_{95}	Post-treatment LMM CSA in Gp2 > Gp3; Rt ($p < 0.001$), Lt ($p < 0.01$). Secondary analysis, MD (95% CI) Rt LMM Gp2 minus Gp1= 11.4mm² (9.4 to 13.4mm²), (p < 0.00001) Gp3 minus Gp1 = 7.2mm² (5.9 to 8.5mm²), (p < 0.00001) Gp2 minus Gp3 = 4.2mm² (1.83 to 6.57 mm²), (p = 0.0005) Lt LMM Gp2 minus Gp1 = 11.3mm² (8.9 to 13.68mm²), (p < 0.0000) Gp3 minus Gp1 = 7.3mm² (6.02 to 8.58mm²), (p < 0.00001) Gp2 minus Gp3 = 4mm² (1.34 to 6.7mm²), (p = 0.003) Between-group changes in all groups did not exceed MDC_{95}
Lee et al, 2011 [171]	Gp1: MCE on a gymnastic ball Gp2: GPT Axial CT scan - L4-	12 wks, 3 d/wk, 45 mins	Change from baseline to 12 wks. **Gp1 mean change at L4-L5 = 121.0 ± 43.0mm², ($p < 0.05$)** Gp2 mean change at L4-L5 = 3.3 ± 18.3mm², ($p > 0.05$) Significant increase in LMM CSA in Gp1 only. Change in Gp1 exceeded MDC_{95}	Reported between-group analysis: ($p < 0.05$) Secondary analysis **Gp1 minus Gp2 = 120mm² (100-140mm²)** Gp1 had a greater effect than Gp2, which exceeded MDC_{95}

	5			
Nabavi et al, 2018 [138]	Gp1: MCE + GPT Gp2: GE + GPT USG - L5	4wks, 3x/wk	Change from baseline to 4 wks. Gp1 mean change (95% CI): Rt LMM CSA = 0.4mm² (0.2 to 0.6mm²) (p = 0.01); Lt LMM CSA= 0.5mm² (0.2 to 0.8mm²) (p = 0.01) Gp2 mean change (95% CI): Rt LMM CSA = 0.3mm² (0.0 to 0.6mm²) (p = 0.081); Lt LMM CSA = 0.2mm² (0.1 to 0.5mm²) (p = 0.045). Changes in both groups were smaller than MDC_{95}	Reported between-group analysis. (Gp1 minus Gp2): Rt LMM = 0.1mm² (-0.1 to 0.2mm²) (p = 0.86) Lt LMM = 0.3mm² (-0.1 to 0.2mm²) (p = 0.66) No significant between-group changes were noted in bilateral LMM CSA Between-group differences were smaller than MDC_{95}
Tagliaferri et al, 2020 [172]	Gp1: MCE + manual therapy Gp2: GSA MRI – L1-L5	Gp1: 3 months:10 sessions, 30 mins 4-6 months 2x/wk, 30 mins Gp2: 3 months: 2x/wk, 60 mins 4-6 months : 1-2x/wk, 60 mins	Changes from baseline to 3 months at different levels Gp1 mean changes (95% CI): L1 = -10.2mm^2 (-18.8 to -1.6mm^2), (p = 0.019); L2 = -10.0mm^2 (-21.3 to 1.0mm^2), (p = 0.052); L3 = -9.1mm^2 (-37.0 to 18.8mm^2), (p = 0.521); L4 = -13.9mm^2 (-47.3 to 19.6mm^2), (p = 0.416); L5 = -3.0mm^2 (-29.7 to 23.9mm^2), (p = 0.831) Gp2 mean changes (95% CI): L1 = 9.7mm^2 (-2.3 to 21.6mm^2), (p = 0.112); L2 = 12.2mm^2 (-8.6 to 33.0mm^2), (p = 0.251); L3 = 9.9mm^2 (-9.6 to 29.5mm^2), (p = 0.318); L4 = 23.7mm^2 (-6.1 to 53.5mm^2), (p = 0.119); L5 = 37.7mm^2 (11.2 to 64.2mm^2), (p = 0.005) Significant increase in LMM size at L1 at 3 months in Gp1 Significant increase in LMM size at L5 at 3 months in Gp2 Changes from baseline to 6 months at different levels	Between group differences at different levels At 3 months L1 = 19.9mm^2 (5.0 to 34.8mm^2), (p = 0.009) L2 = 23.1mm^2 (-0.8 to 47.1mm^2), (p = 0.058) L3 = 19.1mm^2 (-14.5 to 52.8mm^2), (p = 0.266) L4 = 37.6mm^2 (-7.1 to 82.3mm^2), (p = 0.099) L5 = 40.6mm^2 (2.9 to 78.3mm^2), (p = 0.035) A significant increase in LMM size was noted at L1 and L5 at 3 months in Gp2 compared to Gp1. At 6 months L1 = 9.3mm^2 (-5.7 to 24.4mm^2), (p = 0.225) L2 = 13.2mm^2 (-11.1 to 37.4mm^2), (p = 0.287) L3 = 26.3mm^2 (-7.8 to 60.4mm^2), (p = 0.130) L4 = 43.6mm^2 (-1.7 to 88.9mm^2), (p = 0.059) L5 = 33.0mm^2 (-5.1 to 71.2mm^2), (p = 0.090) No significant between-group differences in LMM size from L1 to L5 at 6 months were noted.

		6months: 3x/wk, 20-40min	Gp1 mean changes (95% CI): L1 = -2.8mm^2 (-11.6 to 6.0mm^2), (p = 0.529); L2 = -9.0mm^2 (-20.0 to 2.0mm^2), (p = 0.109); L3 = -0.0mm^2 (-28.6 to 28.6mm^2), (p = 0.999); L4 = -5.8mm^2 (-40.1 to 28.5mm^2), (p = 0.741); L5 = 13.0mm^2 (-14.5 to 40.4mm^2), (p = 0.355) Gp2 mean changes (95% CI): L1 = 6.5mm^2 (-5.5 to 18.5mm^2), (p = 0.287); L2 = 3.8mm^2 (-17.0 to 24.6mm^2), (p = 0.721); L3 = 26.3mm^2 (6.7 to 45.8mm^2), (p = 0.008); L4 = 37.8mm^2 (8.0 to 67.6mm^2), (p = 0.013); L5 = 46.0mm^2 (19.5 to 72.5mm^2), (p = 0.001) Significant increase in LMM size at L3, L4 and L5 at 6 months in Gp2 only Changes in both groups were smaller than MDC_{95} at 3 and 6 months.	
Resting thickness				
Akbari et al, 2008 [74]	Gp1: MCE Gp2: GE USG - L4-5	8 wks, 2x/wk, 30 mins	Gp1 mean ± SD: pre = 8.6 ± 2.4mm; post = 9.7 ± 2.5mm (p < 0.01) Gp2 mean ± SD: pre = 8.8 ± 1.5mm; post = 9.3 ± 1.6mm (p < 0.01) A significant increase in resting LMM thickness in both the groups was noted. Secondary analysis (post minus pre) Gp1 = 1.1mm (-0.3 to 2.5mm), (p = 0.11) Gp2 = 0.5mm (-0.4 to 1.4mm), (p = 0.26) Changes in both groups did not exceed MDC_{95}	Between-group analysis data was not reported. Secondary analysis Gp1 minus Gp2 = 0.4mm (-0.8 to 1.6mm) (p = 0.61) No significant between-group difference was noted. Between-group difference was smaller than MDC_{95}
Berglund et al, 2017 [75]	Gp1: MCE Gp2: HLL	12 sessions over	Gp1 mean ± SD: Larger side: pre = 2.7 ± 0.4mm; post = 2.7 ± 0.5mm; % change = 0.4 ± 18.0%	No significant between-group difference for both sides were reported (p = 0.495) Secondary analysis (Gp1 minus Gp2)

	USG - L5	2 months	Smaller side: pre = 2.5 ± 0.4mm; post = 2.6 ± 0.5mm; % change = 8.0 ± 20.9% Gp2 mean ± SD: Larger side: pre = 2.6 ± 0.5mm; post = 2.7 ± 0.6mm; % change = 1.7 ± 14.1% Smaller side: pre = 2.4 ± 0.5mm; post = 2.7 ± 0.5mm; % change = 11.2 ± 18.1% Increases in LMM thickness on the smaller side > the larger side in both groups (p = 0.001) Secondary analysis (post minus pre) Gp1: Larger side = 0mm (-0.2 to 0.2mm), (p = 1); Smaller side = 0.1mm (-0.1 to 0.3mm), (p = 0.37) Gp2: Larger side = 0.1mm (-0.2 to 0.4), (p = 0.47); Smaller side = 0.3mm (0.1 to 0.5), (p = 0.02) Changes for all groups were smaller than MDC_{95}	Larger side = 0.0mm (-0.3 to 0.3mm) Smaller side = -0.1mm (-0.3 to 0.1mm) Between-group changes were smaller than MDC_{95}
Hosseinifar et al, 2013 [76]	Gp1: MCE Gp2: McKenzie exercise USG - L4-5	6wks, 3x/wk, 60 mins	Gp1 mean ± SD: Rt LMM pre = 30.0 ± 2.9mm, post = 31.5 ± 4.8mm (p < 0.05); Lt LMM pre = 30.8 ± 4.6mm, post = 32.6 ± 4.8mm (p < 0.05). Gp2 mean ± SD: Rt LMM pre = 29.4 ± 5.9mm, post = 31.1 ± 5.7mm (p < 0.05); Lt LMM pre = 29.7 ± 5.5mm, post = 31.1 ± 5.0mm (p < 0.05). Significant increases in resting Rt and Lt LMM thickness in Gp1 and Gp2 Secondary analysis (post minus pre) Gp1 MD (95%CI): Rt LMM = 1.5mm (-1.3 to 4.3mm), (p = 0.30); Lt LMM = 1.8mm (-1.6 to 5.1), (p = 0.29)	Between-group analysis was not reported Secondary analysis (Gp1 minus Gp2) Rt LMM = 0.4mm (-3.4 to 4.2mm) (p > 0.05) Lt LMM = 1.5mm (-2.0 to 5.0mm) (p > 0.05) No significant between-group differences Between-group differences were smaller than MDC_{95}

			Gp2 MD (95%CI): Rt LMM = 1.7mm (-2.5 to 5.9mm), (p = 0.42); Lt LMM = 1.4mm (-1.4 to 4.2mm), (p = 0.33) Changes in both groups were smaller than MDC_{95}	
Nabavi et al, 2018 [138]	Gp1: MCE + GPT Gp2: GE + GPT USG - L5	4 wks, 3x/wk	Change from baseline to 4 wks. Gp1 mean changes (95% CI): Rt LMM = 1.5mm (1.1 to 2.1mm) (p = 0.01); Lt LMM = 1.5mm (0.9 to 2.4mm) (p = 0.01) Gp2 mean changes (95% CI): Rt LMM = 1.8mm (1.0 to 2.2mm) (p = 0.01); Lt LMM = 1.7mm (0.8 to 2.5mm) (p = 0.01). Significant increase in bilateral resting LMM thickness in both the groups Changes in both groups were smaller than MDC_{95}	Reported Between-group analysis (Gp2 minus Gp1): MD (95% CI): Rt LMM = 0.3mm (0.1to 0.5mm) (p = 0.53) Lt LMM = 0.2mm (0.0 to 0.4mm) (p = 0.64) No significant between-group differences in bilateral resting LMM thickness at L5 at the 4th wk Between-group differences were smaller than MDC_{95}
Contracted thickness				
Hosseinifar et al, 2013 [76]	Gp1: MCE Gp2: McKenzie exercises USG - L4-5	6wks, 3x/wk, 60mins	Gp1 mean ± SD: Rt LMM pre = 36.3 ± 4.0mm, post = 37.8 ± 4.7mm; **Lt LMM pre = 37.1 ± 3.9mm, post = 39.9 ± 4.4mm (p < 0.05)** Gp2 mean ± SD: Rt LMM pre = 35.0 ± 6.2mm, post = 36.3 ± 5.2mm; Lt LMM pre = 36.6 ± 5.3mm, post = 37.4 ± 4.9 mm (p > 0.05) Significant increase in contracted Lt LMM thickness in Gp1 only Secondary analysis (post minus pre) Gp1: Rt LMM = 1.5mm (-1.6 to 4.6), (p = 0.35); Lt LMM = 2.8mm (-0.2 to 5.8), (p = 0.07)	Between-group analysis was not reported Secondary analysis (Gp1 minus Gp2) Rt LMM = 1.5mm (-2.1 to 5.1mm), (p = 0.41) Lt LMM = 2.5mm (-0.8 to 5.8mm), (p = 0.14) No significant between-group difference was noted. Between-group difference in the changes of Lt LMM exceeded MDC_{95}

			Gp2: Rt LMM = 1.3mm (-2.8 to 5.4), (p = 0.53); Lt LMM = 0.8mm (-2.9 to 4.5), (p = 0.67) Change in Lt LMM in Gp1 exceeded MDC_{95}	
Kehinde et al, 2014 [169]	Gp1: MCE Gp2: MCE + TENS. Gp3: MCE + massage. Gp4: analgesics USG - L4-5	8 wks, 2x/wk	Gp1 mean ± SD: pre = 2.7 ± 0.7mm, post = 3.2 ± 0.7mm (p = 0.01) Gp2 mean ± SD: pre = 2.8 ± 0.5mm, post = 3.3 ± 0.5mm (p = 0.01) Gp3 mean ± SD: pre = 2.7 ± 0.6mm, post = 3.0 ± 0.5mm (p = 0.01) Gp4 mean ± SD: pre = 2.9 ± 0.6mm, post = 3.0 ± 0.5mm (p = 1.00) Significant increase in contracted LMM thickness at L4-L5 at 8 wk in Gps1, 2 and 3 only Secondary analysis (post minus pre) Gp1 = 0.5mm (0.2 to 0.9mm), (p = 0.005) Gp2 = 0.5mm (0.3 to 0.8mm), (p < 0.0001) Gp3 = 0.3mm (0.0 to 0.6mm), (p = 0.04) Gp4 = 0.1mm (-0.2 to 0.4mm), (p = 0.48) Changes for all groups were smaller than MDC_{95}	Between-group analysis was not reported. Secondary analysis Gp1 minus Gp3 = 0.2mm (-0.1 to 0.5mm), (p = 0.20) Gp1 minus Gp4 = 0.2mm (-0.1 to 0.5mm), (p = 0.20) Gp1 minus Gp2 = -0.1mm (-0.4 to 0.2mm), (p = 0.52) Gp2 minus Gp3 = 0.3mm (0.1 to 0.6mm), (p = 0.02) Gp2 minus Gp4 = 0.3mm (0.1 to 0.6mm), (p = 0.02) Gp3 minus Gp4 = 0.0mm (-0.3 to 0.3mm), (p = 1.00) Significant increase in contracted LMM thickness was noted in Gp2 compared to Gp1, Gp3 and Gp4 Between-group differences were smaller than MDC_{95}

Note: The bold values indicate that the changes exceeded MDC_{95}

Abbreviations: CSA, cross-sectional area; CT, computed tomography; d/wk, days per week; FU, follow up; GE, general exercises; Gp, group; GPT, general physiotherapy ; GPT, general physiotherapy; GSA, general strengthening and aerobic exercises; HLL, high load lifting; IRR, infra-red radiation; LMM, lumbar multifidus muscle; Lt, left; MCE, motor control exercise; MD(95%CI), mean difference (95% confidence intervals); MDC_{95} , minimal detectable change at 95% confidence interval; mins, minutes; MRI, magnetic resonance imaging; Rt, right; SD, standard deviation; TENS, transcutaneous electrical nerve stimulation; US, therapeutic ultrasound therapy; USG, ultrasonography; wk = week.

Table 3. 3 Summary of effectiveness of motor control exercise on the morphometry of lumbar multifidus muscle.

Publications	Interventions	LMM Measurements	Between-group differences
Tagliaferri et al, 2020 [172]	Gp1: MCE + manual therapy Gp2: GSA	LMM volume	At 3 months & 6 months: ND .
Hides et al, 1996 [168]	Gp1: MCE + drugs Gp2: Drugs only	LMM CSA	At 4th week: +
Kim and Kim 2013 [170]	Gp1: GPT Gp2: MCE using sling + GPT. Gp3: MCE using sling + GPT + pushups.	LMM CSA	+
Lee et al, 2011 [171]	Gp1: MCE on a gymnastic ball Gp2: GPT	LMM CSA	+
Nabavi et al, 2018 [138]	Gp1: MCE + GPT Gp2: GE + GPT	LMM CSA	ND
Tagliaferri et al, 2020 [172]	Gp1: MCE + manual therapy Gp2: GSA	LMM CSA	At 3 months: + At 6 months: ND
Akbari et al, 2008 [74]	Gp1: MCE Gp2: GE	Resting thickness	ND
Berglund et al, 2017 [75]	Gp1: MCE Gp2: HLL	Resting thickness	ND
Hosseinifar et al, 2013 [76]	Gp1: MCE Gp2: McKenzie exercise	Resting thickness	ND
Nabavi et al, 2018 [138]	Gp1: MCE + GPT Gp2: GE + GPT	Resting thickness	ND
Hosseinifar et al, 2013 [76]	Gp1: MCE Gp2: McKenzie exercises	Contracted thickness	ND
Kehinde et al, 2014 [169]	Gp1: MCE Gp2: MCE + TENS. Gp3: MCE + massage. Gp4: analgesics	Contracted thickness	+

Abbreviations: CSA, cross-sectional area; GE, general exercises; Gp, group; GPT, general physiotherapy; GPT, general physiotherapy; GSA, general strengthening and aerobic exercises; HLL, high load lifting; IRR, infra-red radiation; LMM, lumbar multifidus muscle; MCE, motor control exercise; TENS, transcutaneous electrical nerve stimulation; US, therapeutic ultrasound therapy.

+ denotes MCE is better; ND denotes no difference between groups.

3.3.4.1 Volume of LMM

Only one study [172] with high risk of bias investigated the effects of MCE plus manual therapy on volume of LMM.

Within-group comparisons

Low-quality evidence suggested that 10 sessions of MCE plus manual therapy did not significantly increase the volume of LMM in comparison to general strengthening plus aerobic exercises [172].

Between-group comparisons

Low-quality evidence suggested that 10 sessions of MCE plus manual therapy was not significantly better than general strengthening plus aerobic exercises in increasing LMM volume [172].

3.3.4.2 CSA of LMM

Five studies [138, 150, 168, 170, 172] with high risk of bias investigated the effects of MCE on LMM CSA.

Within-group comparisons

Very low- to low-quality evidence substantiated that 12 sessions or more MCE with or without adjunct treatments (e.g., resistance training, TENS, massage, manual therapy) significantly increased CSA of LMM at multiple lumbar levels [138, 168, 170-172]. Similarly, there was very low- to low-quality evidence that 36 sessions of MCE caused post-treatment increases in LMM CSA by 121 mm^2, which exceeded MDC_{95} [171] (Table 3.2).

Between-group comparisons

Low-quality evidence supported that MCE along with analgesics induced significantly greater increases in LMM CSA than analgesic alone among people with acute LBP [168], likewise, there was very low-quality evidence that 18 or more sessions of MCE or MCE plus

general physiotherapy caused significantly greater increases in LMM CSA than general physiotherapy alone in people with CLBP [170, 171]. However, only 36 sessions of MCE induced significantly greater increase in LMM CSA that exceeded MDC_{95} (by 120 mm^2) than general physiotherapy in people with CLBP (Table 2) [171]. However, there was low-quality evidence that 12 sessions of MCE plus general physiotherapy/MCE plus manual therapy were not significantly different from 12 sessions of general exercise plus general physiotherapy/general strengthening plus aerobic exercises in altering LMM CSA [138, 172].

3.3.4.3 Resting LMM thickness

Four studies [74-76, 138] examined changes in the resting LMM thickness at the L4-5 level among people with CLBP. The treatments ranged from 2-3 days/week, with 30-60 minutes each for 4 to 8 weeks. All four studies demonstrated a high risk of bias [74-76, 138].

Within-group comparisons

Very low- to low-quality evidence suggested that 12 to 18 sessions of MCE with/without adjunct treatment, general exercises, high-load lifting, McKenzie exercise, or general exercises plus general physiotherapy significantly increased resting LMM thickness [74-76, 138]. Although these post-MCE increases in the resting LMM thickness ranged from 1.1mm to 1.8mm, they did not exceed MDC_{95} [74, 76, 138] (Table 3.2).

Between-group comparisons

There was very low- to low-quality evidence that 12 to 18 sessions of MCE or MCE plus general physiotherapy was not significantly better than other treatments (e.g., general exercises [74], high load lifting exercise [75], McKenzie exercise [76], general exercise plus physiotherapy [138], in increasing LMM resting thickness (Table 3.2).

3.3.4.5 Contracted LMM thickness

Two studies with high risk of bias [76, 169] evaluated the effects of 16 to 18 sessions of MCE on the contracted thickness of LMM at the L4-5 level in people with CLBP.

Within-group comparisons

Low-quality evidence suggested that MCE with/without adjunct treatment significantly increased the contracted thickness of LMM ranging from 0.3mm to 2.8mm [76, 169]. However, only 18 sessions of MCE caused signficant increases in contracted thickness of left LMM that exceeded MDC_{95} (Table 3.2) [76].

Between-group comparisons

There was low-quality evidence that MCE was comparable to McKenzie exercise in increasing LMM contracted thickness [76]. Low-quality evidence suggested that although MCE plus TENS caused significantly greater increases in contracted LMM thickness than MCE plus massage or analgesic alone, the differences did not exceed MDC_{95} (Table 3.2) [169].

3.3.5 Effects of MCE on percent LMM thickness changes during contraction and LMM fatty infiltration.

Despite the comprehensive search, no RCT investigated the effects of intervention on percent LMM thickness changes during contraction or LMM fatty infiltration.

3.3.6 Effects of MCE on LBP intensity of the included studies

Of the 9 included RCTs, 7 trials reported post-treatment decreases in LBP intensity (Table 3.4and 3.5). Seven included studies [74-76, 138, 168, 171, 172] used VAS to measure LBP intensity, which comprises a 10cm straight line with the two endpoints indicating no pain (0cm) and maximum pain (10cm), respectively [173].

Table 3. 4 Effect of motor control exercise on low back pain

Publications	Interventions	Pain measures	Within-group change in pain	Between-group differences (MD (95% CI) s
Akbari et al, 2008 [74]	Gp1: MCE Gp2: GE	VAS (mm)	Gp1 mean ± SD: pre = 7.3 ± 1.0mm, post = 2.5 ± 1.2mm, (p = 0.0001) Gp2 mean ± SD: pre = 8 ± 1.2mm, post = 4 ± 1.5mm, (p = 0.0001) Secondary analysis (pre minus post) Gp1 = 4.8mm (4.19 to 5.41mm), (p < 0. 00001) Gp2 = 4mm (3.23 to 4.77mm), (p < 0.00001) Significant post-treatment reduction in LBP in Gp1 and Gp2. Significant post-treatment reduction in LBP in Gp1 and Gp2. Changes for both groups were smaller than MCID	Between-group analysis data was not reported. Reported p value. (p = 0.015) Secondary analysis Gp1 minus Gp2 = -1.5mm (-2.26 to 0.74mm) (p = 0.0001) Gp1 showed significantly larger decreases in LBP than Gp2. Between-group difference was smaller than MCID
Berglund et al, 2017 [75]	Gp1: MCE Gp2: High load lift exercise	VAS (mm)	Gp1 mean ± SD: pre = 48.7 ± 27.0mm, mean change ± SD at 2 months: -18.5 ± 26.7mm, (p value was not reported) Gp2 mean ± SD: pre = 41.3 ± 23.8mm, mean change ± SD at 2 months: -19.0 ± 25.5mm, (p value was not reported) Significant post-treatment reduction in LBP in Gp1 and Gp2. Changes for both groups were smaller than MCID	Between-group analysis data was not reported. Reported p value (p = 0.95) Secondary analysis Gp1 minus Gp2 = 0.5mm (-12.71 to 13.71mm) (p = 0.94) No significant post-treatment differences between Gp1 and Gp2
Hides et al, 1996 [168]	Gp1: MCE plus drugs (analgesics +	VAS (mm)	Significant decreases in pain intensity in both groups. (Values were not reported)	No significant difference between the two groups from 1 to 4 weeks (p = 0.96) LBP assessment at 10th wk was not reported.

	nonsteroidal anti-inflammatory) Gp2: Drugs			
Hosseinifar et al, 2013 [76]	Gp1: MCE Gp2: McKenzie exercise	VAS (mm)	Gp1 mean ± SD: pre = 4.3 ± 1.6mm, post = 1.5 ± 1.4mm, ($p < 0.05$) Gp2 mean ± SD: pre = 4.4 ± 2.0mm, post = 2.7 ± 1.4mm, ($p < 0.05$) Secondary analysis (pre minus post) Gp1 = 2.8mm (1.72 to 3.88mm), ($p < 0.\ 00001$) Gp2 = 1.7mm (0.46 to 2.94mm), ($p < 0.00001$) Significant post-treatment reduction in LBP in Gp1 and Gp2 Changes for both groups were smaller than MCID	Between-group analysis data was not reported. Reported p value ($p < 0.05$) Secondary analysis Gp1 minus Gp2 = -1.20mm (-2.20 to -0.20mm) ($p = 0.02$) Gp1 showed significantly larger decreases in LBP than Gp2. Between-group difference was smaller than MCID
Lee et al, 2011 [171]	Gp1: MCE on a gymnastic ball Gp2: GPT	VAS (mm)	Gp1 mean ± SD: pre = 59mm ± 19mm, post at 12^{th} wk = 13 ± 11mm, ($p < 0.05$) Gp2 mean ± SD: pre = 56mm ± 20mm, post at 12^{th} wk = 21 ± 15mm, ($p < 0.05$) Secondary analysis (pre minus post) **Gp1 = 46mm (45.56 to 56.44mm)**, ($p < 0.00001$) **Gp2 = 35mm (22.75 to 47.25mm)**, ($p < 0.00001$) Significant post-treatment reduction in LBP in Gp1 and Gp2 Within-group changes in both groups exceeded MCID	Between-group analysis was not reported Secondary analysis Gp1 minus Gp2 = -8mm (-17.02 to 1.02mm) ($p = 0.08$) No significant difference between Gp1 and Gp2 at the 12^{th} wk Between-group difference was smaller than MCID
Nabavi et al, 2018 [138]	Gp1: MCE	VAS (mm)	**Gp1 MD (95%CI): 33mm (22 to 43mm),** post-treatment decreases in LBP ($p = 0.01$)	Between-group differences: ($p = 0.82$) Gp2 minus Gp1 = 2.0mm (0.2 to 3.4mm) ($p = 0.82$)

	plus GPT Gp2: GE plus GPT		**Gp2 MD (95%CI): 35mm (22 to 41mm)**, post-treatment decreases in LBP ($p = 0.01$) Significant post-treatment reduction in LBP in Gp1 and Gp2 Within-group changes in both groups exceeded MCID	No significant difference between Gp1 and Gp2 Between-group difference was smaller than MCID
Tagliaferri et al, 2020 [172]	Gp1: MCE + manual therapy Gp2: GSA	VAS (mm)	Gp1: Significant decrease in LBP at 6 ($p < 0.05$), 8 ($p < 0.01$), 10 ($p < 0.001$), 12 ($p < 0.001$), 14 ($p < 0.001$), 16 ($p < 0.001$), 18 ($p < 0.01$), 20 ($p < 0.001$), 20 ($p < 0.001$), 22 ($p < 0.001$), and 24 ($p < 0.001$) weeks. Gp2: Significant decrease in LBP at ($p < 0.05$), 8 ($p < 0.05$), 10 ($p < 0.05$), 12 ($p < 0.01$), 18 ($p < 0.01$), 20 ($p < 0.05$), 22 ($p < 0.05$), 24 ($p < 0.01$). Significant post-treatment reduction in LBP at 6 months in both Gp1 ($p < 0.001$) and Gp2 ($p = 0.008$)	Gp1 was better than Gp2 in decreasing LBP at 14 and 16 weeks ($p = 0.003$) No significant difference between Gp1 and Gp2 at 6 months

Note: The bold values indicate the within-group changes exceeded minimal clinical important difference.

Abbreviations: 95%CI, 95% confidence interval; FU, follow up; GE, general exercises'; Gp, group; GPT, general physiotherapy; GSA, general strengthening, and aerobic exercises; HLL, High load lifting; LBP, low back pain; MCE, motor control exercise; MCID, minimal clinical important difference; mins, minutes; mm, millimeter; SD, standard deviation; VAS, visual analogue scale; wk, week

Table 3. 5 Summary of effectiveness of motor control exercise on low back pain

Publications	Interventions	Pain measures	Between-group differences
Akbari et al, 2008 [74]	Gp1: MCE Gp2: GE	VAS (mm)	+
Berglund et al, 2017 [75]	Gp1: MCE Gp2: High load lift exercise	VAS (mm)	ND
Hides et al, 1996 [168]	Gp1: MCE plus drugs (analgesics + nonsteroidal anti-inflammatory) Gp2: Drugs	VAS (mm)	ND
Hosseinifar et al, 2013 [76]	Gp1: MCE Gp2: McKenzie exercise	VAS (mm)	+
Lee et al, 2011 [171]	Gp1: MCE on a gymnastic ball Gp2: GPT	VAS (mm)	ND
Nabavi et al, 2018 [138]	Gp1: MCE plus GPT Gp2: GE plus GPT	VAS (mm)	ND
Tagliaferri et al, 2020 [172]	Gp1: MCE + manual therapy Gp2: GSA	VAS (mm)	At 14 and 16 weeks: + At 6 months: ND

Abbreviations: GE, general exercises'; Gp, group; GPT, general physiotherapy; GSA, general strengthening, and aerobic exercises; HLL, High load lifting; LBP, low back pain; MCE, motor control exercise; mm, millimeter; SD, standard deviation; VAS, visual analogue scale.

+ denotes MCE is better; ND denotes no difference between groups.

Within-group comparisons

There was very low- to low-quality evidence that 4 to 24 weeks of MCE [74], McKenzie exercise [76], general exercises [74], high-load lifting exercises [75], MCE plus manual therapy [172], general strengthening plus aerobic exercises [172], and general physiotherapy [138, 171] significantly decreased pain. The average pain reduction following MCE alone ranged from 2.8mm to 18.5mm on VAS, which were smaller than MCID [74-76]. There was very low- to low-quality evidence that combining MCE or general exercises with general physiotherapy [138], MCE on a gymnastic ball or general physiotherapy alone [171] significantly reduced CLBP intensity by 33mm to 46mm on VAS, which exceeded the MCID for pain using VAS (>20mm) (Table 3.3) [166]. Similarly, low-quality evidence supported that MCE with analgesics and nonsteroidal anti-inflammatory drugs significantly reduced acute LBP although the extent of pain reduction was not reported [168].

Between-group comparisons

There was low-quality evidence that MCE alone caused significantly greater CLBP reduction than general exercise alone [74], or McKenzie exercise alone [76] .However, there was no evidence that MCE with or without adjunct treatments was significantly better than high load lift exercise [75], general physiotherapy [171], general strengthening plus aerobic exercises [172], general exercise plus general physiotherapy [138], or drug alone [168] in reducing acute or chronic LBP. Given the high clinical heterogeneity among studies, meta-analysis was not conducted.

3.3.7 Temporal relations between changes in LMM morphology and changes in LBP intensity or LBP-related disability.

Only two included RCTs with high risk of bias investigated the correlations between changes in LMM morphology and the corresponding changes in LBP intensity among people with

acute (n=41) [168] or CLBP (n=65) [75]. There was no evidence that post-treatment increases in LMM resting thickness [75] or CSA [168] were related to LBP reduction (Table 3.4). Likewise, no evidence suggested that post-treatment increases in LMM CSA were related to changes in Roland Morris Disability Index scores in people with acute LBP.[168] (Table 3.6)

Table 3. 6 Correlation between post-treatment change in lumbar multifidus muscle (LMM) morphology and the corresponding changes in low back pain (LBP) intensity or LBP-related disability.

Publications	**Interventions**	**Duration**	**Pain/disability measures**	**Results**
Berglund et al, 2017 [75]	Gp1: MCE Gp2: High load lift exercise	2 months	Visual analogue scale (cm)	No correlation between changes in LMM resting thickness and pain intensity (p = 0.411).
Hides et al, 1996 [168]	Gp1: MCE plus drugs (analgesics + nonsteroidal anti-inflammatory) Gp2: Drugs	4 weeks	Visual analogue scale (mm)	No significant correlation between changes in pain and increase of LMM CSA in Gp 1 (p value was not reported) No correlation analysis between changes in pain and LMM CSA in Gp 2 as there was no increase in CSA of LMM in Gp 2. LBP assessment at 10th wk was not reported.
Hides et al, 1996 [168]	Gp1: MCE plus drugs (analgesics + nonsteroidal anti-inflammatory) Gp2: Drugs	4 weeks	Roland Morris Disability Index	No significant correlation between changes in disability score and LMM CSA in Gp1. (p value was not reported)

Abbreviations: cm, centimeter; CSA, cross-sectional area; Gp, group; LMM, lumbar multifidus muscle; MCE, motor control exercise; mm, millimeter

Protocol deviations from PROSPERO registration.

Although the original protocol planned to summarize evidence regarding the effectiveness of various physiotherapy interventions in restoring normal LMM morphology and reducing pain in people with LBP, the search yielded diverse treatments. Since the initial review question was too broad and MCE was the most commonly studied LBP treatment, we narrowed it down to a more specific research objective. Therefore, the current review focused on the effectiveness of MCE in restoring normal LMM morphology and decreasing pain in people with LBP.

3.4 DISCUSSION

This is the first systematic review to summarize the evidence regarding the effects of MCE on LMM morphology, LBP, and the correlations between changes in LMM morphology and LBP intensity or LBP-related disability. Our findings suggest that MCE may be little or no better than other interventions in changing LMM morphology or decreasing pain intensity. Similarly, there is no correlation between changes in LMM morphology and LBP or LBP-related disability.

3.4.1 Effects of MCE on LMM morphology

The weak effects of post-MCE changes in LMM morphology (e.g., thickness or CSA) may be related to insufficient exercise dosages (i.e., frequency, intensity, type, and duration of MCE). Sokunbi et al found that thrice weekly MCE for 6 weeks caused significantly greater increases in LMM CSA than once weekly MCE [174]. Exercise-induced skeletal muscle hypertrophy usually occurs after exercising for at least 6-weeks [175]. Previous research has shown that muscle strengthening at 2-3 sessions per week yielded significantly greater CSAs of quadriceps and elbow flexors than exercising once weekly [176]. Our findings suggest that the number of treatment sessions rather than exercise types might elicit post-treatment LMM

morphological changes. However, there was conflicting evidence regarding whether these post-treatment changes in CSA exceeded the measurement error. Future studies should investigate the dose-response relationship between MCE interventions frequency/duration/intensity and the corresponding changes in LMM morphometry at different lumbar levels to determine optimal treatment dosage.

Interestingly, MCE [76, 168] and high-load lifting exercises [75] appear to selectively increase the resting thickness [75] and contracted thickness [75, 76] of LMM on the painful side to reduce asymmetry, which is not uncommon among people with acute [53]/chronic LBP [26, 54]. However, since most of the studies had small sample sizes and short-treatment durations, future large-scale prospective studies with longer follow-ups are warranted to determine the long-term effect of MCE or high-load lifting exercises on restoring LMM symmetry among people with acute/chronic LBP and to identify the mechanisms underlying the selective muscle hypertrophy.

The current review found low-quality evidence that there were no clinically important differences between MCE and other physiotherapy interventions in reducing CLBP. Our finding concurred with a prior meta-analysis [177] and a Cochrane review [155], which revealed low-to high-quality evidence that MCE and other interventions had comparable effects on reducing non-specific LBP. However, these findings contradict another meta-analysis on eight studies, which concluded that MCE was more effective than general exercises in decreasing pain in people with CLBP [178]. The disparity might be ascribed to the differences in measurement scales used in studies to measure pain intensity, treatment duration and dosages, criteria used for exercise progression, and follow-up periods. The discrepancy in results might also be attributed to less people (n=603) involved in Gomes-Neto et al. meta-analysis [178] as compared to that of Smith and colleagues [177] (n=2,258).

3.4.2 Correlation between changes in LMM morphology and changes in LBP or LBP-related disability

The current review found no evidence to support a significant correlation between changes in LMM morphology and changes in LBP or LBP-related disability [75, 168]. These findings differed from that of cohort studies, which found that people with improved LBP displayed improved LMM morphometry (e.g., increased percent thickness change during contraction) [27, 179]. The discrepancy may be due to the fact that many prior studies only evaluated the immediate post-treatment changes in LMM morphology and LBP intensity without long-term follow-ups. It is plausible that post-treatment morphological changes may be transient or may take time to develop. Future RCTs should clarify the association between temporal changes in LMM morphometry and the corresponding changes in LBP/ LBP-related disability at different follow-up time points.

Additionally, while multiple factors may affect the clinical outcomes of people with CLBP (e.g., depression, anxiety, fear avoidance, catastrophizing and sleep) [180-182], all included RCTs in the current review did not adjust for these confounders in their analyses, which might have affected the reported temporal relations. Future studies should conduct path analyses to determine if LMM morphology may mediate or moderate LBP intensity/LBP-related disability after considering other potential confounders. The findings may help refine assessments and treatments for people with LBP and concomitant aberrant LMM morphology.

Multiple factors may affect the measured LMM morphometry. First, since LMM thickness is a 2-dimensional measurement, changes in resting/contracted thickness as measured by ultrasonography can be affected by multiple factors (e.g., the tightness of surrounding tissues, line of force, etc.) [78]. Therefore, LMM CSA measurements may be better to reveal morphometric changes. Second, LMM morphology as measured by ultrasonography is user dependent. The assessors' experiences may affect the measured results. Unfortunately, all

included RCTs did not report the test-retest reliability of their LMM measurements. Although the current review used previously reported MDC_{95} to determine whether the reported LMM morphometric changes exceed measurement errors, the actual measurement error in each study might differ. Third, changes in LMM CSA as measured on CT scans are not directly related to muscle function although bigger CSAs are thought to be associated with greater muscle strength. Future studies should evaluate the effects of MCE on LMM function (e.g., electromyographic activity) in addition to morphology. A future clinical trial is warranted on a certain population for which there is likely to be LMM dysfunction that shows relation to clinical response (e.g., maybe surgical back pain populations who have had direct surgical intervention over low back pain).

3.4.3 Strengths and Limitations

This review had several strengths. Comprehensive literature searches in 6 databases, standardized screening, data extraction, and methodological quality assessments of the studies were performed to ensure proper extraction and evaluation of data. The study protocol was registered with PROSPERO, while the reporting of the review followed the PRISMA guideline to ensure credibility and comprehensiveness of data. Further, since this review only included RCTs, our conclusion was drawn based on studies with the highest level of evidence. Our review had some limitations. First, given the heterogeneity of outcome measures, exercise intensity, and underreporting of the side of LMM morphology in the included studies, no meta-analysis was conducted. Future studies should standardize the reporting/definition of LMM morphology and interventions to enable meta-analyses. Second, the sample sizes of the RCTs were small, ranging from 30 [76, 170] to 122,[169] which might have limited the statistical power. Future research should estimate the sample size based on the effect sizes of existing studies to ensure sufficient power to detect post-treatment changes in LMM morphology. Third, only RCTs published in English were included. Future systematic reviews

should include non-English publications to improve the generalizability of findings. Fourth, the mean age of participants in the RCTs ranged from 30.9 [168] to 50.8 [169] years. Our findings may not be generalized to younger/older people with LBP.

3.5 CONCLUSIONS

There is little evidence to support that MCE changes LMM morphology, although that positive effects were seen in 36 or more sessions of MCE raises the possibility of inadequate MCE training dosage in people with CLBP. However, existing evidence does not support that MCE is more effective than other exercises in treating acute/chronic LBP. That said, future research is warranted to determine the effects of MCE on segmental or global morphometry (including intramuscular fatty infiltration) of LMM and clinical outcomes, as well as to quantify the causal relationships between changes in LMM morphology and LBP/LBP-related disability.

Chapter 4. Differences in proprioception between young and middle-aged adults with and without chronic low back pain

4.1 INTRODUCTION

Low back pain (LBP) is the leading cause of disability worldwide [2, 183]. Over 80% of people may experience LBP at least once in their lifetime. Up to 90% of LBP cases have unknown aetiology and are diagnosed with non-specific LBP [5]. Although most people with acute LBP recover spontaneously, approximately 20% of cases develop CLBP [184] that lasts continuously for 3 months or more [185], resulting in disability and high medical costs [186]. Importantly, CLBP is more prevalent among middle-aged adults aged 50 years or older (24.8%) [187] as compared to young adults aged 20 to 30 years (4.2%) [188].

Pain can induce inflammatory response in paraspinal muscles causing transformation of slow twitch muscle fibres to fast twitch fibres, muscle atrophy, and altered muscle function (e.g., proprioception) [189]. Altered lumbar proprioception has been found to be a risk factor for the development, maintenance, and/or recurrence of LBP in young adults [190, 191]. Proprioception involves conscious and unconscious awareness of joint position sense, kinesthesia, and force sense of body parts without vision [192-194]. Since paraspinal muscles contain abundant muscle spindles [195], they play an important role in generating proprioceptive signals to monitor midrange spinal motion [190, 195]. Impaired lumbar proprioception may affect the quality of trunk movement, and increase the risk of back injury [196].

Unconscious lumbar proprioception can be assessed by the relative proprioceptive reweighting (RPW) ratio following disturbance in proprioceptive signals in paraspinal and calf muscles with standing without vision [197, 198]. Proprioceptive reweighting is a process by which the central nervous system (CNS) alters the weight allocated to proprioceptive signals in different body parts to maintain standing balance [197]. Compared to age-matched

asymptomatic individuals, young adults aged 18 to 25 years with CLBP cannot adjust their proprioceptive weighting and rely more on ankle proprioception than back extensor proprioception to maintain standing balance, irrespective of stable/unstable surfaces [191, 198, 199]. Conversely, symptomatic older people (average age: 75 years) with spinal column stenosis and spondylitis deformans showed no significant difference in proprioceptive reweighting from age-matched asymptomatic controls [200]. This discrepancy may highlight an age-related deterioration in proprioceptive reweighting of asymptomatic older adults [201]. However, it remains unclear whether proprioceptive reweighting starts to deteriorate in middle-aged adults with/without non-specific CLBP. The finding may inform clinical management such as proprioceptive training to decrease the fall risk [202] or back injuries in middle-aged adults. Conscious trunk proprioception can be objectively evaluated by assessing the accuracy in repositioning of the trunk to a predetermined target position [194]. Studies revealed that people with CLBP (age range:18-74years) displayed greater repositioning errors than asymptomatic counterparts [61, 190], although contradictory findings have also been reported [203, 204]. While joint reposition sense and proprioceptive reweighting reflect conscious and unconscious proprioception, respectively, no studies have evaluated whether these two aspects of proprioception are interrelated in people with and without CLBP.

Given the above, the present study aimed to: (1) compare RPW and lumbar repositioning errors in young adults with and without CLBP, as well as in middle-aged adults with and without CLBP; and (2) determine the relation between RPW and lumbar repositioning errors in young adults with and without CLBP, as well as in middle-aged adults with and without CLBP. It was hypothesized that (1) young adults with CLBP have significantly higher RPW and lumbar repositioning errors than asymptomatic counterparts, but middle-aged adults with and without CLBP will not have significant differences in RPW or lumbar repositioning

errors; and (2) RPW are significantly correlated with lumbar repositioning errors in young adults with or without CLBP, and in middle-aged adults with or without CLBP.

4.2 METHODS

4.2.1 Participants and study design

This cross-sectional study was conducted in a laboratory at a university. The study was approved by the Human Subjects Ethics Sub-committee of the university (HSEAR20151027007-01). Participants aged between 18 and 65 years with and without CLBP were recruited from a public hospital and the University campus, respectively. Participants were stratified into young (18-44 years) and middle-aged (45-65 years) subgroups to enable the within-group comparison of proprioception between those with and without CLBP. The middle-age range was chosen according to the definition documented in the 2020 report of the Lancet Commission.[205]

Inclusion criteria for symptomatic participants included: (1) non-specific CLBP that required medical consultation and lasted over 3 consecutive months in the last 12 months; and (2) LBP intensity of at least 5/10 on a 11-point numeric pain rating scale (NPRS). Inclusion criteria for asymptomatic controls were no LBP at the time of visit, no history of LBP in the last 12 months, and no LBP that lasted for more than a week in the last 36 months. Exclusion criteria for all participants were history of neurological disease or vestibular impairment, systemic inflammatory disease, prior spinal surgery, neuropathy, radiculopathy, spinal infections/fractures/tumors, metabolic disorders, pregnancy, LBP conditions indicated for surgery, and red flags.

4.2.2 Experimental procedure

After providing the written informed consent, participants completed a battery of questionnaires including a questionnaire for the demographic data and history of LBP. Participants then underwent proprioception postural control tests and lumbar reposition tests.

4.2.2.1 Questionnaires

Pain intensity was measured using an 11-point NPRS (0=no pain; 10=worst pain). Participants were asked to pick a number representing the: (1) current level of pain; (2) best and worst levels of pain during the past 24 hours. The average of the 3 ratings was used to estimate their level of pain over the past 24 hours.[206]

Hong Kong-Chinese version of Roland-Morris Disability Questionnaire was used to assess LBP-related disability [207]. The 24-item questionnaire evaluates the impacts of LBP on daily function, with scores ranging from 0-24 (0=no disability; 24=maximum disability).The total score was used to classify the disability into mild (0-8), moderate (9-16), and high (17-24) severity [207]. This questionnaire has demonstrated excellent reliability [intraclass correlation coefficient (ICC)=0.94] in assessing people with non-specific CLBP [207].

The kinesiophobia level was assessed by the 16-item Hong Kong-Chinese version of Fear Avoidance Beliefs Questionnaire (FABQ). It has shown excellent internal consistency (α=0.8) [208], reliability and validity in measuring fear-avoidance beliefs in people with CLBP.[38] Each item was rated on a 7-point Likert-type scale (0=completely disagree; 6=completely agree). It comprises the Physical Activity (FABQ-PA) [4 items (2,3,4,5); score range: 0-24] and the Work (FABQ-W) [7 items (6,7,9,10,11,12,15); score range: 0-42] subscales, while the remaining five items are excluded from calculation [38]. The FABQ-PA scale is classified as low (0-14) and high fear level (15-24). The FABQ-W scale is classified as low (0-33) and high fear level (34-42) [209].

4.2.2.2 Proprioceptive Postural Control Test

The RPW was evaluated using a validated force plate [210] (500Hz, Kistler, Winterthur, Switzerland) and two pairs of muscle vibrators (60Hz, Maxon motor Ltd., Suzhou, China).[211] Two pairs of muscle vibrators were attached bilaterally to triceps surae (TS) and lumbar multifidus muscles (LMM) at L5-S1 level, respectively. To test RPW, participants

were instructed to maintain standing in an upright with bare feet about hip-width apart on a force plate, with arms hanging by the side. The participant used a pair of noise cancellation earphones to minimize noise, and goggles to occlude vision. The test comprised 4 standing conditions on a force plate with: (1) vibration to bilateral LMM; (2) vibration to bilateral TS; (3) a foam and vibration to bilateral LMM; (4) a foam and vibration to bilateral TS (Figures 4.1and 4.2) [211]. The testing surfaces with and without a foam were considered as stable and unstable surfaces, respectively. Vibrators were used to vibrate the target muscles at an amplitude of approximately 0.5mm. This created an illusion of muscle lengthening in the respective muscle spindles to alter proprioceptive afferents [190]. The participant's center of pressure (COP) displacement data from the force plate was processed by a customized MATLAB software program (R2017a, MathWorks, Inc., Natick, MA, USA). Sagittal COP displacements were estimated using a formula: COP = Mx/Fz, where Mx is reaction moment in the sagittal plane and Fz is ground reaction force (i.e., participant's weight). The COP displacements in the trials were recorded over two periods (15 seconds before, and 15 seconds during muscle vibration).[68, 191, 198, 211]

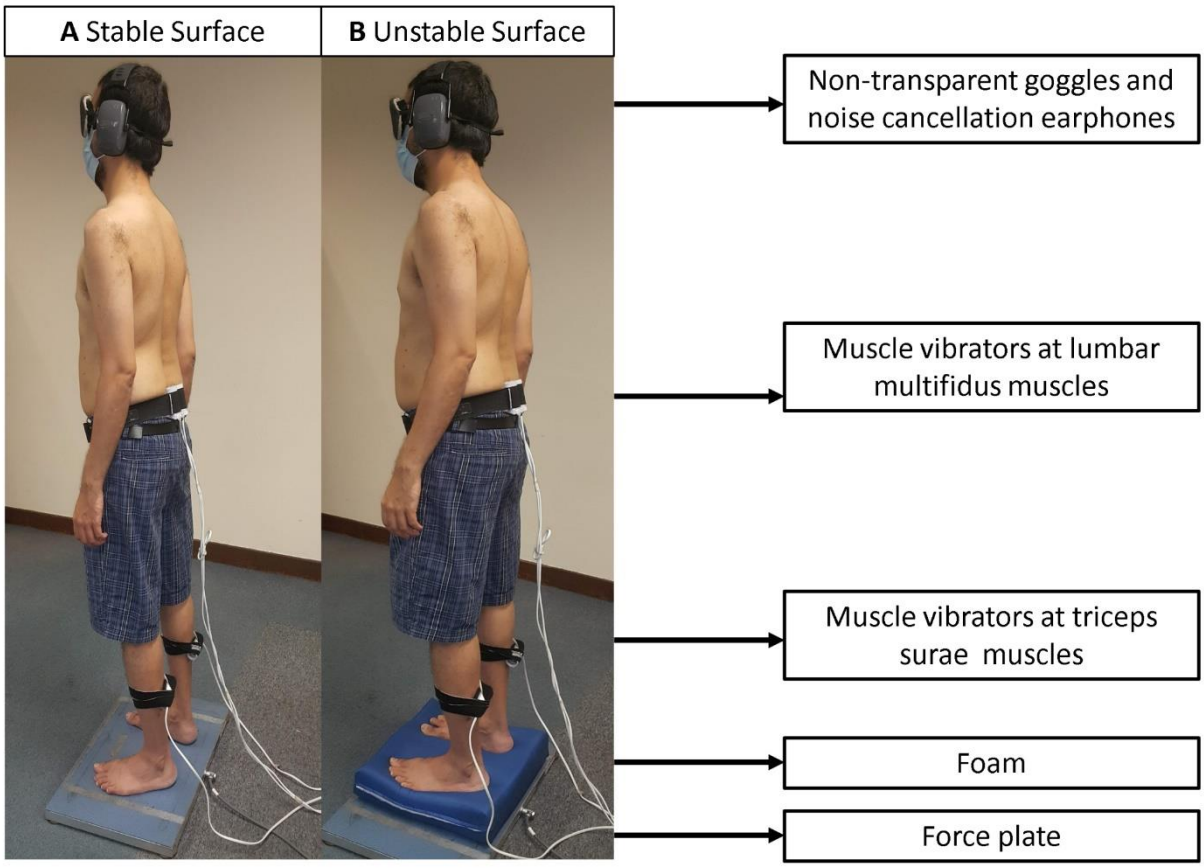

Figure 4. 1 Experimental set-up: (A) standing on a stable surface (force plate); and (B) standing on an unstable surface (foam) with application of muscle vibrators on lumbar multifidus and triceps surae muscles.

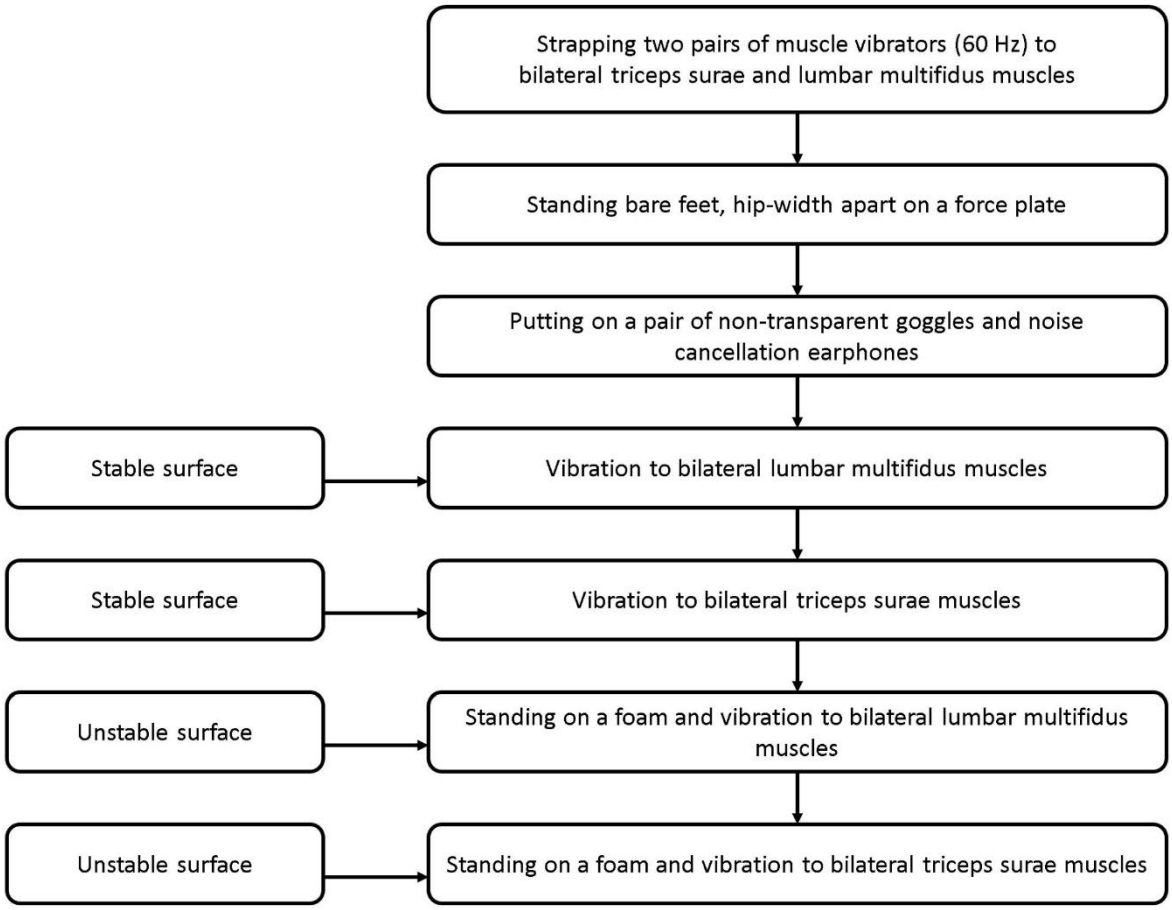

Figure 4. 2 The experimental procedure for evaluating proprioceptive postural control.

The proprioceptive postural control strategy was estimated by RPW [RPW= absolute TS/ (absolute TS + absolute LMM)], where absolute TS is the absolute value of mean sagittal COP displacement during the TS vibration trial, while absolute LMM is the absolute value of mean sagittal COP displacements during the LMM vibration trial. Higher RPW values indicate more reliance on ankle proprioceptive inputs. Conversely, lower RPW values imply increased reliance on LMM proprioceptive signals [212].

4.2.2.3 Lumbar Repositioning Test

The participant was instructed to sit on a stool with hips and knees at 90° flexion, and arms by the side without touching any objects. The physiotherapist identified and marked the participant's T1, T12 and S1 spinous processes and attached three electromagnetic motion sensors (MyoMotion, Noraxon, Scottsdale, AZ, USA) using a double-sided self-adhesive tape. An electromagnetic motion-tracking device (Noraxon Myomotion wireless 3D kinematic analysis system, Phoenix, USA) emits a low-frequency electromagnetic field to detect the locations of these sensors. The static and dynamic accuracy of the system is documented to be 1° and 2°, respectively, at a sampling frequency of 100 Hz [211]. To collect data, an examiner guided the participant to move into and stay in a neutral sitting position for 5 seconds to remember the target sitting position. The participant was instructed to relax in full flexion for 5 seconds before reproducing the target position. The procedure was repeated thrice. No verbal feedback on the performance was given between trials. The sagittal information of the sensors during the trials was collected at 100Hz. The data was analyzed by a customized MATLAB program to calculate the average sagittal repositioning errors with reference to the target position. The average absolute sagittal repositioning error of three measurements was calculated for data analysis.

4.2.2.4 Statistical analysis

Statistical analyses were performed using SPSS software (Version 22, IBM Corp., Armonk, NY). Since Shapiro-Wilk tests showed that our data was not normally distributed, non-parametric tests were used for data analysis. Data were expressed as median and inter-quartile range (IQR). Demographic variables of symptomatic and asymptomatic participants were compared by Mann-Whitney U tests (for continuous variables) or chi-square tests (for nominal variables). The significance level was set at 0.05 (2-tailed) for all tests. Effect sizes (*r*) of each observed difference were calculated by dividing the Z value by the square root of the total number of participants in that pair of groups [213]. Cohen's guidelines for *r* effect sizes (0.1=small,0.3=medium,0.5=large) were referenced [214]. To determine the differential RPW characteristics of young and middle-aged adults with and without CLBP, subgroup analyses of median RPW values of people with and without CLBP in young and middle-aged subgroups [215] were performed using Mann-Whitney U tests. The relation between RPW and repositioning errors in people with and without CLBP was evaluated by Spearman's rank correlation coefficients. The strength of the correlation can be classified as very weak (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79) and very strong (0.80-1.0).[216]

4.3 RESULTS

4.3.1 Participants' characteristics

Demographic data of 151 participants (n=78 with CLBP, n=73 without CLBP) is shown in Table 4.1. There were no significant differences in age, percentage of male, and body mass index between groups. Median age of the CLBP cohort was 46 years. People with CLBP demonstrated significantly higher pain intensity, disability, and FABQ scores than asymptomatic controls ($P<0.001$). Their average LBP intensity in the last 24 hours ranged from 3/10 to 6/10 on NPRS. This is reportedly due to the fluctuating pain intensity among

participants with CLBP [217]. Table 4.1 indicates that participants with CLBP had mild-moderate average pain intensity [218], mild disability [207] and significant fear avoidance beliefs [219]. Similar between-group demographic results were observed in young and middle-aged subgroups except that symptomatic young adults were significantly older than asymptomatic counterparts (Table 4.1).

Table 4. 1 Characteristics of participants with and without chronic low back pain (CLBP) [Median (interquartile range)]

Characteristics	**CLBP (n = 78)**	**Asymptomatic (n = 73)**	**Young (18-44 years)**		**Middle-aged (45-65 years)**	
			CLBP (n = 33)	**Asymptomatic (n = 31)**	**CLBP (n = 45)**	**Asymptomatic (n = 42)**
Age (year)	46.0 (35.8-54.0)	48.0 (30.0-54.5)	34.0* (29.0-37.0)	29.0* (23.0-34.0)	53.0 (48.5-57.5)	53.5 (45.0-64.0)
BMI (kg/m)	23.0 (21.0-25.0)	22.0 (20.0-24.0)	22.0 (20.0-25.0)	21.9 (20.0-23.0)	23.0 (21.0-25.5)	22.7 (20.7-25.0)
Gender (male %)	41.0% (32)	36.6% (26)	48.4% (16)	36.6% (11)	35.5% (16)	36.5% (15)
RMDQ	5.5***** (3.0-9.0)	0.0***** (0.0-1.0)	3.7* (2.7-5.0)	0.0* (0.0-1.0)	6.5* (4.3-9.8)	0.0* (0.0-1.0)
FABQ (0-96)	44.0***** (27.0-53.0)	0.0***** (0.0-22.0)	34.5* (25.0-51.8)	0.0* (0.0-21.8)	46.5* (31.5-56.8)	0.0* (0.0-26.0)
FABQPA (0-24)	18.0* (14.0-22.0)	0.0* (0.0-11.3)	20.0* (15.0-21.0)	0.0* (0.0-10.8)	18.0* (14.3-23.0)	0.0* (0.0-12.0)
FABQW (0-42)	22.0* (10.0-27.0)	0.0* (0.0-8.0)	19.0* (8.0-29.0)	0.0* (0.0-8.0)	27.0* (18.0-37.0)	0.0* (0.0-4.5)
Average pain intensity on NPRS (0-10)	4.2* (3.0-5.6)	0.0* (0.0-0.0)	3.7* (2.7-3.7)	0.0* (0.0-0.3)	4.5* (3.4-5.9)	0.0* (0.0-0.0)
Current pain intensity on NPRS (0-10)	4.0* (3.0-6.0)	0.0* (0.0-0.1)	3.5* (3.0-5.0)	0.0* (0.0-0.6)	5.0* (3.3-6.0)	0.0* (0.0-0.0)

Calculation of p-values was performed using Mann-Whitney U test (for continuous variables) and chi-square test (for nominal variable). BMI=body mass index; CLBP=chronic low back pain; FABQ=fear avoidance beliefs questionnaire; FABQPA=fear avoidance belief questionnaire physical activity; FABQW=fear avoidance beliefs questionnaire work; NPRS= numeric pain rating scale; RMDQ=Roland Morris Disability Questionnaire. *$p<0.05$ for comparisons between participants with and without CLBP

4.3.2 Proprioceptive postural control

Participants with CLBP generally demonstrated a significantly higher average RPW value than asymptomatic counterparts only on stable surface (Table 4.2). Subgroup analyses revealed that average RPW values of young CLBP people were significantly higher than asymptomatic counterparts on both stable (p=0.006) and unstable surfaces (p=0.017) (Figure 4.3). While non-significant difference in RPW was noted between middle-aged adults with and without CLBP on the two testing surfaces (Figure 4.4, Table 4.2).

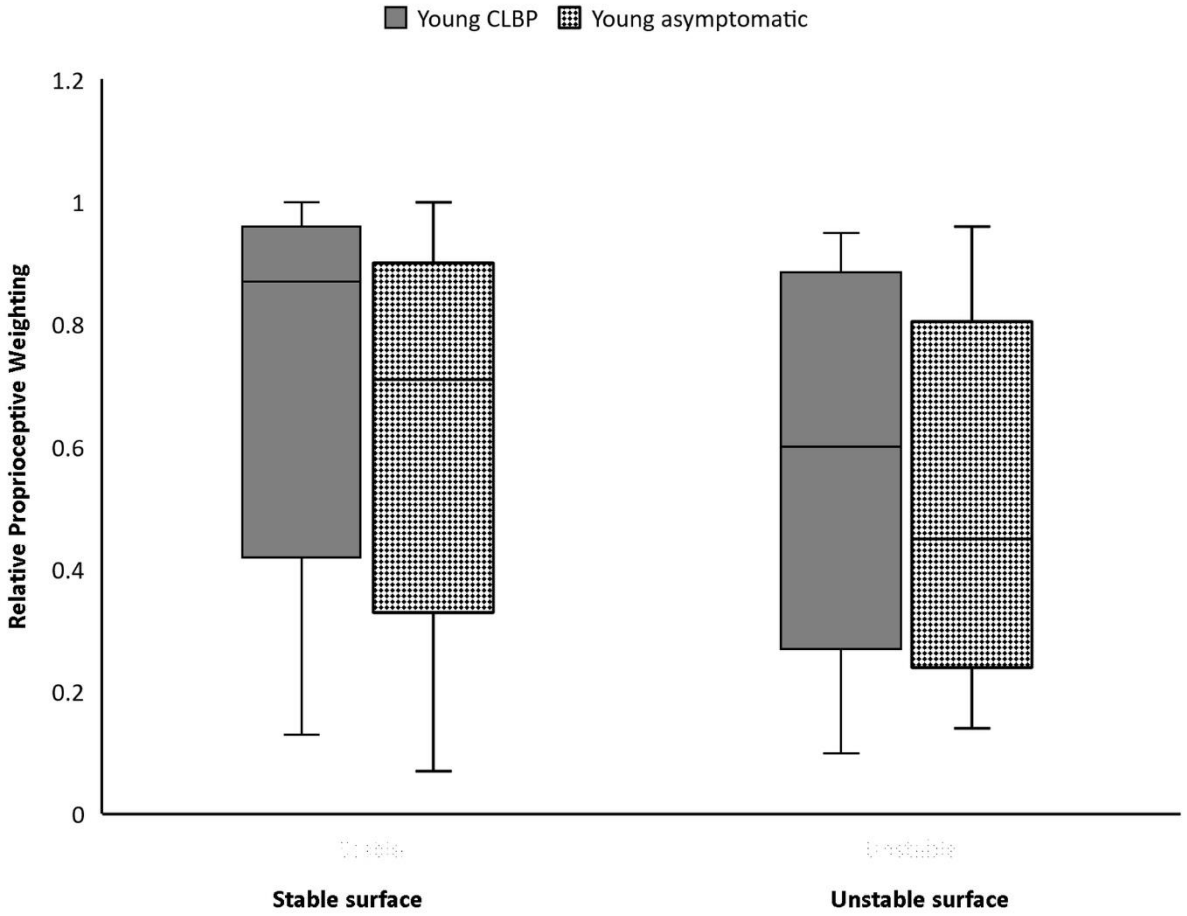

Figure 4. 3 Boxplots of Relative proprioceptive weighting scores of the young people with and without chronic low back pain (CLBP).

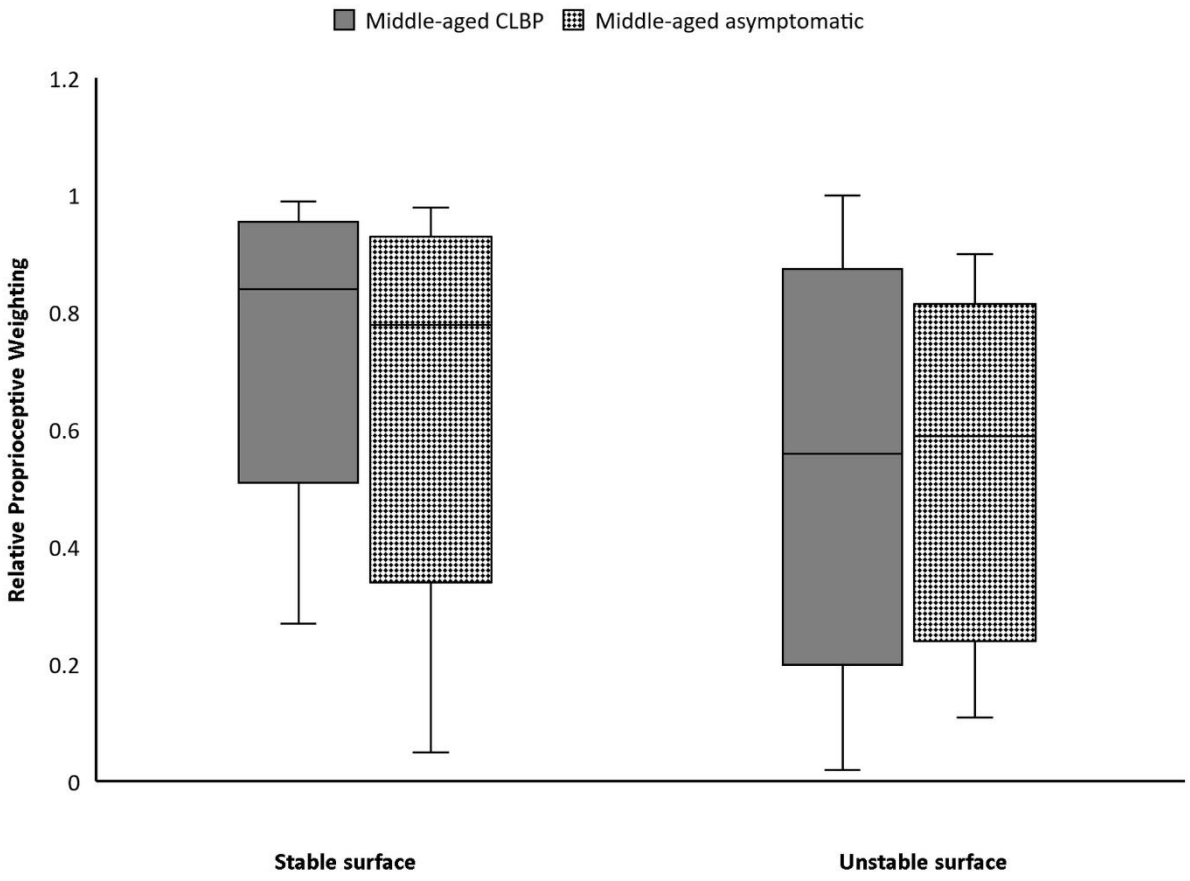

Figure 4. 4 Boxplots of Relative proprioceptive weighting scores of the middle-aged people with and without chronic low back pain (CLBP).

Table 4. 2 Proprioception in people with and without chronic low back pain (CLBP) [Median (interquartile range)]

Variables	**CLBP**	**Asymptomatic**	**p-value**	**Effect size**
RPW on stable surface	0.9 (0.7-0.9) (76)	0.7 (0.6-0.8) (71)	0.0*	-0.3
RPW on unstable surface	0.6 (0.4-0.8) (76)	0.6 (0.4-0.7) (71)	0.3	-0.1
Lumbar RE (degrees)	2.0 (0.9-3.6) (72)	1.4 (0.4-3.4) (71)	0.1	-0.1
Subgroup analysis (young)	**CLBP**	**Asymptomatic**		
RPW on stable surface	0.9 (0.7-0.9) (31)	0.7 (0.6-0.8) (29)	0.0*	-0.4
RPW on unstable surface	0.6 (0.4-0.8) (31)	0.5 (0.3-0.7) (29)	0.0*	-0.3
Lumbar RE (degrees)	2.0 (0.9-3.5) (29)	1.3 (0.3-3.8) (30)	0.2	-0.2
Subgroup analysis (middle-aged)	**CLBP**	**Asymptomatic**		
RPW on stable surface	0.8 (0.8-0.9) (45)	0.8 (0.6-0.9) (41)	0.1	-0.2
RPW on unstable surface	0.6 (0.4-0.8) (45)	0.6 (0.4-0.7) (40)	0.8	-0.0
Lumbar RE (degrees)	2.0 (0.7-3.7) (43)	1.7 (0.6-3.4) (41)	0.4	-0.1

Calculation of p-values was performed using Mann-Whitney U test. Effect sizes (r) of each observed difference were calculated by dividing the Z value by the square root of the total number of participants in that pair of groups. Cohen's guidelines for r effect sizes were used to interpret the result (0.1=small,0.3=medium,0.5=large). RPW=relative proprioceptive weighting; RE=repositioning error *$p<0.05$

4.3.3 Lumbar repositioning test

Absolute mean repositioning error in people with CLBP was larger than among asymptomatic counterparts in the whole cohort and in both subgroups. There were no significant differences in average lumbar repositioning errors between people with and without CLBP in both subgroups (Figure 4.5, Table 4.2). Additionally, there was no significant correlation between lumbar repositioning errors and RPW in people with and without CLBP in both age subgroups under both stable and unstable surface conditions (Table 4.3).

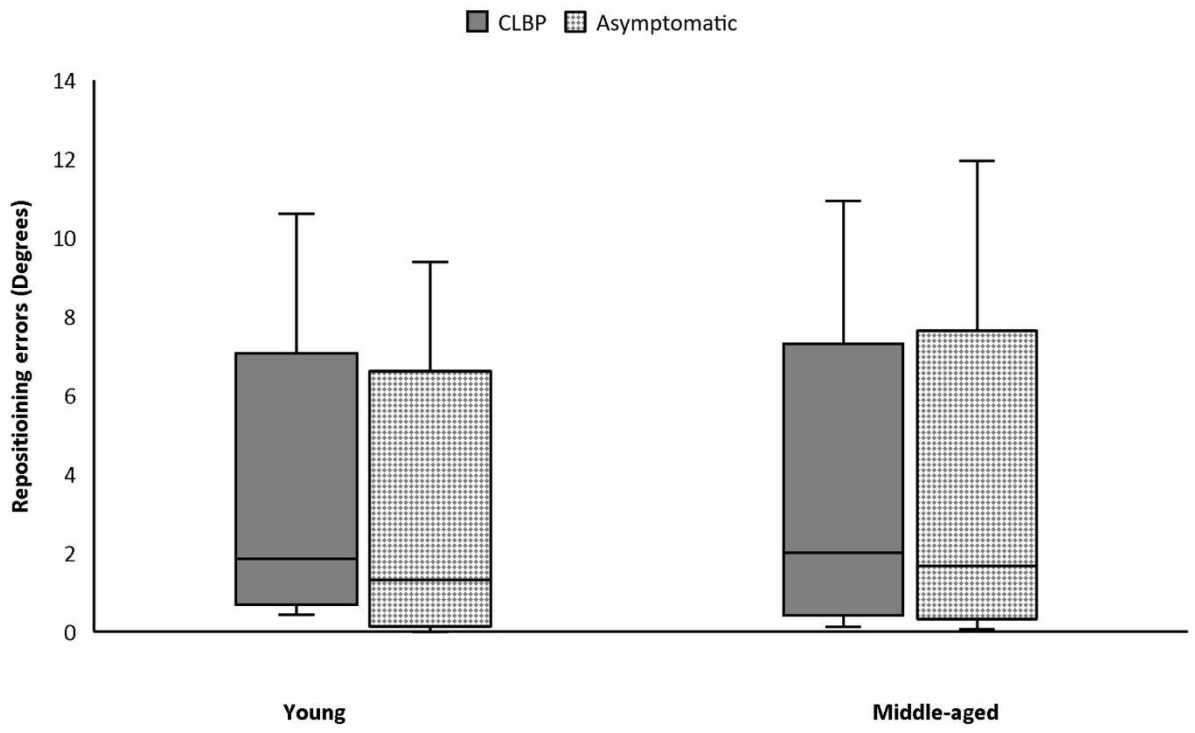

Figure 4. 5 Boxplots of reposition data of young and middle-aged participants. CLBP= chronic low back pain.

Table 4. 3 Correlations between lumbar repositioning errors (REs) and relative proprioceptive weighting (RPW) in people with chronic low back pain (CLBP) and asymptomatic controls.

	Variables	**Spearman's rank correlation coefficients**	**p-value**
CLBP young (18-44 years)	RPW on stable surface and lumbar RE	-0.02	0.9
	RPW on unstable surface and lumbar RE	0.11	0.6
CLBP middle-aged (45-65 years)	RPW on stable surface and lumbar RE	-0.15	0.3
	RPW on unstable surface and lumbar RE	0.07	0.6
Asymptomatic young (18-44 years)	RPW on stable surface and lumbar RE	-0.20	0.3
	RPW on unstable surface and lumbar RE	0.02	0.9
Asymptomatic middle-aged (45-65 years)	RPW on stable surface and lumbar RE	0.20	0.2
	RPW on unstable surface and lumbar RE	0.67	0.1

Calculation of p-values and correlation coefficients was performed using Spearman rank correlation test. The Spearman correlation coefficient values can range from +1 to -1 where +1 indicates a perfect positive association of ranks, 0 indicates no association between ranks and -1 indicates perfect negative association of ranks. The strength of the correlation can be classified as very weak (0.00 to 0.19), weak (0.20 to 0.39), moderate (0.40 to 0.59), strong (0.60 to 0.79) and very strong (0.80 to 1.0)

4.4 DISCUSSION

This is the first study to examine conscious and unconscious proprioception in middle-aged people with and without CLBP. Both young and middle-aged adults with CLBP had significantly higher LBP-related disability levels and fear-avoidance beliefs than their asymptomatic counterparts. While our CLBP cohort only had mild disability, they all demonstrated high FABQ-PA. Compared to asymptomatic individuals, people with CLBP generally relied more on ankle proprioception than LMM proprioception for maintaining standing balance on a stable surface without vision. As hypothesized, young adults with CLBP significantly relied more on ankle proprioception for maintaining standing balance on both stable and unstable surfaces than asymptomatic counterparts. Such phenomenon was not observed in middle-aged adults with CLBP. Interestingly, no significant differences in lumbar repositioning errors were noted between people with and without CLBP regardless of age. The magnitude of lumbar repositioning error was also unrelated to RPW in both people with and without CLBP regardless of age.

4.4.1 Relative proprioceptive reweighting

Young adults with CLBP rely on ankle proprioception for balance and do not change proprioceptive weighting of ankle and trunk even when signals from TS become unreliable on unstable surface. These results concur with prior research involving young adults with CLBP (age:18.5±0.5years) [199]. Acute and chronic LBP can impair LMM proprioception [194], which may persist even after pain remission [220]. Activation of nociceptors may disrupt proprioceptive signals from muscle spindles leading to reduced reliance on trunk proprioceptive signals for balance control [221]. Pain may also cause the reorganization of somatosensory cortex compromising the processing of proprioception signals [194]. Therefore, LBP may affect joint position sense and kinesthesia in the lumbar region [190, 199, 222]. This may lead to a vicious cycle of joint instability and pain [223].

Middle-aged individuals showed difficulty in proprioceptive reweighting regardless of LBP status. This phenomenon may be attributed to age-related deterioration in the neuromuscular (especially proprioception) system. Prior studies reported age-related deterioration in proprioceptive perception (e.g., joint sense or threshold of perception of joint motion) and cortical processing of proprioceptive signals in older adults [224-228]. However, little is known regarding proprioception changes in middle-aged individuals. Our findings open a new avenue for hypothesis formulation and research.

Our results suggest that asymptomatic middle-aged adults with and without CLBP start to show decreased proprioception reweighting capacity on both stable and unstable surfaces. The proprioceptive deficits in asymptomatic middle-aged people may be attributed to age-related changes in peripheral and/or central nervous systems. Although no prior research has investigated age-related deterioration in LMM proprioception (peripheral level) in middle-aged adults, LMM degeneration (muscle atrophy and increased fatty infiltration) are evidenced in these people, which may also affect muscle spindles in LMM. Atrophy of LMM starts at approximately 50 years and accelerates after the age of 60, resulting in impaired muscle strength and function [229]. Also fatty infiltration in LMM increases with age [230]. Interestingly, age-related fatty infiltration affects lumbar paraspinal muscles (9-58%) more than thigh (6-25%) or calf muscles (8-24%) in individuals aged between 24 and 76 years [231]. Age-related selective LMM degeneration in middle-aged adults may lead to similar age-related decreases in sensitivity and number of intrafusal muscle fibers in LMM, as well as degenerated ascending and descending pathways [232]. This results in compromised proprioceptive reweighting ability in asymptomatic middle-aged adults.

Changes in CNS of middle-aged adults may also affect their proprioceptive processing. Cortical proprioceptive processing involves primary motor cortex, primary and secondary somatosensory cortices, and supplementary motor areas [233-235]. Brain atrophy commences

at a rate of 5% per decade after 40 years of age [236]. Research has shown that cortical thinning begins after 40 years old due to cellular shrinkage and decreases in dendrite branching [237]. Likewise, decreases in frontal white matter have been reported after 45 years [238], while gray matter in frontal lobes in middle-aged adults (age: 48 years; range: 41-60 years) is significantly less than younger counterparts (average age: 29 years, range: 23-40 years) [239]. Additionally, proton magnetic resonance spectroscopy research demonstrates that middle-aged adults (average age: 47±3 years) have significantly lower concentration of neurotransmitters (e.g., N-acetyl-aspartate, g-aminobutyric acid, and glutamate) in prefrontal and sensorimotor cortices than young adults [240]. These structural and neurotransmitter changes may explain the suboptimal proprioceptive reweighting in middle-aged adults.

Interestingly, young people with CLBP display brain changes comparable to age-related brain changes in middle-aged adults. Reduced gray matter in brainstem and somatosensory cortex have been reported in people with CLBP [241]. A magnetic resonance imaging (MRI) study reported that gray matter density in primary somatosensory cortex is decreased in people with CLBP [242], leading to reorganization of primary somatosensory cortex and impaired connection with primary motor cortex [243]. This eventually affects spinal motor control [244]. Decreased connectivity and neural processing in supplementary motor areas have also been reported in people with CLBP [245, 246]. One study [247] found significant decreases in neurotransmitters in the primary somatosensory cortex in people with CLBP (average age: 34±11 years) as compared to asymptomatic controls. Taken together, these alterations may interrupt the interconnections between primary motor cortex, as well as primary and secondary somatosensory cortex, affecting processing of proprioceptive signals. These findings suggest that young adults with CLBP may have muscle spindle dysfunction and/or alterations in CNS that is comparable to middle-aged adults. Future research is warranted to use functional MRI and electroencephalogram to investigate structural and connectivity

changes in primary motor cortex, as well as primary and secondary somatosensory cortex, in relation to altered proprioceptive reweighting ability in young and middle-aged adults with and without CLBP.

4.4.2 Repositioning errors

No difference in repositioning errors between people with and without CLBP in young and middle-aged adults accords with previous research. One study performed the same repositioning test on young adults with LBP [age: 38±7 years; pain intensity on visual analogue scale=54±24mm] and found no significant difference in repositioning error between people with and without CLBP [204]. Although another study reported that people with CLBP [age: 40±6 years; pain intensity on visual analogue scale: 6.3±8.2cm] had significantly larger trunk repositioning error than age-matched asymptomatic controls [248], their testing method differed from the current study. Specifically, their participants underwent active repositioning test in the chair of an isokinetic dynamometer, with upper trunk, bilateral thighs and pelvic immobilized by straps, which might provide extra sensory feedback to improve the test results. Further, since their participants had higher pain intensity than our symptomatic participants [median NPRS score: 4.2/10, interquartile range:3-6/10], more severe LBP may cause greater lumbar repositioning error than those with less symptoms.

4.4.3 Correlation between RPW and repositioning errors

The non-significant correlations between repositioning error and RPW in the current study may stem from the fact that the repositioning test is insensitive to detect conscious proprioceptive deficits [249]. Since the repositioning error in the repositioning test is affected by both the proprioceptive sense and cognitive/memory function. Participants need to have good concentration and memory to remember pre-determined target position [250, 251]. If participants have a distraction or poor memory, the test results will be affected. These factors might have affected the results of the reposition test.

Our results lay the foundation for future research in middle-aged people with and without LBP. Proprioception involves joint position sense, kinesthesia, movement detection threshold, and force sense. Future studies should use established motor perception threshold tests in sitting or side lying [223, 249, 252] to evaluate an individual's ability in detecting the smallest amount of axial or sagittal trunk rotation. Similarly, dynamometer can be used to measure force sense of people with CLBP in different age subgroups [253]. Future mechanistic research is warranted to determine whether the observed changes in proprioceptive reweighting of middle-aged people occur at spinal and/or supraspinal levels. Histological studies are also needed to examine if the quantity and quality of muscle spindles in LMM in middle-aged adults are associated with other LMM characteristics (e.g., atrophy/fatty infiltration).

4.4.4 Limitations

This study had some limitations. First, prior research suggested that people with LBP classified as having a flexion pattern in the O'Sullivan classification system displayed impaired lumbar proprioception.[67] Our participants were not classified into different subgroups based on that classification system, which has prevented further subgroup analyses. Second, the use of a neutral position as the target position for the lumbar repositioning tests may be highly predictable and cannot detect subtle differences between individuals. Although this method has been used in previous research [59], future studies should use more challenging repositioning tasks. Third, the duration of CLBP might affect the motor control and proprioception differently but this data was not documented. Fourth, the current study only vibrated LMM and TS at 60Hz. While this vibration frequency was commonly used in prior studies to distinguish people with and without LBP [198], different vibration frequency may stimulate different mechanoreceptors and yield different results [201]. Future studies should use a range of vibration frequency to determine whether a specific set of vibration

frequency is more sensitive to discern middle-aged and older people with and without LBP. Fifth, since good postural stability relies on proper integration of visual, proprioceptive and vestibular inputs in CNS [192]. Dysfunctions in any of the three systems at the peripheral, spinal and/or supraspinal level(s) may affect the postural control. Although people diagnosed with vestibular impairment were excluded in the current study, it could not rule out the possibility that some middle-aged participants might have age-related changes in their vestibular system that might confound our findings. Future studies can use advanced technologies (e.g., near-infrared spectroscopy) [254] and established tests (e.g., galvanic vestibular stimulation and vestibule-ocular reflex tests, or vestibular evoked myogenic potentials) [255] to determine the mechanisms underlying the non-significant difference in RPW between middle-aged adults with and without CLBP. Sixth, the inclusion of people aged 60 to 65 years might have confounded the results in the middle-aged subgroup because of aging and more severe spinal degeneration. However, our sensitive analyses yielded the same results after removing people aged 60 years or older from the analyses. According to the World Health Organization, 45-65 years of age are considered as middle-age for people living in developed countries but not for those living in developing countries due to lower life expectancy in the latter [256]. Seventh, the order of testing for RPW was not randomised. It is possible that they are better for unstable surfaces just because they have already had practice with receiving vibration to the TS and LMM (i.e., unstable surfaces always tested after stable surfaces). As such, the generalizability of our results should be interpreted with caution.

4.5 CONCLUSIONS

This is the first study to reveal that asymptomatic middle-aged people display difficulty in proprioceptive reweighting, which is comparable to that of young and middle-aged adults with CLBP. This finding indicates that asymptomatic middle-aged adults are at risk of

suboptimal spinal control, and may explain the higher prevalence of LBP in middle-aged people than younger counterparts [257]. Future investigation is warranted to answer whether asymptomatic middle-aged people with more impaired proprioceptive reweighting capacity have a higher risk of developing LBP in the future. Proprioception training and spinal manipulative therapy may improve back muscle proprioception [258, 259]. This warrants further investigation to determine whether a single or a combination of these interventions can improve back proprioception and symptoms in people with LBP across lifespan.

Chapter 5. Are morphometric and biomechanical characteristics of lumbar multifidus related to pain intensity or disability in people with chronic low back pain after considering psychological factors or insomnia?

5.1 INTRODUCTION

Low back pain (LBP) affects approximately 80% of adults at least once in their lifetime and is one of the leading causes of disability globally [183]. LBP is defined as pain or discomfort between the twelfth ribs and buttocks [137]. Although most LBP cases recover spontaneously, some people with LBP may experience chronic LBP (CLBP) lasting for 3 months or more [260]. The point prevalence of CLBP in the United States has been documented to be 13.1%.[261] CLBP is one of the major causes of exorbitant treatment costs, and indirect costs due to sick leaves in the United States [186].

Morphometric and functional changes in lumbar multifidus muscle (LMM) may be related to CLBP [40, 189, 262]. Since LMM is a spinal stabilizer that provides approximately two-thirds of spinal stability [263], aberrant changes in morphometry (e.g., muscle atrophy [142, 264] or fatty infiltration [21, 148]) or functional deficits of LMM (e.g., altered muscle activity and/stiffness) [22, 92, 265] may be related to the development or maintenance of CLBP. For instance, Danneels et al reported low levels of surface electromyography activity in LMM among people with CLBP as compared to healthy individuals. Similarly, Masaki et al [92] reported that the average LMM stiffness of people with CLBP was significantly higher than that of asymptomatic controls. Higher LBP intensity was significantly associated with higher LMM stiffness among people with CLBP [92]. However, because prior research investigating the associations between LMM characteristics and CLBP clinical outcomes did not consider the influences of other confounders, it remains unclear whether their associations persist after taking confounders into account.

Multiple confounding factors are known to be related to CLBP. Compared to healthy individuals, people with CLBP are 2.3 to 3.2 folds more likely to have comorbidities (e.g., depression, anxiety and insomnia) [186]. Previous research has suggested that various psychological factors [e.g., anxiety, depression, pain catastrophizing, fear-avoidance beliefs (FAB), etc.] are associated with pain intensity and/or disability in people with CLBP [33-38]. In addition to mood disturbances, impaired sleep has been reported in people with CLBP [266, 267]. Approximately 55% of people with CLBP experience insomnia [39], which is defined as sleep disturbance or difficulty in initiating sleep [268]. People with CLBP also demonstrated significantly poorer sleep quality/quantity than asymptomatic individuals [266, 269].

Given the above, it is conceivable that correlations between various characteristics (e.g., resting and contracted LMM thickness, percent thickness changes during contraction, and resting muscle stiffness) of LMM and clinical outcomes in people with CLBP may be modified after considering various psychological and/or sleep-related factors. A better understanding of these associations can improve the clinical management of these people. Therefore, the current study aimed to: (1) compare the psychology, insomnia, and LMM characteristics between people with and without CLBP; (2) quantify the correlations between various psychological factors, sleep disturbance, or LMM characteristics and clinical outcomes (intensity of LBP and LBP-related disability) in people with CLBP; and (3) determine whether LMM characteristics are related LBP or LBP-related disability in people with CLBP after considering other confounders.

5.2 METHODS

5.2.1 Participants and study design

This case-control study was conducted in a university laboratory. Individuals aged between 18 and 65 years were eligible for the study. Participants with CLBP (n=78) were recruited

from a public hospital, while asymptomatic participants (n=73) were recruited from the university campus. People with CLBP were recruited if: (1) they experienced non-specific CLBP (defined as pain not attributable to a specific cause [270]) with or without leg pain that lasted for 3 months or more [260], that required medical consultation; and (2) their LBP intensity was at least 5 out of 10 on an 11-point numeric pain rating scale (NPRS). Age-matched asymptomatic controls should not experience an episode of LBP in the last 24 months. Exclusion criteria for all participants were: history of neurological disease, systemic inflammatory disease, previous spinal surgery, spinal fractures/tumours, metabolic disease, confirmed or suspected pregnancy, and indication for spine surgery.

5.2.2 Data Collection Procedures

Following the provision of informed written consent as suggested by the Human Subjects Ethics Sub-committee of the university (HSEAR20151027007-01), participants were instructed to complete a battery of questionnaires related to their demographics, pain intensity, LBP-related disability, fear-avoidance beliefs, pain catastrophizing, anxiety, depression, and insomnia.

5.2.3 Demographic questionnaire

The questionnaire asked questions related to the participant's age, gender, body mass index, education level, work status, married status, and smoking and drinking habits.

5.2.4 Standardized questionnaires

Pain: An 11-point numeric pain rating scale (NPRS) was used to quantify LBP intensity, with "0" representing "no pain at all" and "10" representing "the worst imaginable pain" [271]. Participants were asked to choose a number best represented: (1) the current level of pain; as well as (2) the least and (3) worst levels of pain during the past 24 hours. The pain level over the past 24 hours was estimated using the average of three ratings [206]. The pain intensity level was categorized as mild (1-5), moderate (6-8) and severe (9-10) [272]. A cut-off score of

>4 is considered as the minimal clinically important change in people with CLBP [273]. The scale has shown excellent test-retest reliability [intraclass correlation coefficient (ICC)=0.99] in assessing pain intensity among people with musculoskeletal pain [274].

LBP-related disability: participants' functional disability was assessed by the Hong Kong-Chinese version of the 24-item Roland-Morris Disability Questionnaire (RMDQ) [207]. It evaluates the impact of LBP on daily function, with scores ranging from 0 to 24 (0 means no disability; 24 means maximum disability). From the total score, the disability was classified into mild (0-8), moderate (9-16), and high (17-24) severity [207]. A cut-off score of >4 indicates people with dysfunctional LBP [275]. RMDQ has demonstrated excellent test-retest reliability (ICC=0.94) in assessing LBP-related disability in people with non-specific CLBP [207].

Mood: The Chinese version of the Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression [276]. It consists of two 7-item subscales measuring anxiety (HADS-A) and depression (HADS-D). Each of the 14 items is scored from 0 to 3 [277]. Total scores of <7, 8-10, 11-14, and 15-21 in each subscale indicate non-cases, mild, moderate, and severe problems, respectively [278]. A cut-off value of >8 is considered as clinically significant scores in each subscale of anxiety or depression [279]. For the total score, >13 is considered as clinically significant scores for both anxiety and depression [279]. This questionnaire has shown excellent internal consistency (Cronbach's alpha=0.84) in evaluating anxiety and depression among Chinese people with cancer and their family caregivers [280].

Pain catastrophizing: The Chinese version pain catastrophizing scale (PCS) was used to assess pain catastrophizing [281]. This 13-item questionnaire consists of 3 subscales: rumination, magnification, and helplessness [281]. Total PCS scores of 30 or above signify clinically significant pain catastrophizing in people with chronic pain [282]. It has demonstrated excellent internal consistency for the total PCS score ($\alpha = 0.9$) [281].

Fear-avoidance beliefs: The level of pain-related fear was evaluated by the Hong Kong-Chinese version of the 16-item Fear-Avoidance Beliefs Questionnaire (FAB). It has demonstrated excellent internal consistency (α=0.8), reliability, and validity in measuring fear-avoidance beliefs in people with CLBP [38, 208]. Each item was graded on a 7-point Likert-type scale (0 means completely disagree; 6 means completely agree). It consists of 2 subscales: (1) beliefs about damage from physical activity (FAB-PA) [4 items (2,3,4,5); score range: 0 to 24]; and (2) beliefs about damage from work-related activities (FAB-W) [7 items (6,7,9,10,11,12,15); score range: 0 to 42]. The remaining five items are excluded from the calculation. The FAB-PA subscale is classified as low (0-14) and high fear levels (15-24). The FAB-W subscale is also classified as low (0-33) and high fear levels (34-42). The overall total score was calculated by adding the score of both subscales [38]. The cut-off scores of >13 and >29 for FAB-PA and FAB-W, respectively, have been reported to be predictive of poor clinical outcome (disability) in people with LBP [219]. For FAB-Total, cut-off scores of 48 are considered to predict persistent disability in the future [283].

Insomnia: The severity of insomnia was assessed by the Chinese version of the 7-item Insomnia Severity Index (ISI). Each item is rated on a 5-point Likert scale (e.g. 0 = no insomnia; 4 = very severe insomnia) [284]. The total scores were interpreted as no insomnia (0-7), sub-threshold insomnia (8-14), moderate insomnia (15-21), and severe insomnia (22-28) [285]. A cut-off value of 10 is considered to be optimal to detect insomnia in the community [286]. The ISI has demonstrated good test-retest reliability (α=0.88) in people with chronic pain [287].

5.2.5 LMM assessments

LMM morphometry and function: Bilateral parasagittal images of LMM at the L4/L5 and L5/S1 levels at rest and during submaximal contraction were captured with separate brightness-mode ultrasound videos on Supersonic Imagine® (Aixplorer

Innovative UltraFast^{TM} Ultrasound Imaging, France). This non-invasive ultrasonography technique has been used to estimate muscle activation [77]. It has shown good to excellent intra-examiner (ICC= 0.86-0.90) and inter-examiner (ICC=0.86-0.93) reliability in evaluating resting/contracted thickness and percentage thickness change in LMM [78, 288]. The participant in the prone position performed contralateral leg lifts three times to touch a bar fixed at 5-cm height in order to elicit submaximal voluntary contraction of LMM [289]. The lumbar curve at rest was maintained at around 10°. The resting and contracted LMM thicknesses in the recorded brightness-mode videos were then measured on the ultrasonography device. The thickness was determined from the distance between the posterior tip of the facet joint and the inside edge of the overlying fascia (Figure 5.1). The average of three measured thickness ratios (thickness contracted − thickness rest/thickness rest x 100%) of each LMM muscle was used for statistical analysis. The greater values represent greater activation induced change in LMM thickness.

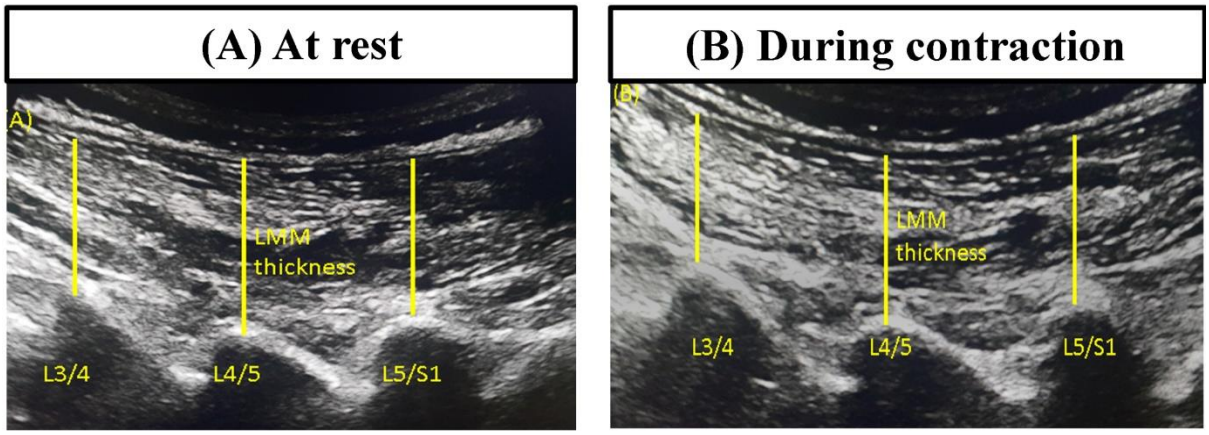

Figure 5. 1 Thickness measurements of lumbar multifidus muscles using bright-mode ultrasound images (A) at rest and (B) during contraction.

The shear modulus (stiffness) of bilateral LMM at the L4/L5 and L5/S1 levels of the participants were assessed at rest by supersonic shear wave imaging (SSI) function of Supersonic Imagine®. It has shown good to excellent intrarater reliability ≥0.85 for 3 conditions: prone-trunk in neutral position, prone-trunk flexion at 40°, and trunk extension at 20° [290]. The resting LMM stiffness at each muscle level was measured thrice. A curved (1-6MHz) SSI ultrasound probe was placed parallel to LMM fibers at the target level [291]. The probe sent multiple ultrasound push beams focused on various depths to deform and to create shear waves in LMM. The machine detected the shear waves and generated the resulting 2-dimensional shear modulus color maps at 1 sample/second. On each map, 2 standardized circular regions of interest (ROIs) with 5mm diameter were placed between 1 and 2 cm depth of the target LMM (Figure 5.2). The average pixel intensity within the ROIs on each map indicates the LMM shear modulus. The shear modulus (μ) within each ROI was automatically calculated by the software using the formula $\mu = \rho v^2$, where ρ is the muscle mass density and v is shear wave speed.[292] The resting LMM stiffness was estimated by averaging the shear modulus of each LMM muscle at rest.

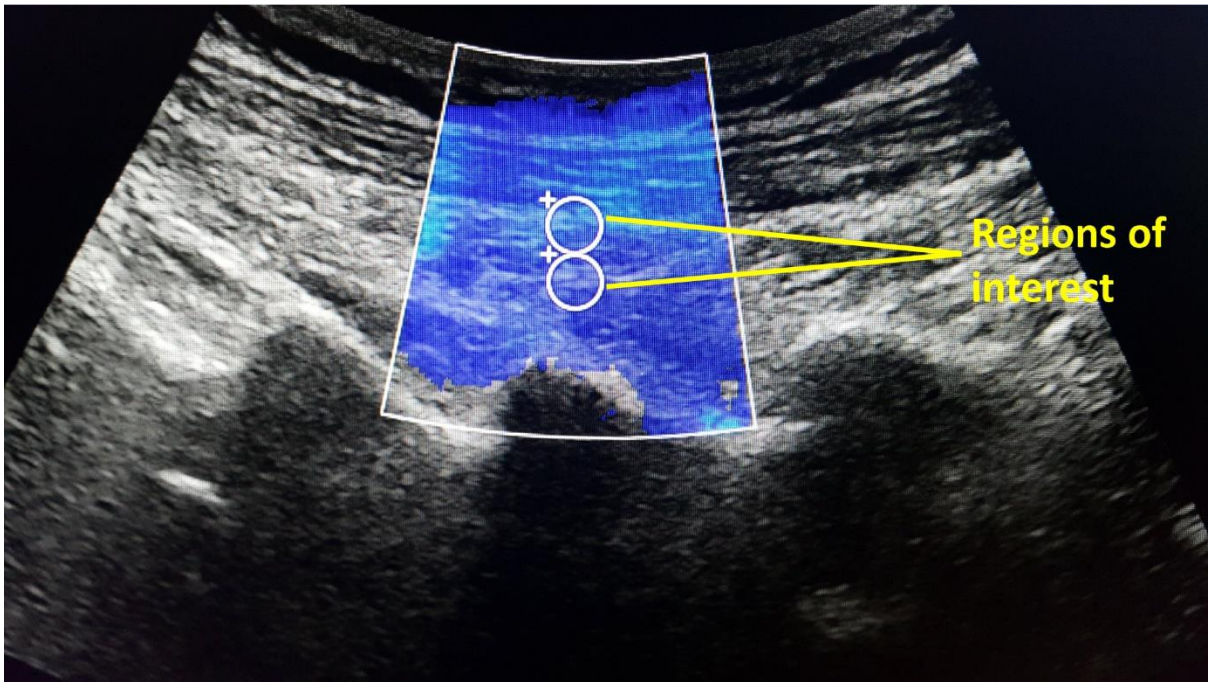

Figure 5. 2The supersonic shear wave imaging for lumbar multifidus stiffness measurements based on average pixel intensity within two regions of interest (5mm diameter).

5.2.6 Data analyses

Statistical analyses were performed using SPSS software (Version 26, IBM Corp., Armonk, NY). Since Shapiro-Wilk tests indicated that our data was not normally distributed, non-parametric tests were used for data analyses. Descriptive statistics were conducted to summarize demographic characteristics (median and interquartile range) pain intensity, and RMDQ scores, HADS scores, FAB scores, PCS scores, ISI scores, while the mean and standard deviation were used to report LMM parameters in people with and without CLBP. Mann-Whitney U tests were used to compare between-group differences in psychological and insomnia scores. Linear mixed model analysis, which is robust for non-parametric data, was used for between-group comparisons of LMM characteristics after adjusting for age, gender and body mass index (BMI).[293] LMM characteristics. Spearman's rank correlation coefficients were used to evaluate the relationships among demographic characteristics, pain intensity, RMDQ scores, HADS scores, FAB scores, PCS scores, ISI scores, and LMM stiffness and LMM thickness ratios. The strength of the correlation was classified as very weak (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80-1.0).[216] Partial correlation analyses between pain intensity and LMM parameters were performed by adjusting for psychological variables that were significantly related to pain intensity. Likewise, partial correlation analyses between LBP-related disability and LMM parameters were conducted by adjusting for psychological variables that significantly related to LBP-related disability. Psychological, insomnia, and LMM variables that demonstrated significant correlations with the 11-point NPRS or RMDQ score were then entered into two separate multiple linear regression models using a stepwise approach ($p<0.05$ for entry, $p>0.10$ for removal) to evaluate the relation between LMM characteristics and pain intensity or LBP-related disability in people with CLBP after accounting for various confounders. The significance level was set at $p<0.05$ for all tests.

Additionally, hierarchical cluster analyses were performed using pain scores, psychological and sleep scores. Cluster analyses were also performed for pain scores and LMM parameters. Similarly, cluster analyses were conducted using RMDQ scores, psychological scores and sleep scores, and separately for disability scores and LMM parameters.

5.3 RESULTS

5.3.1 Demographic Data

Demographic data of 78 participants with CLBP and 73 asymptomatic participants are shown in Table 5.1. There were no significant differences in age, body mass index, percentage of male, occupation, smoking status, and alcohol use, except for education levels and marital status between groups.

Table 5. 1 Characteristics of participants with chronic low back pain (CLBP) and asymptomatic individuals [Median (interquartile range)]

Characteristics	**CLBP**	**Asymptomatic**
Age (years)	46.0 (35.8 to 54.0)	48.0 (30.0 to 54.5)
Body mass index (kg/m^2)	23.0 (21.0 to 25.0)	22.0 (20.0 to 24.0)
Gender male *n* (%)	32 (41.0%)	36.6% (26)
Education level *n* (%) *****		
Less than College	34 (44.7 %)	20 (28.2%)
College or above	42 (55.3%)	51 (71.8%)
Occupation *n* (%)		
Employed	53 (74.7%)	50 (75.8%)
Unemployed/retired.	18 (25.4%)	16 (24.2%)
Marital status *n* (%) *****		
Married	49 (66.2%)	30 (47.6%)
Others	25 (33.8%)	33 (52.4%)
Smoking status *n* (%)		
No	72 (94.7%)	69 (97.2%)
Yes	4 (5.3%)	2 (2.8%)
Alcohol use *n* (%)		
No	54 (71.1%)	53 (74.6%)
Yes	22 (28.9%)	18 (25.4%)

Note: Married and others (Unmarried/divorced/widowed)

Calculation of p-values was performed using Mann-Whitney U test (for continuous variables) and chi-square test (for nominal and ordinal variables). *****$p<0.05$ for comparisons between people with CLBP and asymptomatic participants.

5.3.2 Psychological and sleep parameters

People with CLBP demonstrated significantly higher pain intensity, disability, HADS, FAB, PCS and ISI scores than asymptomatic participants ($p<0.05$). Fifty percent and 61% of people with CLBP had clinically significant pain and disability, respectively, while 40% and 38% had clinically significant mood and fear-avoidance beliefs problems, respectively. Ten percent and 59% had clinically significant pain-catastrophizing and insomnia, respectively (Table 5.2).

Table 5. 2 Summary of scores of psychological and sleep variables

Variables	**Measures**	**CLBP**		**Asymptomatic**
		Scores [Median (IQR)]	Clinically significant n (%)	Scores [Median (IQR)]
Pain intensity	NPRS*	4.2 (3.0 to 5.6)	38 (50%) (dysfunctional LBP)	0.0 (0.0 to 0.0)
Low back pain-related disability	RMDQ*	5.5 (3.0 to 9.0)	46 (60.5%)	0.0 (0.0 to 1.0)
Anxiety and depression	HADS Total*	11.5 (7.2 to 16.8)	30 (39.47%)	8.0 (4.0 to 12.0)
	HADS-A*	7.0 (4.0 to 8.0)	18 (23.68%)	4.0 (2.0 to 6.5)
	HADS-D*	5.0 (3.0 to 8.0)	18 (23.68%)	3.0 (1.0 to 6.0)
Fear-avoidance beliefs	FAB-Total*	44.0 (27.0 to 53.0)	29 (38.16%)	0.0 (0.0 to 22.0)
	FAB-PA*	18.0 (14.0 to 21.0)	59 (77.63%)	0.0 (0.0 to 11.3)
	FAB-Work*	22.0 (10.0 to 27.0)	14 (18.42%)	0.0 (0.0 to 8.0)
Pain-catastrophizing	PCS Total*	17.0 (8.0 to 26.0)	10 (13.2%)	2.0 (0.0 to 11.0)
	PCS-H*	7.0 (3.3 to 11.8)		1.0 (0.0 to 3.0)
	PCS-M*	4.0 (2.0 to 6.0)		1.0 (0.0 to 3.0)
	PCS-R*	6.0 (2.0 to 9.0)		0.0 (0.0 to 4.0)
Sleep	ISI*	12.0 (7.3 to 15.0)	45 (59.2%)	5.00 (3.0 to 11.00)

FAB=fear-avoidance belief questionnaire; FAB-PA=fear-avoidance beliefs-physical activity; FAB-W=fear-avoidance beliefs questionnaire-work; HADS=hospital anxiety and depression scale; HADS-A=hospital anxiety and depression scale- anxiety; HADS-D=hospital anxiety and depression scale-depression; IQR= interquartile range; ISI=insomnia severity scale; NPRS=numeric pain rating scale; PCS=pain catastrophizing. *$p<0.05$ for comparison between people with CLBP and asymptomatic participants

5.3.3 LMM Parameters

Between-group comparisons of LMM characteristics at L4/L5 and L5/S1 are reported in Table 5.3. After adjusting for age, gender and BMI, the percent thickness change of LMM during contraction at L4/L5 was significantly greater in asymptomatic participants than that in people with CLBP ($p<0.05$). There were no significant differences in LMM resting thickness, contracted thickness, or LMM resting stiffness at both levels between people with and without CLBP. Likewise, the percent thickness change of LMM at L5/S1 during contraction was not statistically different between group

Table 5. 3 Between-group comparisons of LMM parameters

Variables	**CLBP**			**Asymptomatic**		
	Average	Right	Left	Average	Right	Left
LMM resting thickness at L4/L5 (cm)	2.63 ± 0.46	2.63 ± 0.49	2.63 ± 0.50	2.52 ± 0.43	2.49 ± 0.44	2.55 ± 0.49
LMM resting thickness at L5/S1 (cm)	2.74 ± 0.52	2.75 ± 0.55	2.74 ± 0.57	2.62 ± 0.46	2.61 ± 0.49	2.64 ± 0.48
LMM contracted thickness at L4/L5 (cm)	3.20 ± 0.51	3.20 ± 0.52	3.20 ± 0.54	3.16 ± 0.45	3.14 ± 0.47	3.17 ± 0.51
LMM contracted thickness at L5/S1 (cm)	3.11 ± 0.57	3.09 ± 0.58	3.13 ± 0.60	3.10 ± 0.44	3.12 ± 0.44	3.08 ± 0.47
Percent thickness change during contraction at L4/L5*****	0.22 ± 0.81	0.22 ± 0.12	0.23 ± 0.11	0.27 ± 0.10	0.27 ± 0.12	0.26 ± 0.11
Percent thickness change during contraction at L5/S1	0.18 ± 0.11	0.17 ± 0.12	0.19 ± 0.15	0.18 ± 0.09	0.18 ± 0.10	0.17 ± 0.10
LMM resting stiffness at L4/L5 (kPa)	43.31 ± 21.53	43.71 ± 25.94	42.86 ± 26.75	41.27 ± 18.72	39.45 ± 20.22	43.09 ± 27.48
LMM resting stiffness at L5/S1 (kPa)	43.51 ± 21.16	42.40 ± 27.39	44.87 ± 24.74	41.91 ± 19.42	40.91 ± 25.31	42.90 ± 23.32

Notes: Adjusted for age, BMI, and gender, *$p<0.05$ for comparison between people with CLBP and asymptomatic participants
Abbreviations: CLBP=chronic low back pain; cm=centimeters; kPa = kilopascal; LMM=lumbar multifidus muscle

5.3.4 Correlations between pain intensity and demographic, psychological, or LMM parameters

None of the demographic variables were associated with pain intensity. Table 5.4 shows the interrelation among various psychological and sleep variables, LMM variables, LBP intensity, and LBP-related disability. Spearman's correlation analyses showed that pain intensity was significantly but weakly correlated with PCS-Total scores (ρ = 0.29, p<0.05), and was moderately correlated with the scores of PCS-H (ρ = 0.34, p<0.05), FAB-Total (ρ = 0.30, p<0.05), FAB-W (ρ = 0.39, p<0.05), and ISI (ρ = 0.44, p<0.05) in people with CLBP. Partial correlation analysis revealed no significant association between any LMM parameters and LBP intensity. The cluster analysis yielded 3 clusters of psychological factors with pain intensity. Cluster 1 consisted of HADS-A, HADS-D, and HADS-T; cluster 2 comprised PCS-H, PCS-M, PCS-R, and PCS-T; and cluster 3 consisted of pain intensity, FAB-PA, FAB-W, and FAB-T. There was no significant difference in factors among the three clusters. Similarly, another cluster analysis yielded 2 groups of LMM parameters with pain intensity. Cluster 1 consisted of resting and contracted thickness at L4-5 and L5-S1 levels, while cluster 2 consisted of resting stiffness and percent thickness change at L4-5 and L5-S1 levels, and pain intensity. There was no significant difference in factors between two cluster

Table 5. 4 The interrelations among various psychological and insomnia variables, lumbar multifidus muscle (LMM) variables, low back pain (LBP)

	Age	Gender	BMI	Education level	Occupation	Smoking	Alcohol use	Marital status	HADS-T	HADS-A	HADS-D	PCS Total	PCS-H	PCS-M	PCS-R	FAB-Total	FAB-PA	FAB-W	ISI	Thickness Rest L4/L5	Thickness Rest L5/S1	Contracted thickness L4/L5	Contracted thickness L5/S1	Percentage thickness L4/L5	Percentage thickness L5/S1	Stiffness at rest L4/L5	Stiffness at rest L5/S1
NPRS	.20	-.01	-.19	-.22	.10	-.02	.07	.06	.21	.15	.21	.29*	.34*	.23	.20	.30*	.04	.39*	.44*	.05	.04	.05	05	-.10	-.07	-.16	-.10
RMDQ	.26****	.02	.13	-.36*	-.09	-.05	-.10	.04	.26*	.20	.28*	.25*	.33*	.17	.14	.34*	.24*	.26*	.24*	.20	.12	.14	.06	-.21	.00	-.09	-.12

intensity, and LBP-related disability in people with chronic LBP.

Spearman rank correlation coefficient. *p < 0.05. FAB=fear-avoidance beliefs questionnaire; FAB-PA=fear-avoidance beliefs questionnaire-physical activity; FAB-W=fear-avoidance beliefs questionnaire work; HADS=hospital anxiety and depression scale; HADS-A=hospital anxiety and depression scale-anxiety; HADS-D=hospital anxiety and depression scale-depression; ISI=insomnia severity index; NPRS=numeric pain rating scale; PCS=pain catastrophizing scale; PCS-H=pain catastrophizing scale-helplessness; PCS-M=pain catastrophizing scale-magnification; PCS-R=pain catastrophizing scale-rumination; RMDQ=Roland Morris disability questionnaire.

The Spearman correlation coefficient values can range from +1 to -1 where +1 indicates a perfect positive association of ranks, 0 indicates no association between ranks and -1 indicates perfect negative association of ranks. The strength of the correlation can be classified as very weak (0.00 to 0.19), weak (0.20 to 0.39), moderate (0.40 to 0.59), strong (0.60 to 0.79) and very strong (0.80 to 1.0)

5.3.5 Correlations between LBP-related disability and demographic, psychological, or LMM parameters

Spearman's correlation analyses showed that RMDQ scores were significantly, but weakly correlated with age (ρ = 0.26, p<0.05), HADS-total (ρ = 0.26, p<0.05), HADS-D (ρ = 0.28, p<0.05), PCS-Total scores (ρ = 0.29, p<0.05). RMDQ scores were also moderately correlated with the education level (ρ = -0.36, p<0.05), FAB-Total scores (ρ = 0.34, p<0.05), FAB-PA scores (ρ = 0.24, p<0.05), FAB-W scores (ρ = 0.24, p<0.05), PCS-H scores (ρ = 0.33, p<0.05), ISI scores (ρ = 0.24, p<0.05) in people with CLBP. No significant correlation was noted between RMDQ scores and any LMM parameters. Partial correlation analysis found that LMM parameters were not significantly related to LBP-related disability. The cluster analysis yielded 3 clusters involving psychological factors and/or RMDQ scores. Cluster 1 comprised HADS-A, HADS-D, and HADS-T; cluster 2 contained PCS-H, PCS-M, PCS-R, and PCS-T; and cluster 3 consisted of FAB-PA, FAB-W, FAB-T, ISI and RMDQ scores. There was no significant difference in factors among the three clusters. Similarly, another cluster analysis yielded 2 groups of LMM parameters with pain intensity. Cluster 1 consisted of resting and contracted thickness of LMM at L4-5 and L5-S1 levels, whereas the cluster 2 comprised resting stiffness and percent thickness change of LMM at L4-5 and L5-S1 levels, and RMDQ scores. There was no significant difference in factors between the two clusters.

5.3.6. Factors explaining LBP-intensity.

Since no significant associations were noted between LMM parameters and LBP intensity or disability, only those psychological and sleep parameters were included in the regression models. Three independent variables were eligible for the entry to the regression model for predicting LBP intensity (FAB-W, PCS-H, and ISI scores). The final model accounted for approximately 24% of the variance of pain intensity (R^2 = 0.241;

adjusted R^2 = 0.220). Specifically, high ISI scores and FAB-W scores were associated with higher pain intensity in people with CLBP (Table 5.5). The unique variance explained by each of the two independent variables indexed by the squared semi-partial correlations was relatively low (insomnia and fear-avoidance beliefs about work each only accounted for approximately 8% of the variance of pain intensity).

Table 5. 5 Summary of stepwise regression model predicting numeric pain rating scale scores.

Model	**B**	**SE-B**	**β**
Constant	2.907	0.379	
ISI*****	0.087	0.030	0.305
FAB-W*****	0.040	0.014	0.301

FAB-W=Fear-avoidance beliefs questionnaire-work subscale; ISI=Insomnia severity index.
B=regression coefficient; SE-B=standard error of B; β= standardized regression coefficient
Note: The dependent variable was numeric pain rating scale scores.
R^2 = 0.241, Adjusted R^2 = 0.220. F (2,73) =11.60 p<0.001

5.3.7 Factors explaining LBP-related disability.

A two-stage hierarchical linear regression analysis was used to predict the level of disability reported by people with CLBP. In the first block, age and education levels were entered as a covariate; in the second block, HADS-D, FAB-T, PCS-H and ISI scores were entered simultaneously as the primary variables of interest. Results of the hierarchical regression analysis are shown in Table 5.6. Only education level, entered on the first block, was a significant covariate, F (2, 73) = 4.035, p=0.022. For the final block, the model was statistically significant F (6,69) = 5.926, p<0.001, R^2 = 0.340, Adjusted R^2 = 0.283 and the FAB-T score accounted for 34% of the variance in RMDQ scores.

Table 5. 6 Summary of hierarchical regression model predicting of Roland Morris Disability Questionnaire scores.

Block	R^2	**Model**	**B**	**SE-B**	**β**
1	.100	Constant			
		Age	0.068	0.050	0.177
		Education (college or above)	-1.617	1.161	-0.183
2	.340	Constant			
		FAB-Total*	0.063	0.032	0.241

FAB-Total= fear-avoidance beliefs-Total
B=regression coefficient; SE-B=standard error of B; β= standardized regression coefficient
Note: The dependent variable was RMDQ scores. $R^2 = 0.340$, Adjusted $R^2 = 0.283$ *p ≤ 0.05

5.4 DISCUSSION

Although individuals with CLBP had significantly smaller percent thickness change of LMM at the L4/L5 level during submaximal contraction than asymptomatic controls, no LMM parameters were significantly related to LBP-intensity or LBP-related disability in people with CLBP. Conversely, multiple psychological factors (e.g., pain catastrophizing and fear-avoidance beliefs) and insomnia were significantly related to LBP-intensity or LBP-related disability in individuals with CLBP. After considering various factors, FAB-W and ISI scores together explained 24% of the variance of pain intensity in individuals with CLBP. Similarly, FAB-Total scores explained 34% of the variance of LBP-related disability in people with CLBP.

5.4.1 Percent thickness change during contraction

The average percent thickness change at L4/L5 during submaximal contraction in people with CLBP was less than that of asymptomatic participants accords with previous research by Kiesel et al.[22] They found significant differences in percent thickness change at L4/L5 between people with CLBP and healthy individuals [22]. However, our other LMM measurements showed no significant differences in resting or contracted LMM thickness at L4/L5 and L5/S1 levels, or no significant difference in resting LMM stiffness at L4/L5 and

L5/S1 levels between people with and without CLBP. These findings concur with prior research. Sweeney et al. revealed no significant difference in resting thickness at L4/L5 and L5/S1 levels between people with CLBP and healthy individuals [146]. Wong et al [288] demonstrated that the contracted thickness of LMM at L3/L4 and L4/L5 levels in individuals with CLBP did not differ from that of asymptomatic individuals. Likewise, previous research found no significant difference in LMM stiffness at L4/L5 level between people with and without CLBP in different postures [294]. Koppenhaver et al. also found that LMM resting stiffness at L4/L5 in individuals with CLBP (n=60) was comparable to that of healthy people (n=60) [24]. Although consistent non-significant findings may be attributed to the great variability in LMM thickness or stiffness among people with and without CLBP, it may also imply that certain pain related LMM changes only occur in some patient subgroups, or other LMM measurements (e.g., electromyography, functional cross-sectional area on magnetic resonance images) may be more sensitive to detect subtle differences in LMM parameters between people with and without CLBP.

Our non-significant correlations between the percent thickness change at L4/L5 or L5/S1 during contraction and pain or disability concur with previous research [295]. Zielinski et al [295] reported no significant correlation between percent thickness change of LMM at L3/L4 and LBP or LBP-related disability in people with CLBP at baseline. Interestingly, although their participants reported a significant reduction in disability after performing stabilization exercises, post-treatment improvements in Oswestry Low Back Pain Disability Questionnaire scores in these participants were not significantly related to the corresponding alteration in percent thickness change at the L3/L4 level. Similarly, two systematic reviews found that post-treatment changes in resting thickness, cross-sectional area or endurance of LMM were unrelated to the improvements in LBP or LBP-related disability in people with LBP [27, 296]. Similar to our findings, a cross-sectional study found that neither LMM cross-sectional area

nor thickness at the L4/L5 or L5/S1 level was significantly correlated to RMDQ scores among 45 people with CLBP [297]. Another systematic review also found inconsistent evidence regarding the association between baseline percent thickness change of LMM during contraction and ensuing clinical outcomes after various nonsurgical treatments [28]. Given that most of the available evidence suggests no association between LMM morphometric variables and clinical outcomes, the recommendation is that CLBP seems to be characterised by psychological impact and that further exploration of LMM morphometric features are not warranted and may hold more relevance in the transition from acute to chronic LBP.

5.4.2 Pain catastrophizing

Similar to previous research, the current study found that pain catastrophizing was correlated with disability in people with CLBP [298, 299], but it did not predict LBP-related disability when it was concurrently evaluated together with other cognitive factors [300]. Depression is one of the most common mental health conditions affecting people with chronic pain [301]. Our study revealed that HAD-total scores and its depression subscale had weak positive correlations with LBP-related disability. These findings agreed with previous research. Hung et al. reported that the depression subscale was correlated with Oswestry Disability Index in people with CLBP (n=225; r=0.46) [302]. Further, negative thoughts, low self-esteem, and decreased motivation for activity are symptoms of depression, which can negatively affect daily functioning and may contribute to disability [303].

5.4.3 Fear-avoidance beliefs

Fear-avoidance beliefs are known to be related to pain intensity and LBP-related disability in people with LBP [304-306]. Mannion et al [307] reported that reduced FAB total scores were significantly correlated with decreases in the disability scores. Numerous reasons may lead to the presence of fear-avoidance beliefs in people. Individuals experiencing pain may reduce their physical activity level because they fear that any movement may aggravate their pain

intensity, which in turn becomes a vicious cycle leading to disability [308, 309]. Fear may also disturb the neural control pathway for automaticity, resulting in deficits in trunk motor control and increased trunk variability during walking in uncontrolled daily-living environments [310], which may heighten the risk of LBP. Further, some people with CLBP believe that any painful movements may damage their spine or may intensify their suffering [311]. Additionally, healthcare professionals' fear-avoidance beliefs regarding LBP may inadvertently influence the beliefs of people experiencing LBP [312]. Therefore, healthcare professionals should evaluate and minimize fear-avoidance behaviours of people experiencing LBP. Given that psychological interventions (e.g., cognitive-behaviour therapy) are significantly better than routine treatment [313], back-care advice [314] or exercises [315, 316] in reducing fear-avoidance beliefs in people with LBP, healthcare professionals should be either trained to deliver behavioural psychological interventions [317] or refer indicated people experiencing LBP to psychologists for proper management.

5.4.4 Insomnia

Almost 60% of our participants with CLBP reported clinically significant insomnia. Our findings also suggest that insomnia is one of the significant predictors of pain intensity in people with CLBP, which concurs with previous research that higher ISI scores were associated with higher pain intensity in people with CLBP [318]. Similarly, a recent systematic review revealed low- to moderate-quality evidence that improved sleep quantity/quality is significantly related to improved LBP-related disability or reduced LBP in patients with CLBP [319]. However, sleep disturbances and pain may affect each other reciprocally to form a vicious cycle because some brain regions (e.g., mesencephalic periaqueductal gray, thalamus, and raphe magnus) responsible for the initiation and maintenance of sleep are also involved in pain modulation [320].

Other factors may also explain the relation between sleep disturbances and pain. Different patients with chronic pain may have different circadian pain rhythms [321] and chronotypes [322]. Some may have the highest pain intensity at wake-up that decreases during the day, while others may experience similarly high pain intensity in the morning that gradually decreases until it increases again from afternoon to night. Conversely, some may have the lowest pain intensity at waking and pain gradually increases over time [321]. It has been postulated that those with high pain intensity in the morning may have suboptimal melatonin secretion at night, which may contribute to chronic sleep disturbances and increased pain perception in these people [323]. Interestingly, people with chronotype E (i.e., most active in the evening) experience a higher degree of musculoskeletal pain compared to those with chronotype M (i.e., most active in the morning). Collectively, circadian pain rhythms and chronotypes may have influence on pain [322].

In addition to the circadian pain rhythms, sleeplessness may affect pain sensitivity [324, 325]. Insomnia is a known risk factor for developing back pain in asymptomatic individuals [326]. Studies have found that sleep disturbance may affect the descending inhibitory pain pathways causing increased pain sensitivity [266, 327]. Impaired sleep may also increase inflammatory cytokines that increase pain sensitivity [328, 329]. A meta-analysis found that impaired sleep was significantly associated with higher levels of pro-inflammatory cytokines [e.g., interleukin (IL)-6] and biomarkers (e.g., C-reactive protein in the blood) [330] which might be related to more disability [331]. Although the mechanisms underlying cytokines and disability remain to be determined, it is plausible that cytokines (e.g., IL-6, IL-1 and tumor necrosis factor-α) directly cause sarcopenia and functional impairments [332-335]. Sleep-related changes in pain modulation may also limit functional abilities or activities of daily living in people with CLBP [336, 337]. Regardless of the mechanisms, a large-scale prospective study involving 6,200 people with CLBP revealed that those with frequent

sleeplessness at baseline had a lower probability of LBP recovery 11 years later [338]. Therefore, preventing/reducing sleep-related problems in people with CLBP may improve their long-term prognosis. Future studies are warranted to evaluate the effects of sleep or pain interventions in modifying sleep, pain, and disability in people with CLBP.

5.4.5 Limitations

There are several limitations in the current study. First, the cross-sectional study design cannot determine the causal relationship between various LMM, psychological, or sleep parameters and LBP or LBP-related disability in people with CLBP. Future longitudinal studies should determine whether the presence of one or more psychological factors are related to pain intensity or LBP-related disability at future follow-ups. Second, the duration of CLBP was not evaluated in the current study because many participants could not recall their durations of CLBP accurately, which could affect the relations between various factors and CLBP intensity and LBP-related disability. Third, data were collected from self-reported questionnaires, which may lead to social desirability bias and/or recall bias [339]. That said, because all the self-reported questionnaires were validated screening tools for various psychological problems in people with chronic pain [38, 280, 281, 287], they should be suitable for clinical practice and research. Fourth, since the current study only investigated the morphometric changes of LMM in people with CLBP, the potential associations between aberrant changes in motor control or proprioception of LMM and pain among people CLBP [340, 341] remain uncertain. Future studies should evaluate the correlations between deficits in motor control, proprioception, and/or clinical spinal instability and LBP/LBP-related disability after controlling for psychological and sleep factors. Fifth, FAB, depression and anxiety has been reported to be positively correlated with neuroticism, which is one of the personality traits in people with CLBP [342]. It was not within the context of the study to explore personality traits in people with CLBP. Future studies should investigate the influence

of psychological factors and LMM dysfunctions on LBP-related disability in people with CLBP having neuroticism.

5.4.6 Strengths

This is the first study to evaluate the associations between various LMM parameters and clinical outcomes in people with CLBP after adjusting for various psychological factors, insomnia, and demographic factors. Our findings highlight the necessity of assessing fear-avoidance beliefs and sleep disturbances in the routine clinical assessments of people with CLBP, which may better manage these people.

5.5 CONCLUSIONS

Since aberrant LMM morphometry or stiffness may only occur in some, but not all, people with CLBP, the current study revealed no significant difference in LMM characteristics between people with and without CLBP (except greater percent thickness change of LMM at L4/L5 level during contraction in asymptomatic individuals). It may also explain why there were no significant associations between any LMM characteristics and LBP-intensity/LBP-related disability in people with CLBP. Conversely, fear-avoidance beliefs or insomnia closely related to pain intensity or disability in people with CLBP. As such, it is important for clinicians to use validated tools to screen for maladaptive fear and sleep disturbances in patients with CLBP so that timely treatments can be given.

Chapter 6. Are LMM characteristics correlated with clinical outcomes after controlling for spinal phenotypes, psychological factors and insomnia in people with CLBP?

6.1 INTRODUCTION

A global prevalence of 568.4 million low back pain (LBP) cases was reported in 2019, indicating that LBP is one of the major public health concerns. Approximately 90% of LBP cases have unknown causes and are diagnosed as nonspecific LBP [343]. Although 95% of LBP cases recover spontaneously, more than two-thirds of the cases relapse within 12 months and 20% may develop chronic LBP (CLBP) lasting for at least 12 weeks [184, 260, 344].

Compared to asymptomatic individuals, those with CLBP may show functional and morphological changes in lumbar multifidus muscle (LMM) (e.g., smaller total cross-sectional area (CSA) and/or more intramuscular fatty infiltration) [345]. Although it is thought that these changes in LMM morphometry may be related to the development/maintenance of CLBP, baseline or temporal changes in LMM morphometry (e.g., fatty infiltration/thickness) may not necessarily be related to clinical outcomes (e.g., pain/disability) in individuals with CLBP [27, 288, 296]. While a study involving a mixed cohort of individuals with acute and chronic LBP found significant positive correlations between fatty infiltration in LMM and pain or disability [346], other investigations showed that the percentage of fatty infiltration in LMM among CLBP patients was not significantly related to pain intensity/disability [21].

The inconsistent associations between LMM morphometry and LBP-related clinical outcomes may be partly attributed to the fact that CSA of LMM is not a true measure of LMM morphometry as compared to LMM volume. Unfortunately, prior research has not investigated the correlation between LMM volume and clinical outcomes among people with CLBP.

Additionally, various spinal phenotypes, psychological factors (e.g., fear-avoidance beliefs), and insomnia may also confound the associations between LMM morphometry and LBP/LBP-related disability in individuals with CLBP [347]. Several lumbar degenerative phenotypes (e.g., intervertebral disc (IVD) degeneration, high-intensity zones (HIZs), Modic changes (MC), Schmorl's nodes (SN), facet joint degeneration (FJD), and facet joint tropism (FT)) as observed on magnetic resonance images (MRI) have been separately found to be associated with LBP [97, 98, 348-350]. Notably, the presence of IVD degeneration [105-107] or Modic change type 1 (MC1) [112, 351] is significantly related to higher LBP intensity. Additionally, IVD degeneration and FJD may impact kinematics and compromise lumbar stability, resulting in accelerated LMM degeneration [352]. Psychological factors like fear-avoidance beliefs are associated with clinical outcomes (pain intensity and/or disability) in individuals with CLBP [36]. Likewise, sleep disturbances/insomnia has found to be associated with pain intensity in patients with CLBP [318]. Given the proximity of LMM, vertebrae, IVDs, and facets, LMM characteristics, spinal phenotypes and LBP-related clinical outcomes may mutually affect one another. However, no prior research has investigated these inter-relations nor the associations between LMM morphometry and clinical outcomes after accounting for the confounding effects of demographics, spinal degenerative phenotypes, fear-avoidance beliefs, and insomnia.

Given the above, the current study aimed to: (1) compare the fear-avoidance beliefs, insomnia, spinal phenotypes and LMM characteristics between individuals with and without non-specific CLBP; (2) quantify the correlations between fear-avoidance beliefs, insomnia, LMM parameters or other spinal phenotypes and clinical outcomes (pain intensity and disability) in the presence of CLBP; and (3) determine the relationship between LMM CSA and LMM volume in individuals with CLBP.

6.2 METHODS

This case-control study was approved by the Human Subjects Ethics Sub-committee of a university (HSEAR20151027007-01) and was conducted at a single centre.

6.2.1. Participants

The sample size was calculated based on a previous study, in which the lean muscle CSA to fatty CSA index in LMM was significantly higher in the LBP group than in healthy controls with the Cohen's d effect size of 0.9 and a standard deviation of 3.8 [353]. By assuming the same effect size, a sample of at least 34 participants per group was required to find significant difference with an alpha level of 0.05 and 80% statistical power. Further, the sample size was estimated based on the recommendation that at least 10 people per determinant is needed to construct a multivariate predictive model [354]. If six predictors (e.g. some sociodemographic factors, baseline LMM characteristics, IVD degeneration, Modic change, or psychosocial factors and their interactions) are presented in the final models for predicting future LBP in asymptomatic and LBP participants, respectively, a minimum of 60 asymptomatic and 60 LBP volunteers were required. If the dropout rate is 15%, 100 participants per group should be recruited at baseline. Given the above, 70 asymptomatic and 70 LBP volunteers were required.

The same sample was recruited as in Chapter 5. Individuals aged between 18 and 65 years were recruited. Participants with CLBP (n=78) were recruited from a tertiary referral centre for spinal pathologies and were screened by specialists rule out pathologies that required surgical interventions. Age- and sex-matched asymptomatic participants (n=73) were recruited through posters posted on the university campus (Figure 6.1). People with CLBP were recruited if: (1) they experienced non-specific CLBP (NSCLBP) (defined as LBP that is not attributed to a recognisable pathology[355]) with or without leg pain that lasted for three months or more in the last 12 months, requiring surgical intervention; and (2) their LBP

intensity was at least 5/10 on an 11-point numeric pain rating scale (NPRS), because LBP intensity between 5 and 6 is considered as moderate in people with LBP.[356, 357] Asymptomatic participants were required to be free of LBP at the time of visit, free of LBP history within the past 12 months, and free of LBP that lasted for more than week in the previous 36 months. Individuals with neurological deficits/disease, spondylolisthesis, spinal tumors/cancer, spinal fractures, spinal operation, systemic inflammatory disease, metabolic disorders, and pregnancy (confirmed or suspected) were excluded from the study.

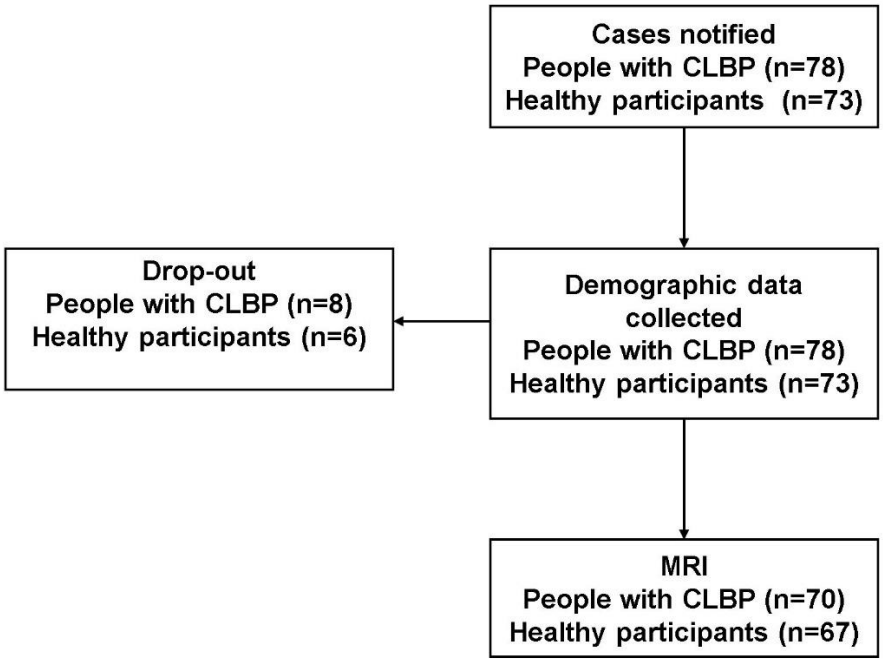

Figure 6. 1 Case reporting and completeness of data collection.

6.2.2 Procedures

Participants completed a set of questionnaires to provide their demographic information, pain intensity, LBP-related disability, fear avoidance beliefs, and the severity of insomnia. Participants then underwent lumbar MRI from L1 to S1 levels in a 1.5 MRI scanner (Siemens, Berlin and Munich, Germany; or Phillips, Amsterdam, and Netherlands) and both T1 and T2 weighted images were obtained. The MRI sequence is described in Table 6.1.

Image sequence	Details
Field of view	20cm for axial scan and 28cm for sagittal scan
Slice thickness	4mm for both axial and sagittal scans.
Slice spacing	1 mm for axial scan and 0 mm for sagittal scan
Imaging matrix	288x192 for axial scans and 512x224 for sagittal scans
Repetition time	300ms to 1000ms for T1 and 2500ms to 11000ms for T2
Echo time	12ms to 18ms for T1 and 85ms to 106ms for T2

Table 6. 1 MRI Protocol and sequence

6.2.3 Clinical outcome questionnaires

Pain intensity was measured using the 11-point NPRS [274, 358], where 0 was defined as no pain and 10 as the worst imaginable pain. Participants rated their current pain intensity, as well as least pain intensity and worst pain intensity during the past 24 hours [271]. Three ratings were averaged to determine the pain intensity over the past 24 hours [206].

LBP-related disability was measured by a validated Hong Kong-Chinese version of the Roland-Morris Disability Questionnaire (RMDQ).[207] It consisted of 24 yes/no items to describe the negative impacts of LBP on people. Higher scores indicated more disability.

6.2.4 Psychological factors and Insomnia

Pain-related fear avoidance beliefs were assessed using a validated Hong Kong Chinese version of the 16-item Fear-Avoidance Beliefs Questionnaire (FABQ).[208] It comprised two subscales to determine: (1) beliefs that physical activities cause damage; and (2) beliefs that work-related activities cause damage. By adding both subscale scores, the overall score was calculated.[38] Higher scores imply more fear avoidance beliefs.

The Chinese version of a 7-item Insomnia Severity Index (ISI) was used to assess the severity of insomnia.[287] A 5-point Likert scale is used to rate each item (e.g., 0 = no insomnia; 4 = very severe insomnia).[286] A total score of zero indicates no insomnia [286].

6.2.5 Phenotype grading

One author was trained by an Orthopaedic Surgeon (spine specialist) to perform the assessments. Each participant's spinal phenotypes at the L3 to S1 levels were rated by validated scales. Specifically, IVD degeneration was graded on T2 weighted MR images by a 5-point Pfirrmann grading system[100] (Figure 6.2).

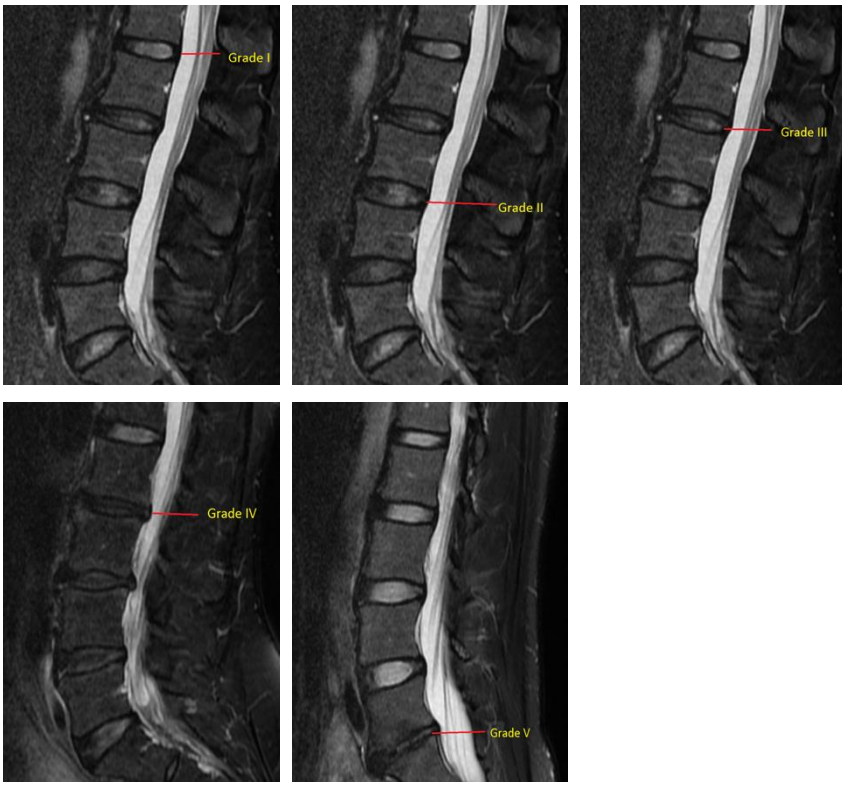

Figure 6. 2 Sagittal images demonstrating Pffirrmann grading.

HIZs in the disc were graded on T2 weighted MR images and were dichotomized as presence/absence regardless of the location, shape or signal intensity[97] (Figure 6.3).

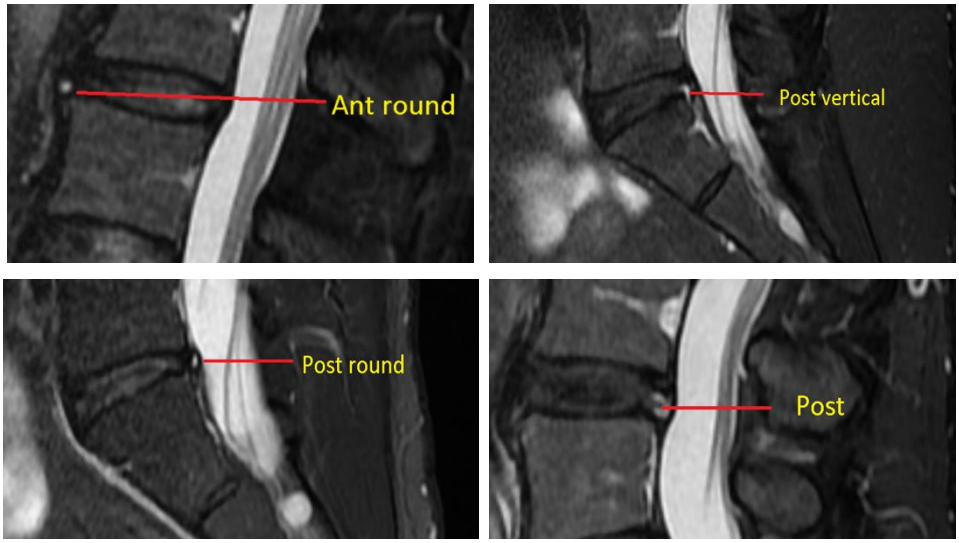

Figure 6. 3 Sagittal T2 weighted image showing HIZ.

The presence/absence of MCs at a given disc level was determined based on the existence of any type of MCs in adjacent vertebrae[359] (Figure 6.4).

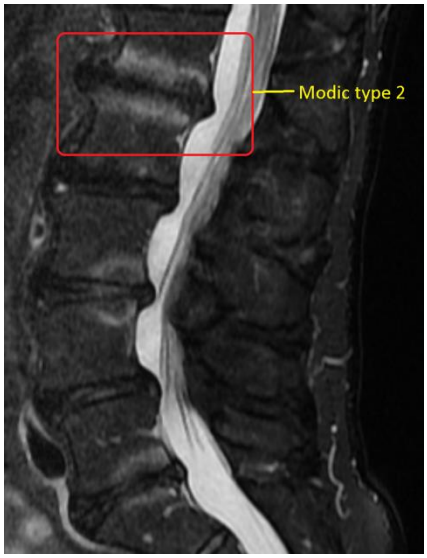

Figure 6. 4 Sagittal images demonstrating modic changes.

The presence/absence of SNs on the caudal endplate of upper vertebra/cephalic endplate of the lower vertebra[123] was documented (Figure 6.5).

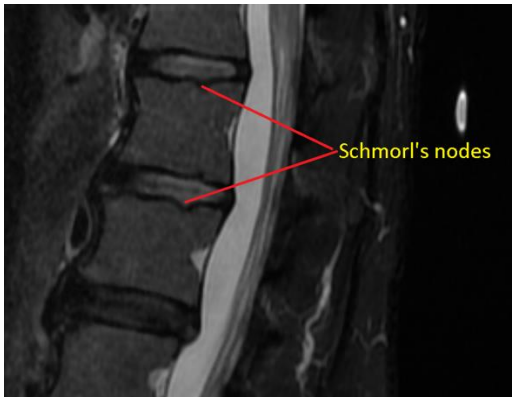

Figure 6. 5 Sagittal view of lumbar spine demonstrating schmorl’s nodes.

Bilateral FJD were graded by a validated 4-point scale developed by Weishaupt et al [132] (Figure 6.6).

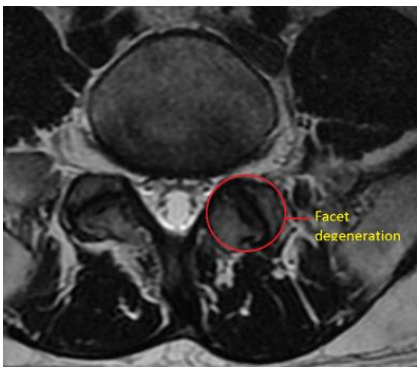

Figure 6. 6 Axial T2 weighted image

FT was dichotomized as presence/absence at each level[133] (Figure 6.7).

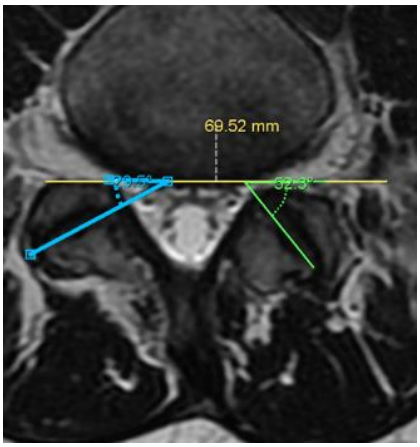

Figure 6. 7 Axial T2 reference image for facet joint measurements to the coronal plane (horizontal line).

6.2.6 LMM measurements

One trained author with a physiotherapy background performed the assessments. The CSAs of bilateral LMM were manually traced according to the recommendation of previous research [360, 361] using a customized MATLAB program (R2019b, The MathWorks Inc, Natick, Massachusetts) (Figure 6.8).

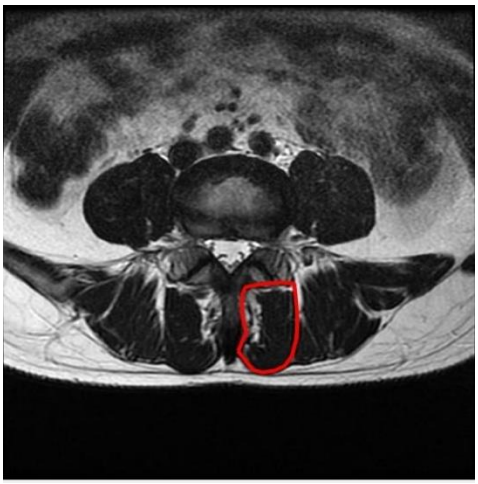

Figure 6. 8 Axial T2 weighted image of LMM CSA at L4/5

After demarcating the region of interest of bilateral LMM from the L3 to S1 levels, the program automatically measured the respective total CSA, lean muscle CSA and intramuscular fatty infiltration. The total muscle volume was estimated based on the thickness of each slide (4mm) multiplied by the number of slides per vertebral level (4). The percentages of fatty infiltration and lean muscle volume at L3/4, L4/5. L5/S1, L3-S1, and L4-S1 level(s) were calculated starting from the cephalic endplate of L3 to L3/4 disc to estimate L3 LMM volume using thresholding method that uses pixel to quantify fat infiltration. The process was repeated for the other levels. The CSA for each level was measured on the slide on caudal IVD level. To measure the intra-observer reliability of each spinal phenotype grading and LMM CSA measurement, these parameters were remeasured on the MR images of 20 randomly selected participants after three weeks.

6.2.7 Statistical analysis

Descriptive and frequency analyses were conducted on all data. Statistical tests were performed using SPSS software (Version 25, IBM Corp., Armonk, NY). Pfirrmann grading was dichotomized as “no/mild degeneration (grades 1-3)” and “severe degeneration (grade 4 or 5)”[362] and MCs were dichotomized as presence/absence regardless of the type at each of the L3/4 to L5/S1 levels. FJD was dichotomized as "no/mild degeneration (grade 0 or 1)" or "severe degeneration (grade 2 or 3)" on both sides. Further, FJD was dichotomized as presence/absence using a cutoff of grade 2 irrespective of right/left side [10]. Cohen’s Kappa

(κ) were used to evaluate the intra-rater reliability of grading spinal phenotypes [363]. The agreement was interpreted as none to slight (κ=0.01–0.20), fair (κ=0.21–0.40), moderate (κ=0.41–0.60), good agreement (κ=0.61–0.80), or almost perfect (κ=0.81–1.00).[363] The intra-class correlation coefficient (ICC), two-way random effects model, single rater ($ICC_{2,1}$) were used to determine the intra-rater reliability of LMM CSA measurements [364, 365]. The reliability was defined as excellent (ICC>0.90), good (ICC=0.75–0.90), moderate (ICC=0.50–0.75) or poor (ICC< 0.50 [365]. Chi-square or Fisher's exact tests were used for categorical variables. To compare between-group differences in LMM parameters, linear mixed models were used after adjusting for age and sex [293]. Age and sex adjustments were conducted because they were significantly correlated with LMM parameters in people with CLBP [293]. Separate point-biserial tests were used to determine the correlation between each spinal phenotype and LBP intensity or LBP-related disability scores. Spearman's rank correlation coefficients were used to evaluate the correlations between: (1) demographic characteristics (age, gender, and body mass index) and LMM parameters; (2) FABQ or ISI scores and LBP intensity/LBP-related disability, respectively; and (3) CSA and total volume of LMM. The strength of the correlation was classified as very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), or very strong (0.80-1.00) [366]. All possible confounders (demographic characteristics, LMM parameters, FABQ scores, ISI scores and spinal phenotypes) were assessed for their correlations with LBP intensity and /or LBP-related disability) in univariable analyses. Variables with $p \leq 0.20$ were then entered into a hierarchical linear regression to evaluate which variables were independently related to LBP intensity or LBP-related disability in people with CLBP. Unstandardized regression coefficients(B), standard error of B (SE-B), standardized regression coefficient (β) and p values were calculated. Missing data was excluded from the analysis. The statistical significance was set at $p<0.05$ with the 95% confidence interval.

6.3 RESULTS

6.3.1 Demographic Data

Eight participants with and 6 without CLBP dopped out from the study. Demographic data and self-reported questionnaire results of 70 individuals with CLBP and 67 asymptomatic controls are shown in Table 6.2. There were no significant differences in age, body mass index, percentage of males, occupation [employed/(unemployed/retired)], smoking status, and alcohol use, except for education levels and marital status between groups. Excellent intra-rater reliability was noted for IVD degeneration (κ=0.86), HIZ (k= 0.88), MC (k=0.91), SN (k=0.88), FJD (k=0.95), and FT (k=0.89). Likewise, good intra-rater reliability of LMM CSA was noted with ICC of 0.83 (95% CI:0.76, 0.88).

Table 6. 2 Characteristics of participants with chronic low back pain (CLBP) and asymptomatic individuals [Median (interquartile range)]

Characteristics	**CLBP**	**Asymptomatic**
Age (years)	46.0 (35.8 to 54.0)	48.0 (30.0 to 54.5)
Body mass index (kg/m^2)	23.0 (21.0 to 25.0)	22.0 (20.0 to 24.0)
Gender male *n* (%)	32 (41.0%)	36.6% (26)
Education level *n* (%) *		
Less than College	34 (44.7 %)	20 (28.2%)
College or above	42 (55.3%)	51 (71.8%)
Occupation *n* (%)		
Employed	53 (74.7%)	50 (75.8%)
Unemployed/retired	18 (25.4%)	16 (24.2%)
Marital status *n* (%) *		
Married	49 (66.2%)	30 (47.6%)
Others	25 (33.8%)	33 (52.4%)
Smoking status *n* (%)		
No	72 (94.7%)	69 (97.2%)
Yes	4 (5.3%)	2 (2.8%)
Alcohol use *n* (%)		
No	54 (71.1%)	53 (74.6%)
Yes	22 (28.9%)	18 (25.4%)

Note: Married and others (Unmarried/divorced/widowed)

Calculation of p-values was performed using Mann-Whitney U test (for continuous variables) and chi-square test (for nominal and ordinal variables). *****$p<0.05$ for comparisons between individuals with CLBP and asymptomatic participant

6.3.2 Comparisons between individuals with and without CLBP

Participants with NSCLBP had significantly higher LBP intensity, RMDQ scores, FABQ scores and ISI scores than asymptomatic controls ($p<0.05$) (Table 6.3). Individuals with CLBP demonstrated significantly more severe IVD degeneration and FJD at L3/4, L4/5 and L5/S1 levels than asymptomatic controls ($p<0.05$) (Table 6.4). Likewise, FT at the L5/S1 level was significantly greater in individuals with CLBP than asymptomatic controls (Table 6.4).

Table 6. 3 Summary of pain intensity, Disability, FABQ, and Insomnia scores.

Characteristics	**CLBP**	**Asymptomatic**
Pain intensity*	4.2 (3.0 - 5.6)	0.0 (0.0 - 0.0)
Disability*	5.5 (3.0 - 9.0)	0.0 (0.0 - 1.0)
FABQ-total*	44.0 (27.0 – 53.0)	0.0 (0.0 – 22.0)
FABQ-PA*	18.0 (14.0 – 21.0)	0.0 (0.0 – 11.3)
FABQ-W*	22.0 (10.0 – 27.0)	0.0 (0.0 – 8.0)
ISI*	12.0 (7.3 – 15.0)	5.0 (3.0 – 11.0)

FABQ=fear-avoidance beliefs questionnaire; FABQ-PA=fear-avoidance beliefs questionnaire-physical activity; FABQ-W=fear- avoidance beliefs questionnaire-work; ISI=insomnia severity index.

*$p<0.05$ for comparisons between individuals with CLBP and asymptomatic participants

Table 6. 4 Between-group comparisons of spinal phenotypes

Variables	CLBP		Asymptomatic	
	No/mild degeneration. % (n)	Severe degeneration %(n)	No/mild degeneration. %(n)	Severe degeneration % (n)
Pfirrmann L3/4*	87.1% (61)	12.9% (9)	100% (68)	0% (0)
Pfirrmann L4/5*	67.9% (53)	21.8% (17)	100% (68)	0% (0)
Pfirrmann L5/S1*	62.9% (44)	37.1% (26)	98.5% (67)	1.5% (1)
	Present % (n)	Absent % (n)	Present % (n)	Absent % (n)
MC at L3/4	2.6% (2)	87.2% (68)	2.9% (2)	97.1% (66)
MC at L4/5	5.7% (4)	94.3% (66)	2.9% (2)	97.1% (66)
MC at L5/S1	5.7% (4)	94.3% (66)	7.4% (5)	92.6% (63)
	Present % (n)	Absent % (n)	Present % (n)	Absent % (n)
HIZ at L3/4	15.7% (11)	84.3% (59)	7.4% (5)	92.6% (63)
HIZ at L4/5	10.0% (7)	90.0% (63)	10.3% (7)	89.7% (61)
HIZ at L5/S1	12.9% (9)	87.1% (61)	10.3% (7)	89.7% (61)
SN at L3/4	5.7% (4)	94.3% (66)	2.9% (2)	97.1% (66)
SN at L4/5	11.4% (8)	88.6% (62)	4.4% (3)	95.6% (65)
SN at L5/S1	5.7% (4)	94.3% (66)	2.9% (2)	97.1% (66)
	No/mild degeneration. % (n)	Severe degeneration % (n)	No/mild degeneration. % (n)	Severe degeneration % (n)
FJD at L3/4*	80.0% (56)	20.0% (14)	94.1% (64)	5.9% (4)
FJD at L4/5*	57.1% (40)	42.9% (30)	92.5% (62)	7.5% (5)
FJD at L5/S1*	58.6% (41)	41.4% (29)	95.5% (64)	4.5% (3)
	Present % (n)	Absent % (n)	Present % (n)	Absent % (n)
FT at L3/4	27.1% (19)	72.9% (51)	22.4% (15)	77.6% (52)
FT at L4/5	28.6% (20)	71.4% (50)	20.9% (14)	79.1% (53)
FT at L5/S1	41.4% (29)	58.6% (41)	19.4% (13)	80.6% (54)

FJD=facet joint degeneration; FT=facet joint tropism; HIZ=high intensity zones; MC=Modic changes, SN=Schmorl's nodes.

*$p<0.05$ for comparison between individuals with CLBP and asymptomatic participants

Because age and sex were significantly correlated with LMM parameters at all levels, these covariates were used in the between-group comparisons of LMM parameters. After adjusting for age and sex, the mean total volume of LMM at the L3/4 level was significantly greater in individuals with CLBP than that in asymptomatic controls ($p<0.05$). However, there was no significant between-group difference in total volume of LMM at L4/5, L5/S1, L3-S1, and L4-S1 levels ($p>0.05$). Compared to asymptomatic controls, the absolute percentage of lean muscle volume of LMM at the L3-S1 region was significantly smaller in people with CLBP. (Table 6.5).

Table 6. 5 Between-group comparisons of morphometric changes of LMM

Variables	CLBP (n=70)			Asymptomatic (n=67)		
	Mean	Right	Left	Mean	Right	Left
CSA at L3 (mm^2)	717.40 (571.25 to 944.66)	706.25 (547.18 to 950.38)	728.85 (601.18 to 909.60)	613.85 (526.35 to 708.10)	617.90 (519.30 to 703.50)	594.60 (529.30 to 731.10)
CSA at L4 (mm^2)	1002.25 (856.08 to 1127.43)	1022.60 (814.93 to 1157.13)	980.60 (847.83 to 1105.56)	919.75 (828.40 to 1024.10)	918.30 (838.10 to 1031.20)	895.00 (807.10 to 1034.30)
CSA at L5 (mm^2)	1159.77 (993.74 to 1285.44)	1144.40 (986.20 to 1298.43)	1158.60 (952.18 to 1316.50)	1050.70 (976.50 to 1167.15)	1048.10 (960.90 to 1187.60)	1044.80 (976.40 to 1150.10)
Total volume at L3/4 (mm3)	22678.90 (16486.04 to 33102.76)	22577.45 (16514.58 to 30894.75)	22481.30 (17500.70 to 31271.73)	18213.60 (15215.25 to 21511.75)	17842.10 (15487.20 to 21575.50)	18763.60 (15491.00 to 21758.50)
Total volume at L4/5 (mm3)	31210.15 (25522.80 to 36962.73)	31802.50 (25108.38 to 37862.88)	30959.90 (25481.40 to 36302.88)	27696.15 (24472.75 to 33098.20)	27279.20 (24020.40 to 32894.50)	27283.80 (24276.70 to 34070.80)
Total volume at L5/S1 (mm3)	64319.00 (54930.59 to 75249.58)	64525.00 (55091.48 to 74905.55)	65126.45 (54694.23 to 76277.70)	61946.60 (55748.10 to 70108.95)	61207.40 (55049.00 to 68284.30)	62910.80 (56718.80 to 68814.40)
Total volume at L4-S1 (mm3)	92507.75 (84499.62 to 109883.73)	92292.45 (84346.28 to 109471.78)	91627.60 (83745.33 to 110537.70)	91039.85 (81082.45 to 100137.50)	89993.20 (81309.00 to 99398.30)	91167.20 (81075.60 to 100314.50)
Total volume at L3-S1 (mm3) *	124777.65 (102586.56 to164138.98)	121417.35 (101805.60 to 151444.90)	119665.10 (102407.50 to 147924.43)	114056.65 (100150.50 to 121445.20)	111892.10 (100514.30 to 120472.60)	113978.50 (99192.00 to 122230.90)
Lean muscle volume at L3/4 (mm^3)	17271.13 (12922.98 to 27805.76)	16521.65 (12695.60 to 25657.75)	18138.85 (13221.78 to 26522.23)	15030.05 (11614.50 to 18068.08)	14705.30 (10911.33 to 17729.43)	15167.60 (12216.35 to 18930.35)
Lean muscle volume at L4/5 (mm^3)	23597.20 (18531.34 to 28230.71)	23976.10 (17734.90 to 28326.48)	23046.20 (18491.10 to 28705.85)	21307.35 (17658.30 to 26735.35)	20951.40 (16703.10 to 25887.00)	22064.50 (18437.10 to 27095.40)
Lean muscle volume at L5/S1 (mm^3)	43063.58 (36955.41 to 56393.11)	43178.00 (36050.60 to 57153.43)	42781.70 (35668.58 to 57998.33)	45898.70 (38592.90 to 52773.75)	44719.30 (37862.10 to 51654.30)	45273.90 (38297.00 to 53458.40)
Lean muscle volume at L4-S1 (mm^3)	66155.95 (54467.08 to 86062.35)	66984.75 (54771.63 to 84092.58)	65762.35 (54954.18 to 86916.35)	67861.25 (57496.90 to 78326.75)	65294.70 (56943.10 to 79652.20)	69078.60 (58315.50 to 78229.40)
Lean muscle volume at L3-S1 (mm^3)	89460.75 (68443.49 to 127904.65)	89025.55 (66849.53 to 120457.70)	84998.90 (67701.25 to 124473.33)	85140.95 (70528.15 to 99317.10)	83435.80 (71000.00 to 97896.30)	87254.70 (73099.30 to 99231.20)
Percentage of Lean muscle volume at L3/4 (%)	78.42 (69.04 to 84.30)	77.17 (68.77 to 84.69)	79.78 (71.07 to 86.26)	79.67 (75.31 to 85.35)	80.03 (72.63 to 83.47)	82.06 (77.51 to 87.08)
Percentage of Lean muscle volume at L4/5 (%)	76.62 (69.61 to 82.21)	75.65 (68.87 to 80.62)	77.45 (71.64 to 83.76)	78.04 (72.89 to 83.53)	77.10 (69.89 to 82.51)	79.37 (74.70 to 85.05)

Percentage of Lean muscle volume at L5/S1 (%)	70.77 (64.16 to 75.36)	71.56 (64.29 to 75.74)	70.20 (63.14 to 76.03)	72.69 (65.62 to 80.14)	71.47 (64.15 to 79	72.49 (66.36 to 80.90)
Percentage of Lean muscle volume at L4-S1 (%)	72.80 (65.80 to 77.77)	72.33 (66.27 to 77.33)	73.00 (67.33 to 78.44)	73.50 (67.30 to 81.46)	72.88 (66.50 to 81.03)	74.12 (68.10 to 81.59)
Percentage of Lean muscle volume at L3-S1 (%) *	73.14 (66.37 to 79.00)	72.73 (66.43 to 78.40)	74.22 (67.26 to 80.16)	74.60 (67.30 to 81.46)	73.76 (68.71 to 80.91)	75.91 (69.89 to 82.40)
Percentage of Fatty infiltration in LMM at L3/4 (%)	21.58 (15.70 to 30.96)	22.83 (15.31 to 31.23)	20.22 (13.74 to 28.93)	20.33 (14.65 to 24.69)	21.66 (16.58 to 32.74)	18.99 (13.19 to 23.84)
Percentage of Fatty infiltration in LMM at L4/5 (%)	23.38 (17.79 to 30.39)	24.35 (19.38 to 31.13)	22.55 (16.24 to 28.37)	21.96 (16.47 to 27.11)	23.58 (17.74 to 33.25)	21.45 (15.42 to 29.66)
Percentage of Fatty infiltration in LMM at L5/S1 (%)	29.23 (24.64 to 35.84)	28.44 (24.26 to 35.71)	29.80 (23.97 to 36.86)	27.31 (19.86 to 34.38)	30.39 (20.74 to 37.50)	28.19 (19.81 to 35.96)
Percentage of Fatty infiltration in LMM at L4-S1 (%)	27.19 (22.23 to 34.20)	27.67 (22.67 to 33.73)	27.00 (21.56 to 32.67)	26.50 (18.54 to 32.70)	29.11 (19.73 to 36.36)	26.05 (18.71 to 33.37)
Percentage of Fat infiltration in LMM at L3-S1 (%) *	26.86 (21.00 to 33.63)	27.27 (21.60 to 33.57)	25.78 (19.84 to 32.74)	25.40 (18.16 to 30.60)	27.52 (19.48 to 35.16)	25.04 (18.00 to 32.93)

*$p<0.05$ for comparison between individuals with CLBP and asymptomatic participants.

6.3.3 Correlations

6.3.3.1 Correlations between FABQ scores, ISI scores, and clinical outcomes

Pain intensity was weakly association with FABQ-Total scores ($\rho=0.30$, $p<0.05$) and FABQ-Work scores ($\rho=0.39$, $p<0.05$), but moderately associated with ISI scores ($\rho=0.44$, $p<0.05$) (Table 6.6). RMDQ scores were positively and weakly correlated with FABQ-Total scores ($\rho=0.34$, $p<0.05$), FABQ-physical activity (FABQ-PA) ($\rho=0.24$, $p<0.05$), FABQ-Work ($\rho=0.26$, $p<0.05$), and ISI scores ($\rho=0.24$, $p<0.05$) (Table 6.6)

Table 6. 6 Correlation between fear-avoidance beliefs, insomnia severity index and clinical outcomes

	FABQ- Total	FABQ-Physical Activity	FABQ-Work	Insomnia severity index
Pain intensity	0.30*	0.04	0.39*	0.44*
Disability	0.34*	0.24*	0.26*	0.24*

Spearman rank correlation coefficient; *p<0.05

6.3.3.2 Correlations between various spinal phenotypes and clinical outcomes

Point-biserial correlation analysis revealed that only MC at L4/5 (point-biserial=0.26), FJD at L4/5 (point-biserial=0.30) and FJD at L4-S1 (point-biserial=0.28) were significantly correlated with pain-intensity in individuals with CLBP. There were no significant correlations between IVD degeneration, HIZ, SN and FT at L3/4, L4/5, L5/S1, L3-S1, and L4-S1 levels and pain intensity. Similarly, no significant correlations were found between IVD degeneration, HIZ, MC, SN, FJD, or FT and RMDQ scores (Table 6.7).

	Pffirmann grading					High intensity zones					Modic change						Schmorl's nodes					Facet joint degeneration					Facet Tropism				
	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3	L4	L5	S1	L4-S1	L3-S1	L3	L4	L5	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1
Pain-intensity	.09	-.13	-.04	.13	.03	-.08	.09	.05	.10	.02	-.13	.26*	.06	.04	.15	.18	-.09	.19	.06	.16	.07	.00	.30*	.05	.28*	.19	-.18	.22	-.08	-.13	-.01
Disability	.16	.01	.10	.12	.21	.01	-.05	.06	-.08	-.03	-.02	-.07	.11	.19	.00	.02	-.10	-.21	.11	-.12	-.13	-.01	.10	-.04	.07	.034	-.07	-.00	-.10	.01	-.09

Table 6. 7 Correlation between spinal phenotypes and clinical outcomes in people with CLBP

Spearman rank correlation coefficient; *****$p<0.05$

6.3.3.2 Correlations between LMM parameters and clinical outcomes

There was no significant correlation between total volume or percentage of lean muscle volume at the L3/4, L4/5, L5/S1, L3-S1, or L4-S1 level and LBP intensity in individuals with CLBP (Table 6.8). Similarly, no significant correlations were found between the total volume or percentage of lean muscle volume at each of the L3 to S1 level or L3-S1 levels and RMDQ scores in individuals with CLBP (Table 6.8).

Table 6. 8 Correlation between LMM parameters and clinical outcomes in people with CLBP

	Total volume					Percentage of lean muscle volume				
	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1
Pain-intensity	-0.07	-0.03	-0.30	-0.04	0.02	-0.20	-0.21	-0.21	-0.22	-0.22
Disability	-0.12	0.04	-0.17	-0.13	-0.12	-0.03	-0.10	-0.19	-0.16	-0.08

Spearman rank correlation coefficient; *p<0.05

6.3.3.3 Correlations between LMM CSA and total volume

The average LMM CSA at L3 (ρ=0.92 p<0.05), L4 (ρ=0.90, p<0.05) and L5 (ρ=0.83, p<0.05) level were strongly related to the respective LMM total volume (Table 6.9) in individuals with CLBP. Similarly, the average LMM CSA at L3 (ρ=0.829, p<0.05) and L4 (ρ=0.87, p<0.05) were strongly related to the respective total volume in healthy participants, although LMM CSA at the L5 level was weakly related to its volume (ρ=0.37, p<0.05).

Table 6. 9 Correlation between LMM cross-sectional area and total volume in people with and without CLBP

Variable 1	**Variable 2**	**Individuals with CLBP Correlation**	**Individuals without CLBP Correlation**
Total volume L3 to L4	CSA at L3	0.92*	0.83*
Total volume L4 to L5	CSA at L4	0.90*	0.87*
Total volume L5 to S1	CSA at L5	0.83*	0.87*

CLBP=chronic low back pain;
Spearman rank correlation coefficient; *$p<0.05$

The Spearman correlation coefficient values can range from +1 to -1 where +1 indicates a perfect positive association of ranks, 0 indicates no association between ranks and -1 indicates perfect negative association of ranks. The strength of the correlation can be classified as very weak (0.00 to 0.19), weak (0.20 to 0.39), moderate (0.40 to 0.59), strong (0.60 to 0.79) and very strong (0.80 to 1.

6.3.4 Factors explaining pain intensity.

A three-stage hierarchical linear regression analysis was used to predict the pain intensity reported by individuals with CLBP. In the first block, demographics were entered. Psychological variables scores and ISI scores were entered as covariates and spinal phenotypes were entered as the primary variables of interest in the second block (Table 6.10**)**. In the third block, LMM parameters were entered. FABQ-Work and ISI scores were significant covariates, For the final block, the model was statistically significant F (5,67) =7.359, R^2=0.372, adjusted R^2=0.322. The FABQ-Work and ISI scores together accounted for 37% of the variance of pain intensity. The variance explained by each of the two independent variables indexed by the squared semi-partial correlations was low (ISI and FABQ-Work scores accounted for approximately 8% and 9% of the variance of pain intensity, respectively).

Table 6. 10 Summary of hierarchical regression model predicting pain intensity.

Block	Dependent variable	R^2	Model	B	SE-B	β
1	Pain intensity	.530	Constant			
			FABQ-Work*	0.046	0.016	0.315
			Insomnia severity index*	0.097	0.034	0.324
2	Pain intensity	.610	Constant			
			FABQ-Work*	0.042	0.016	0.290
			Insomnia severity index*	0.093	0.033	0.308

FABQ= fear-avoidance beliefs questionnaire, B=regression coefficient; SE-B=standard error of B; β=standardized regression coefficient; $R^2 = 0.610$, Adjusted $R^2 = 0.322$. F (5,67) =7.359; *p<0.05

6.3.5 Factors explaining disability.

A three-stage hierarchical linear regression analysis was also used to determine factors predicting the pain intensity reported by individuals with CLBP. In the first block, demographics were entered. In the second block psychological variables scores, ISI scores and spinal phenotypes were entered as a covariate. LMM parameters were entered in the third block. The regression analysis found no significant predictors of LBP-related disability.

6.4 DISCUSSION

Individuals with CLBP had significantly more severe IVD degeneration and FJD at the L3/4, L4/5 and L5/S1 levels than asymptomatic controls. Individuals with CLBP had a significantly higher frequency of FT at the L5/S1 level than asymptomatic controls. Compared to asymptomatic controls, individuals with CLBP had significantly smaller LMM lean muscle volume over the L3-S1 region. FABQ-Work scores, ISI scores, MC at the L4/5 level, FJD at the L4/5 and L4-S1 levels separately showed significant associations with pain intensity in individuals with CLBP. After considering all these factors, only FABQ-Work and ISI scores together explained 37% of the variance of pain intensity in individuals with CLBP. No LMM characteristics nor spinal phenotypes were related to RMDQ scores.

Since IVD and facet joints form a three-joint complex at each level, they are responsible for bearing the loading of the lumbar spine [367, 368]. An abnormality in any of these three joints may overload the facet joints and IVD at the same level, accelerating the IVD degeneration, FJD, and FT, which may result in CLBP [369]. Our results supported this notion because participants with CLBP had more severe IVD and FJD at the L3/4, L4/5 and L5/S1 levels than asymptomatic controls.

6.4.1 Correlations between spinal phenotypes and clinical outcomes

Significant correlations were found between the presence of MC at the L4/5 level and pain-intensity in participants with CLBP. It is noteworthy that most of the identified MCs belonged to type 1. This finding concurred with a systematic review that concluded a significant positive association between MC and CLBP [121]. The mechanical cause of MC is micro-traumas of the vertebral endplates.[116] Basivertebral nerves from damaged endplates transmit nociceptive signals to the brain. As the severity of defects increase within vertebral endplates, increased activation (frequency and number) of nociceptors can also increase, which may cause pain in individuals with CLBP [370-372]. Our significant correlations between FJD at L4/5 or L4-S1 levels and pain-intensity in participants with CLBP were also in line with prior findings. FJD has been suggested as a major cause of LBP [373]. FJD may damage the surrounding tissues of a given facet and causes inflammation. Increased production of inflammatory chemicals would stimulate the nociceptors in the joint to cause pain [372]. Cortisone injections to a painful facet joint can decrease inflammation and pain [374]. Our results substantiated the important role of FJD in individuals with CLBP. However, the lack of significant correlation between spinal phenotypes and LBP-related disability in our study might be partly attributed to the fact that spinal degenerative changes seen on MRI are part of the ageing process that were unrelated to LBP-related disability [375]. Even though FJD might be related to LBP, the pain intensity might not be large enough to cause LBP-related disability.

Additionally, both physical and psychological factors may affect LBP-related disability in people with CLBP [376]. For instance, lumbar flexion ranges of motion and isometric low back muscle strength were negatively associated with RMDQ scores in individuals with CLBP [376]. A cross-sectional study also revealed a signification correlation between abnormal flexion relaxation ratio/muscle variability of erector spinae and LBP-related

disability in individuals with CLBP [377]. These findings may suggest that the performance/activation of back muscles including erector spinae may affect physical dysfunction in people with CLBP. Likewise, certain psychological factors (psychological distress and fear) mediate the relationship between pain and disability [378].Studies have shown that fear-avoidance beliefs, pain catastrophizing, and depression can predict the LBP-related disability level in people with CLBP [304, 306, 379].

6.4.2 LMM characteristics between people with and without CLBP

Individuals with CLBP had significantly higher total fatty infiltration and smaller lean muscle volume in LMM in the L3-S1 region than asymptomatic individuals. These results concur with the findings from another study, which found that the CSA at L4/5 and L5/S1 levels in individuals with CLBP was significantly smaller than healthy participants [53]. The relatively more fatty infiltration and smaller lean muscle volume in participants with CLBP was noted because NSCLBP might cause diffuse LMM structural changes due to disuse/deconditioning that are not specific to a particular spinal level. Disuse of back muscles may decrease fatty acid oxidation in the muscles, which causes increased intramuscular fatty infiltration and atrophy of LMM in individuals with CLBP [189]. In addition to evaluating morphological changes of LMM, future prospective studies should simultaneously evaluate the histochemical and electromyographic changes of LMM in order to better understand the etiopathology of LMM changes in individuals with CLBP. Since CSA was highly correlated with total volume at each of the L3 to S1 levels, our results substantiate that CSA is sufficient to represent any morphometric changes in the whole LMM in clinical research without the need to measure LMM volume.

6.4.3 Correlations between LMM characteristics and clinical outcomes in individuals with CLBP.

Our non-significant associations between lean muscle volume at L3 to L5 levels and pain intensity or LBP-related disability agree with previous research.[21] Mengiardi et al found that the percentage of fatty infiltration in LMM among 25 individuals with CLBP was unrelated to pain intensity nor disability [21]. Further, the LMM thickness as measured by ultrasonography in the current cohort also found that LMM thickness at rest or during contraction was unrelated to pain or disability after adjusting for psychological variables [347]. Two earlier systematic reviews also revealed that changes in LMM resting thickness, CSA, or endurance after treatment were not associated with the corresponding changes in pain intensity or disability among individuals with LBP [27, 296]. These consistent findings suggest that morphometric characteristics (i.e., CSA, volume, thickness) of LMM are not good imaging biomarkers for indicating the severity of symptoms disability among individuals with CLBP. Other factors may mediate or moderate pain and disability in individuals with CLBP.

6.4.4 Correlations between LMM CSA and total volume

Although most of previous studies measured muscle CSA instead of muscle volume, it can be argued that muscle CSA does not accurately reflect muscle characteristics as much as muscle volume. The findings of the study revealed that the CSA of LMM was strongly correlated with LMM volume at any given level between L3 and S1 region in both people with and without CLBP. As a result of these findings, LMM CSA measurements can be considered an adequate and less time-consuming method to determine LMM morphometry in clinical research. A machine learning algorithm may be used in future studies to capture LMM morphology in order to further improve the effectiveness of the measurements.

6.4.5 Factors explaining pain intensity and disability in individuals with CLBP.

Prior research has shown that fear-avoidance beliefs are associated with pain intensity and LBP-related disability among individuals with CLBP [304, 306]. It is possible that pain or fear may interfere with the neural control pathway for automaticity, which may result in deficits in trunk motor control causing reduced trunk stability, which may affect daily-living activities [310]. Furthermore, some individuals with CLBP believe that any painful movement may worsen their condition [311]. Therefore, they may choose to reduce movements, which in turn may lead to deconditioning/disuse of trunk muscles [380] and/or altered trunk muscle recruitment, resulting in more spinal loading [381], and increased likelihoods of LBP and disability [310].

6.4.6 Strengths and Limitations

This is the first study to determine the association between LMM parameters and pain intensity or LBP-related disability after controlling for multiple factors such as demographics, psychological factors, insomnia, and spinal phenotypes in individuals with CLBP. Our findings suggest that Patients with CLBP may benefit from more thorough assessments of their fear-avoidance beliefs and sleep disturbances during routine clinical assessments.

Like other studies, this study had several limitations. First, the cross-sectional data could not determine the causal relationship between various spinal phenotypes or LMM characteristics, and pain intensity/disability in individuals with CLBP. Future prospective studies should determine whether the presence of one or more spinal phenotypes/LMM parameters can predict pain intensity/disability in the future. Second, only 43% of individuals with CLBP had pain for more than 3 years [382] [383]. It remains unclear whether people with longer pain duration might have different associations between LMM characteristics and pain intensity/disability.

6.5 CONCLUSIONS

This is the first study to evaluate the associations among various spinal phenotypes, LMM volumetric parameters, and clinical outcomes individuals with CLBP after considering other psychological factors. Instead of comparing CSA of LMM at a given spinal level, we evaluated the total volume and lean muscle volume of LMM at each level from L3 to S1, which were supposed to provide more comprehensive information of the LMM morphology in individuals with and without CLBP. Our findings highlight that LMM CSA is a good surrogate for estimating LMM volume at the lower lumbar regions. Our results also revealed that spinal degeneration (MC and FJD) or LMM characteristics were unrelated to clinical outcomes after adjusting for FABQ and ISI scores. Additionally, lumbar MRI may not help clinicians/researchers better understand pain/disability in CLBP. These findings substantiate that CLBP is a multifactorial disorder, which is more likely to be affected by fear avoidance behaviour or insomnia. Lumbar MRI may not help clinicians or researchers better understand pain or disability in individuals with CLBP.

Chapter 7. Factors predicting pain intensity and disability scores in people with CLBP at 2-year follow-up.

7.1 INTRODUCTION

The prevalence of low back pain (LBP) among adults is approximately 80%, making it the leading cause of people lived with disability worldwide [183]. Although most people experiencing LBP recover spontaneously, some may develop chronic LBP (CLBP) that lasts for more than three months [260]. In the United States, CLBP is one of the major causes of excessive high treatment costs, and indirect costs due to sick leaves and reduced productivity [186].

Recently, lumbar multifidus muscle (LMM) has drawn a lot of attention in spinal research. LMM is thought to be a spinal stabilizer that provides approximately two-thirds of spinal stability [263]. Multiple studies have reported that aberrant changes in the morphometry [142] and/or fatty infiltration [21, 160] of LMM may be associated with CLBP development or maintenance. However, because most of these studies used cross-sectional or case-control study design, it remains unclear whether changes in LMM characteristics are the cause or the effect of CLBP.

In order to clarify the causal association between LMM morphometry and LBP/LBP-related disability among people with CLBP, it is necessary to consider various confounding factors (spinal phenotypes,[97, 98] psychological factors [384], sleep disturbances, and multi-site pain[385]). Prior magnetic resonance imaging (MRIs) studies have revealed that several lumbar phenotypes (e.g., intervertebral disc (IVD) degeneration, high-intensity zones (HIZs), Modic changes (MCs), Schmorl's nodes (SNs), facet joint degeneration (FJD), and facet joint tropism (FT) are associated with LBP [97, 98]. Further, various psychological factors, such as anxiety, depression, pain catastrophizing, and fear-avoidance beliefs (FAB) may also affect the perceived pain intensity and/or disability in people with CLBP [33-38]. Likewise,

sleep disturbances are common among people with CLBP [266, 386]. Research found that up to 55% of people with CLBP experienced sleep disturbance or difficulty in initiating sleep [39, 268]. The presence of sleep disturbance may increase pain sensitivity and worsen LBP [387, 388]. Additionally, multi-site pain is associated with poorer recovery in people with CLBP at long-term follow-ups.[385] Therefore, it is crucial to adjust for these confounders in order to clarify the causal relationships between aberrant changes in LMM characteristics and LBP/LBP-related disability among people with CLBP. The findings will have great clinical implications in the conservative treatments of patients with CLBP.

Given the above, the current study aimed to: (1) determine if baseline LMM characteristics in people with and without CLBP could predict LBP/LBP-related disability at a 2-year follow-up, after accounting for various spinal phenotypes, psychological factors, and insomnia among people with CLBP; and (2) compare changes in LMM characteristics, spinal phenotypes, psychological factors, and insomnia/sleep disturbances between people with and without CLBP at the 2-year follow-up.

7.2 METHODS

The current study was a prospective study with a 2-year follow-up. Seventy-eight adults with and 73 without non-specific CLBP (NSCLBP) were recruited from a spine clinic and the community by convenient sampling at baseline. All participants provided their informed consent, and then completed a battery of questionnaires and physical assessments in a laboratory at The Hong Kong Polytechnic University. They also underwent lumbar spine MRI in an MRI centre. Two years later, participants were invited to undergo the same assessment procedure.

7.2.1 Questionnaires

7.2.1.1 Demographic Questionnaires

Participants completed a demographic questionnaire regarding their age, body mass index, gender, educational level, occupation, marital status, smoking status, and alcohol use.

7.2.1.2 Clinical outcomes

LBP intensity: Each participant's LBP intensity was assessed using an 11-point numeric pain rating scale (NPRS) [271].

LBP-related disability: Each participant's disability level was assessed using Hong Kong-Chinese version of the Roland-Morris Disability Questionnaire (RMDQ) [207].

The clinical outcome measures have been described in detail in Chapter 5.

7.2.1.3 Psychological questionnaires

Mood: Anxiety and depression were quantified by the Chinese version of the Hospital Anxiety and Depression Scale (HADS) [389]. This scale consists of two 7-item subscales measuring anxiety (HADS-A) and depression (HADS-D).

Pain catastrophizing: Catastrophizing of pain was assessed using the Chinese version of the pain catastrophizing scale (PCS) [281]. There are three subscales in this 13-item questionnaire: rumination, magnification, and helplessness [281].

Fear-avoidance beliefs: The Hong Kong-Chinese version of the 16-item Fear-Avoidance Beliefs Questionnaire (FABQ) was used to evaluate the pain-related fear avoidance belief. [38, 390] The FABQ is divided into two subscales: FAB-PA, which measures beliefs about physical activity and FABQ-W, which measures beliefs related to work-related activities [38].

Insomnia: The Chinese version of the 7-item Insomnia Severity Index (ISI) was used to assess the severity of insomnia [287].

7.2.2 Imaging

The procedure of MRI and ultrasonography and shear wave elastography have been described in detail in Chapter 6.

Magnetic resonance imaging: Lumbar spine MRIs of the included participants were performed with a 1.5 MRI scanner (Siemens, Berlin and Munich, Germany; or Phillips, Amsterdam, and Netherlands). All participants were examined in the supine position. The MRI sequence is described in Chapter 6. The spinal phenotypes of each participant at the L3 to S1 (IVD degeneration, HIZ, MCs, SNs, FJD, and FT) were rated using validated scales [100, 123, 132, 133, 391, 392]. Using a customized MATLAB program (R2019b, The MathWorks Inc, Natick, Massachusetts), the cross-sectional area (CSAs) of LMM were manually traced based on the recommendation of previous research [360, 361]. The total muscle volume, percentages of fatty infiltration and lean muscle volume from L3 to S1 were also calculated.

Brightness-mode ultrasound imaging: LMM thickness at rest and during contraction was measured using a curvilinear ultrasound probe (Supersonic Imagine®, Aixplorer Innovative UltraFastTM Ultrasound Imaging, France), two separate brightness-mode ultrasound videos were taken to capture bilateral sagittal LMM thickness at the L4/L5 and L5/S1 levels at rest and during submaximal contraction.

Stiffness: Supersonic Imagine® was used to assess the shear modulus (stiffness) of bilateral LMM at the L4/L5 and L5/S1 levels of the participants at rest. The ultrasound measurement procedures have been described in detail in Chapter 5.

7.2.3 Physical assessments

The detailed procedures for evaluating the proprioception of back muscles have been described in Chapter 4.

Relative proprioceptive reweighting: An evaluation of relative proprioceptive reweighting (RPW) was conducted with a force plate [210] (500Hz, Kistler, Winterthur, Switzerland), two pairs of muscle vibrators (60Hz, Maxon motor Ltd., Suzhou, China) at the waist and bilateral calves [211], (60Hz, Maxon motor Ltd., Suzhou, China). Participants stood on the force plate with eye closed under the condition of muscle vibration at the lumbar muscle or bilateral calves. The corresponding displacement of the participant's center of pressure (CoP) in the sagittal and coronal plane during lumbar muscle and calf muscles stimulation could help estimate the relative reliance on the lumbar or calf muscles for proprioception inputs.

Reposition Test: Lumbar repositioning tests were carried out in a sitting position. Three wearable inertial motion sensors (MyoMotion, Noraxon, Scottsdale, AZ, USA) and an electromagnetic motion-tracking device (Noraxon Myomotion wireless 3D kinematic analysis system, Phoenix, USA) were used to capture the relative differences in the trunk kinematics between the predetermined target position and the actual trunk position during the lumbar repositioning tests.

7.2.4 Statistical analysis

Statistical analyses were performed using SPSS software (Version 25, IBM Corp., Armonk, NY). Non-parametric tests were used because Shapiro-Wilk tests indicated that our data was not normally distributed. The median and interquartile range (IQR) were used to describe the data. To compare the demographic characteristics of people with and without CLBP at the two-year follow-up, Mann-Whitney U tests were applied (for continuous variables) and chi-square tests were applied (for nominal and ordinal variables). Mann-Whitney tests were used to anaylze the differences in LMM parameters between people with and without CLBP at follow-up. The frequency of dichotomized spinal phenotypes among people with and without CLBP was analyzed with chi-square tests at 2-year follow-up. Bivariate Spearman's rank and point-biserial correlation coefficients were used to analyze the association between LMM

parameters, MC, FJD, psychological factors, sleep disturbances/multisite pain, and pain intensity/disability scores at baseline. Psychological variables, insomnia, spinal phenotypes, and LMM parameters that demonstrated significant correlations with the pain intensity and or disability score at the baseline were entered into two separate multiple linear regression models using a stepwise approach to predict LBP intensity and LBP-related at 2-year follow-up. The significance level was set at $p<0.05$ for all tests. If the asymptomatic controls develop LBP at the 2-year follow-up, the relevant risk factors at baseline would be identified by performing the correlation analysis between psychological factors, sleep disturbances, spinal phenotypes or LMM parameters and pain intensity or LBP-related disability at the two-year follow-up. Separate multiple regression model would be used to identify risk factors for developing LBP or LBP-related disability in asymptomatic participants.

7.3 RESULTS

7.3.1 Demographic Data

Forty-three participants with and 41 without NSCLBP completed questionnaires and physical assessments at the 2-year follow-up (Figure 7.1).

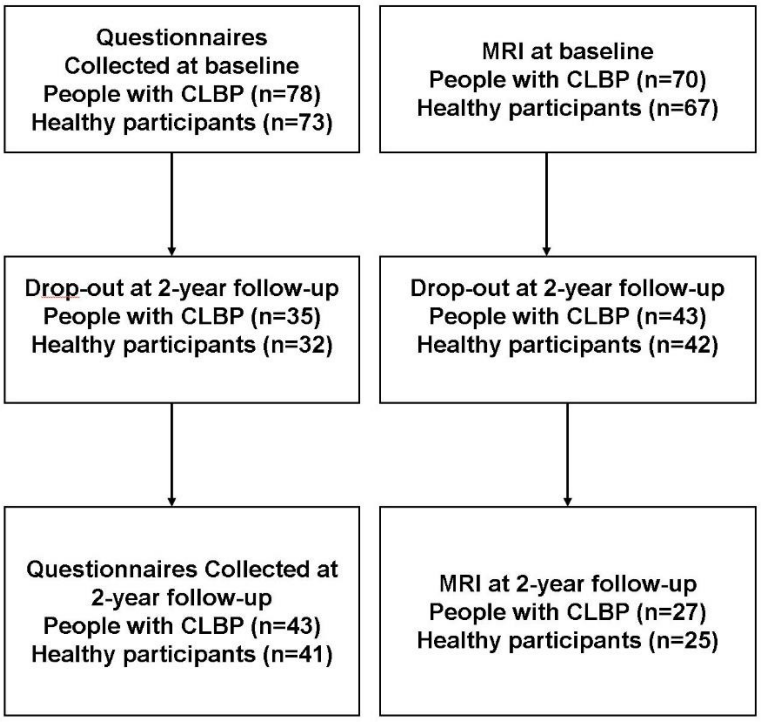

Figure 7. 1 Completeness of data collection at 2-year follow-up

Demographic data and self-reported questionnaire results of these participants at 2-year Follow-Up are shown in (Table 7.1). No significant between-group differences in age, body mass index, percentage of males, occupation [employed/(unemployed/retired)], smoking status, alcohol use, and marital status were noted. However, only 27 participants with and 25 without NSCLBP completed the MRI scans at the 2-year follow-up because many participants refused for follow-up assessments during the novel coronavirus 2019 (COVID-19) outbreak.

Table 7. 1 Characteristics of participants with and without CLBP at 2-year-Follow-Up

Characteristics	**CLBP**	**Asymptomatic**
Age (years)	52.0 (38.0 to 57.0)	53.0 (33.0 to 56.5)
BMI (kg/m^2)	22.89 (20.77 to 26.0)	22.40 (20.32 to 23.44)
Gender male *n* (%)	13 (43.3%)	17 (41.46%)
Education level *n* (%)		
Less than College	18 (43.90%)	12 (29.27%)
College or above	23 (56.10%)	29 (70.73%)
Occupation *n* (%)		
Employed	23 (56.10%)	30 (76.92%)
Unemployed/retired.	18 (43.90%)	9 (23.08%)
Marital status *n* (%)		
Married	28 (66.67%)	22 (59.46%)
Others	14 (33.33%)	16 (43.24%)
Smoking status *n* (%)		
No	41 (97.62%)	40 (87.56%)
Yes	1 (2.38%)	1 (2.44%)
Alcohol use *n* (%)		
No	30 (71.43%)	29 (72.50%)
Yes	12 (28.57%)	11 (27.5%)

Note: Married and others (Unmarried/divorced/widowed)

7.3.2 Comparisons between participants with and without NSCLBP who completed the follow-up assessments.

Compared to the 41 healthy controls, the 43 participants with NSCLBP displayed significantly higher LBP intensity (NPRS scores: mean difference (MD)= 3.50 (0.41), standard deviation (SD)=0.41), LBP-related disability (RMDQ scores [MD(SD)= 4.72(1.05)], HADS-total scores [MD(SD)=5.27(1.66), HADS-anxiety [MD(SD)=2.68(0.93), HADS-depression [MD(SD)=2.32 (0.87) FABQ-total scores [MD(SD)=28.54 (3.82)], FABQ-physical activity [MD(SD)=9.86(1.48)], FABQ-work [MD(SD)=13.67(2.01)], PCS-total scores [MD(SD)=8.41(2.24)], PCS-helplessness [MD(SD)=5.71(1.07)], PCS-Magnification [MD(SD)=2.05 (0.61), PCS-Rumination[MD(SD) = 2.87(0.87) and sleep disturbances (ISI scores) [MD(SD)= 3.53 (1.50)] at the two-year follow-up ($p<0.05$) (Table 7.2)

Table 7. 2 Summary of scores of psychological and sleep variables at 2-year-Follow-Up

Variables	**Measures**	**People with CLBP** Scores [Median (IQR)]	**People without CLBP** Scores [Median (IQR)]
Pain intensity	NPRS*****	[3.83(2.0 to 6.17)]	0.0 (0.0 to 1.0)
Low back pain-related disability	RMDQ*****	[4.0 (2.0 to 9.0)]	0.0 (0.0 to 1.5)
Anxiety and depression	HADS Total*****	12.0 (8.0 to 17.0)	5.0 (2.0 to 11.0)
	HADS-A*****	6.0 (4.0 to 9.0)	3.0 (1.0 to 6.0)
	HADS-D*****	6.0 (3.0 to 8.0)	3.0 (0.5 to 5.5)
Fear-avoidance beliefs	FAB-Total*****	38.0 (23.7 to 50.75)	1.0 (0.0 to 18.5)
	FAB-PA*****	16.0 (10.0 to 19.0)	0.0 (0.0 to 8.5)
	FAB-Work*****	18.5 (7.0 to 25.5)	0.0 (0.0 to 5.5)
Pain-catastrophizing	PCS Total*****	14.5 (4.5 to 22.5)	6.0 (2.0 to 12.0)
	PCS-H*****	8.5 (2.0 to 12.0)	0.0 (0.0 to 3.0)
	PCS-M*****	2.0 (1.0 to 5.0)	0.0 (0.0 to 2.0)
	PCS-R*****	4.0 (0.0 to 8.0)	0.0 (0.0 to 3.0)
Sleep	ISI*****	11.0 (7.0 to 15.0)	6.5 (2.0 to 12.0)

FAB=fear-avoidance belief questionnaire; FAB-PA=fear-avoidance beliefs-physical activity; FAB-W=fear-avoidance beliefs questionnaire-work; HADS=hospital anxiety and depression scale; HADS-A=hospital anxiety and depression scale- anxiety; HADS-D=hospital anxiety and depression scale-depression; IQR= interquartile range; ISI=insomnia severity scale; NPRS=numeric pain rating scale; PCS-H=pain catastrophizing-helplessness; PCS-M= pain catastrophizing-magnification; PCS-R= pain catastrophizing-rumination; RMDQ=Rolland Morris Disability Questionnaire *$p<0.05$ for comparison between people with CLBP and asymptomatic participants.

The MR images also showed that participants with NSCLBP exhibited significantly more severe IVD degeneration at the L4/5 and L5/S1 levels than healthy controls ($p<0.05$) (Table 7.3). FT at the L5/S1 level was also significantly greater in participants with CLBP than healthy controls (Table 7.3).

Table 7. 3 Between-group comparisons of spinal phenotypes at 2-year-Follow-Up

Variables	**CLBP**		**Asymptomatic**	
	No/mild degeneration % (n)	Severe legeneration % n)	No/mild degeneration % (n)	Severe degeneration % (n)
Pfirrmann L3/4	88.89% (24)	11.11% (3)	95.83% (23)	4.17% (1)
Pfirrmann L4/5*	70.37% (19)	29.63% (8)	95.83% (23)	4.17% (1)
Pfirrmann L5/S1*	59.26% (16)	40.74% (11)	87.50% (21)	12.50% (3)
	Present % (n)	Absent % (n)	Present % (n)	Absent % (n)
MC at L3	3.70% (1)	96.30% (26)	4.16% (1)	95.83% (23)
MC at L4	14.81% (4)	85.19% (23)	12.50% (3)	87.50% (21)
MC at L5	22.22% (6)	77.78% (21)	20.83% (5)	79.17% (19)
MC at S1	11.4% (2)	92.59% (25)	12.50% (3)	87.50% (21)
	Present % (n)	Absent % (n)	Present % (n)	Absent % (n)
HIZ at L3/4	22.22% (6)	77.78% (21)	29.17% (7)	70.83% (1)
HIZ at L4/5	14.81% (4)	85.19% (23)	33.33% (8)	66.67% (16)
HIZ at L5/S1	25.93% (7)	74.07% (20)	20.83% (5)	79.17% (19)
SN at L3	7.41% (2)	92.59% (25)	0% (0)	100% (24)
SN at L4	7.41% (2)	92.59% (25)	8.33% (2)	91.67% (22)
SN at L5	11.11% (3)	88.89% (24)	8.33% (2)	91.67% (22)
	No/mild degeneration % (n)	Severe degeneration % (n)	No/mild degeneration % (n)	Severe degeneration % (n)
FJD at L3/4	66.67% (18)	33.33% (9)	87.50% (21)	12.50% (3)
FJD at L4/5	51.85% (14)	48.15% (13)	66.67% (16)	33.33% (8)
FJD at L5/S1	33.33% (9)	66.67% (18)	50.05% (12)	50.0% (12)
	Present % (n)	Absent % (n)	Present % (n)	Absent % (n)
FT at L3/4	40.74% (11)	59.26% (16)	41.67% (10)	58.33% (14)
FT at L4/5	55.56% (15)	44.44% (12)	33.33% (8)	66.67% (16)
FT at L5/S1*	62.96% (17)	37.05% (10)	29.17% (7)	70.83% (17)

FJD=facet joint degeneration; FT=facet joint tropism; HIZ=high intensity zones; MC=Modic changes, SN=Schmorl's nodes.

The average total volume of LMM at the L4/5 level was significantly greater in participants with NSCLBP than that in healthy controls ($p<0.05$) at the two-year follow-up. Individuals with NSCLBP demonstrated higher percent change in total volume only at the L4/5 level compared with asymptomatic controls. However, there was no significant between-group differences in the total volume of LMM or percentage of lean muscle volume at the L3/4, L5/S1, L3-S1, and L4-S1 levels (Table 7.4)

Table 7. 4 Between-group comparisons of morphometric changes of LMM at 2-year follow-up

Variables	**CLBP (n=70)**			**Asymptomatic (n=67)**		
	Average	Right	Left	Average	Right	Left
Total volume at L3-4 (mm3)	24758.05 (21237.15 to 30542.25)	25210.40 (21447.30 to 31111.70)	24674.90 (21244.40 to 29234.40)	24752.68 (21237.15 to 30542.25)	26425.25 (21681.85 to 29383.18)	23835.00 (20940.93 to 28606.45)
Total volume at L4-5 (mm3) *	34653.25 (30453.80 to 42794.65)	36646.20 (31162.10 to 45103.00)	33701.60 (29493.00 to 40486.30)	33580.70 (29308.20 to 39305.81)	32274.70 (28838.30 to 40626.68)	32659.55 (29631.63 to 38615.45)
Total volume at L5-S1 (mm3)	62023.20 (48868.40 to 75759.35)	64338.80 (48405.40 to 74748.60)	59598.50 (50009.60 to 76770.10)	62991.48 (57034.54 to 72062.60)	62342.85 (55534.68 to 72269.50)	61285.15 (57161.45 to 72247.00)
Total volume at L4-S1 (mm3)	94209.45 (79772.65 to 114419.00)	95897.60 (79570.50 to 112917.00)	94712.90 (79450.70 to 115968.00)	98644.58 (87219.31 to 102561.95)	98464.60 (88600.85 to 104587.53)	97652.10 (87061.45 to 105772.78)
Total volume at L3-S1 (mm3)	118724.50 (103755.25 to138066.35)	120364.20(107379.10 to 136654.70)	118090 (104125.60 to 139478.00)	120208.03(111043.94 to 129767.19)	119792.10(111432.73 to 129787.58)	119512.50 (110655.15 to 131017.10)
Lean muscle volume at L3/4 (mm^3)	20051.65 (15932.00 to 24982.65)	19852.20 (15770.20 to 25166.10)	20023.10 (15037.20 to 24799.20)	19007.75 (15103.3375 to 24069.86)	19400.60 (15052.95 to 22953.95)	19153.85 (15182.50 to 24151.95)
Lean muscle volume at L4/5 (mm^3)	26622.05 (21314.95 to 32277.45)	27770.50 (21869.90 to 31935.60)	25902.30 (22288.70 to 32674.90)	24406.58 (20789.29 to 29638.59)	23709.90 (20211.85 to 29674.38)	24562.75 (21529.35 to 29611.40)
Lean muscle volume at L5/S1 (mm^3)	40969.95 (33212.60 to 57765.00)	39581.60 (32912.00 to 57689.20)	40282.60 (33003.60 to 58545.00)	44605.45 (34875.43 to 51339.56)	42833.95 (34543.60 to 49704.43)	45391.40 (35472.68 to 52878.33)
Lean muscle volume at L4-S1 (mm^3)	63496.65 (56055.90 to 90422.90)	64685.20 (55359.40 to 88265.00)	63426.50 (56093.30 to 92580.80)	66925.25 (55770.04 to 81941.88)	65244.30 (56048.98 to 81058.25)	69433.10 (59619.55 to 82097.75)
Lean muscle volume at L3-S1 (mm^3)	83604.40 (72802.95 to 110153.55)	85101.10 (72983.40 to 113161.40)	82107.70 (72572.90 to 112603.80)	87010.50 (72919.18 to 104397.48)	86570.35 (71345.35 to 104803.95)	88729.95 (77776.28 to 107664.45)
Percentage of Lean muscle volume at L3/4 (%)	80.33 (72.43 to 84.94)	79.93 (71.37 to 81.89)	81.52 (74.49 to 87.60)	78.00 (70.06 to 82.47)	77.19 (67.34 to 81.58)	78.21 (73.36 to 84.72)
Percentage of Lean muscle volume at L4/5 (%)	77.67 (67.70 to 82.32)	77.61 (68.50 to 79.54)	69.11 (78.86 to 83.61)	73.55 (67.92 to 80.32)	71.52 (65.22 to 77.11)	76.29 (70.31 to 81.71)
Percentage of Lean muscle volume at L5/S1 (%)	73.35 (65.95 to 80.81)	73.37 (64.38 to 80.45)	73.45 (66.27 to 82.23)	73.46 (64.51 to 78.84)	72.28 (63.44 to 78.77)	74.09 (65.76 to 79.69)

Percentage of Lean muscle volume at L4-S1 (%)	74.32 (66.68 to 80.16)	73.16 (63.88 to 79.94)	75.48 (66.83 to 80.59)	73.57 (64.35 to 76.94)	71.86 (63.54 to 76.27)	74.51 (66.77 to 79.27)
Percentage of Lean muscle volume at L3-S1 (%)	75.64 (66.54 to 80.58)	74.32 (66.74 to 79.69)	76.97 (68.73 to 81.99)	73.81 (65.72 to 77.71)	72.89 (63.07 to 76.84)	74.86 (68.56 to 80.09)
Percentage of Fatty infiltration in LMM at L3/4 (%)	19.67 (15.06 to 27.57)	20.07 (18.11 to 28.63)	18.48 (12.40 to 25.52)	22.00 (17.53 to 29.93)	22.81 (18.42 to 32.66)	21.79 (15.28 to 26.64)
Percentage of Fatty infiltration in LMM at L4/5 (%)	22.33 (17.68 to 32.30)	22.39 (20.46 to 31.50)	21.14 (16.40 to 30.89)	26.45 (19.68 to 32.08)	28.48 (22.89 to 34.78)	23.71 (18.29 to 29.69)
Percentage of Fatty infiltration in LMM at L5/S1 (%)	26.65 (19.19 to 34.05)	26.63 (19.55 to 35.62)	26.55 (17.77 to 33.73)	26.54 (21.16 to 35.49)	27.72 (21.23 to 36.56)	25.91 (20.31 to 34.88)
Percentage of Fatty infiltration in LMM at L4-S1 (%)	26.68 (19.84 to 33.17)	26.84 (20.06 to 36.12)	24.52 (19.41 to 33.17)	26.43 (23.06 to 35.65)	28.14 (23.73 to 36.46)	25.49 (20.73 to 33.23)
Percentage of Fat infiltration in LMM at L3-S1 (%)	24.36 (19.42 to 33.46)	25.68 (20.31 to 33.26)	23.03 (18.00 to 31.27)	26.19 (22.29 to 34.28)	27.11 (23.16 to 36.93)	25.14 (19.90 to 31.44)

*$p<0.05$ for comparison between people with CLBP and asymptomatic participants.

7.3.3 Temporal changes in psychological variables, ISI scores and LMM characteristics from baseline to the two-year follow-up

Participants with CLBP showed significant temporal decreases in FAB-T, FAB-PA, FABQ-W, and PCS-T scores over the two-year period (Tables 7.5). No significant percentage changes in clinical outcomes, psychological variables, and insomnia scores from baseline were noted in people with and without CLBP from baseline (Table 7.6).

Table 7. 5 Temporal changes in clinical outcomes, psychological variables and insomnia scores from baseline in people with and without chronic low back pain (CLBP) from baseline

Variables	**Measures**	**People with CLBP** Scores (MD ± SD)	**People without CLBP** Scores [MD ± SD]
Pain intensity	NPRS	0.19± 2.10	-0.07 ± 1.12
Low back pain-related disability	RMDQ	-0.43 ± 5.03 (37)	-0.39 ± 2.28
Anxiety and depression	HADS Total	-0.83 ± 6.71	0.11 ± 6.61
	HADS-A	-0.36 ± 3.96	0.19 ± 3.66
	HADS-D	-0.47 ± 3.48	-0.35 ± 3.32
Fear-avoidance beliefs	FAB-Total	6.37 ± 17.78*	-1.00 ± 19.18
	FAB-PA	4.15 ± 7.22*	-1.16 ± 7.61
	FAB-Work	5.29 ± 12.97 *	0.43 ± 8.35
Pain-catastrophizing	PCS Total	2.62 ± 11.51	0.35 ± 9.15
	PCS-H	0.30 ± 5.21	0.41 ± 3.32
	PCS-M	0.73 ± 2.89 (37)	0.57 ± 2.13
	PCS-R	1.62 ± 4.68) *****	0.92 ± 3.35
Sleep	ISI	1.35 ± 4.87	-1.05 ± 5.17

FAB=fear-avoidance belief questionnaire; FAB-PA=fear-avoidance beliefs-physical activity; FAB-W=fear-avoidance beliefs questionnaire-work; HADS=hospital anxiety and depression scale; HADS-A=hospital anxiety and depression scale- anxiety; HADS-D=hospital anxiety and depression scale-depression; IQR= interquartile range; ISI=insomnia severity scale; MD = mean difference; NPRS=numeric pain rating scale; PCS-H=pain catastrophizing-helplessness; PCS-M= pain catastrophizing-magnification; PCS-R= pain catastrophizing-rumination; RMDQ=Rolland Morris Disability Questionnaire; SD = standard deviation

*P<0.05, within-group differences

Table 7. 6 Percentage changes in clinical outcomes, psychological variables, and insomnia scores in people with and without CLBP from baseline

Variables	**Measures**	**People with CLBP** Scores (MD ± SD)	**People without CLBP** Scores (MD ± SD)
Pain intensity %	NPRS	7.17 ± 80.72	21.68 ± 53.32
Low back pain-related disability %	RMDQ	12.22 ± 116.44	18.47 ± 136.55
	HADS Total	15.79 ± 68.35	55.05 ± 197.40
	HADS-A	19.88 ± 78.25	17.85 ± 112.97
	HADS-D	21.84 ± 83.74	40.66 ± 152.71
Fear-avoidance beliefs %	FAB-Total	-6.38 ± 64.46	101.73 ± 544.11
	FAB-PA	-24.48 ± 44.01	12.54 ± 64.36
	FAB-Work	-8.15 ± 96.25	28.12 ± 143.32
Pain-catastrophizing %	PCS Total	10.01 ± 115.73	40.08 ± 95.76
	PCS-H	35.21 ± 146.78	8.02 ± 124.02
	PCS-M	3.73 ± 111.12	-5.90 ± 62.60
	PCS-R	0.55 ± 118.89	- 4.65 ± 76.33
Sleep %	ISI	43.95 ± 186.21	64.36 ± 231.74

FAB=fear-avoidance belief questionnaire; FAB-PA=fear-avoidance beliefs-physical activity;FAB-W=fear-avoidance beliefs questionnaire-work; HADS=hospital anxiety and depression scale; HADS-A=hospital anxiety and depression scale- anxiety; HADS-D=hospital anxiety and depression scale-depression; IQR= interquartile range; ISI=insomnia severity scale; MD = mean difference; NPRS=numeric pain rating scale; PCS-H=pain catastrophizing-helplessness; PCS-M= pain catastrophizing-magnification; PCS-R= pain catastrophizing-rumination; RMDQ=Rolland Morris Disability Questionnaire; SD = standard deviation.

People with CLBP also had a significant temporal increase in total volume of LMM at the L4-5 level over the two-year period (Tables 7.7).

Table 7. 7 Temporal changes in lumbar multifidus characteristics from baseline in people with and without chronic low back pain (CLBP)

Variables	**CLBP**	**Asymptomatic**
	Mean ± SD	Mean ± SD
Total volume at L3-4 (mm^3)	-2,232.30 ± 26,258.65	-5849.66 ± 3319.17*
Total volume at L4-5 (mm^3)	-7,374.44 ± 12,551.40*	-4453.63 ± 2996.06*
Total volume at L5-S1 (mm^3)	-8535.10 ± 22347.31	-881.45 ± 12930.94
Total volume at L4-S1 (mm^3)	-15400.50 ± 33527.02	-6787.07 ± 14191.49
Total volume at L3-S1 (mm^3)	11898.67± 147446.34	13094.43 ± 95335.57
Percentage of Lean muscle volume at L3/4 (%)	-3.67 ± 10.75	4.48 ± 5.05*
Percentage of Lean muscle volume at L4/5 (%)	-2.44 ± 10.24	1.62 ± 6.64
Percentage of Lean muscle volume at L5/S1 (%)	-3.82 ± 10.03	2..85 ± 5.20
Percentage of Lean muscle volume at L4-S1 (%)	3.24 ± 9.95	3.49 ± 4.91*
Percentage of Lean muscle volume at L3-S1 (%)	-3.83 ± 10.00	3.60 ± 4.57*

*P<0.05, within-group differences; SD = standard deviation

No significant percentage changes were observed in LMM characteristics from baseline in people with and without CLBP (Table 7.8)

Table 7. 8 Percentage changes in lumbar multifidus characteristics from baseline in people with and without chronic low back pain (CLBP)

Variables	**CLBP**	**Asymptomatic**
	Mean ± SD	Mean ± SD
Percentage change in total volume at L3-4 (%)	56.02 ± 81.03	29.91 ± 17.83
Percentage change in total volume at L4-5 (%)	39.99 ± 76.11	16.03 ± 11.24
Percentage change in total volume at L5-S1 (%)	38.79 ± 71.48	12.23 ± 17.80
Percentage change in total volume at L4-S1 (%)	36.02 ± 70.31	10.38 ± 15.75
Percentage change in total volume at L3-S1 (%)	43.67 ± 75.59	15.06 ± 20.55
Percentage change in lean muscle volume at L3/4 (%)	70.68 ± 89.47	23.65 ± 17.20
Percentage change in lean muscle volume at L4/5 (%)	52.62 ± 81.73	10.63 ± 9.86
Percentage change in lean muscle volume at L5/S1 (%)	51.22 ± 84.57	14.98 ± 19.22
Percentage change of lean muscle volume at L4-S1 (%)	47.99 ± 78.33	11.49 ± 17.14
Percentage change of lean muscle volume at L3-S1 (%)	57.31 ± 84.31	14.37 ± 21.34

SD = standard deviation

.

Percentage changes in psychological variables and ISI scores in participants with CLBP from baseline were unrelated to the corresponding changes in LBP intensity (Table 7.9)

Table 7. 9 Correlations between percentage changes in psychological variables, insomnia and clinical outcomes in people with chronic low back pain (CLBP)

	Percentage change in HADS-T from baseline	Percentage change in HADS-A from baseline	Percentage change in HADS-D from baseline	Percentage change in FAB-T from baseline	Percentage change in FAB-PA from baseline	Percentage change in FAB-W from baseline	Percentage change in PCS-T from baseline	Percentage change in PCS-H from baseline	Percentage change in PCS-M from baseline	Percentage change in PCS-R from baseline	Percentage change in ISI from baseline
Percent change in NPRS score from baseline	-0.27	-0.35	-0.18	0.17	0.18	0.24	0.10	-0.09	0.35	0.27	0.15
Percent change in RMDQ score from baseline	0.49*	0.47*	0.36*	0.25	0.03	0.23	0.37*	0.29	0.37*	0.25	0.15

FAB-T=fear-avoidance belief questionnaire-total; FAB-PA=fear-avoidance beliefs-physical activity; FAB-W=fear-avoidance beliefs questionnaire-work; HADS=hospital anxiety and depression scale; HADS-A=hospital anxiety and depression scale- anxiety; HADS-D=hospital anxiety and depression scale-depression; IQR= interquartile range; ISI=insomnia severity scale; NPRS=numeric pain rating scale; PCS-H=pain catastrophizing-helplessness; PCS-M= pain catastrophizing-magnification; PCS-R= pain catastrophizing-rumination; RMDQ=Rolland Morris Disability Questionnaire.

*Significant correlations $P<0.05$

Likewise, no significant correlations were found between percentage changes in LMM characteristics and temporal changes in clinical outcomes of participants with CLBP over the two-year period (Table 7.10). No significant temporal changes were noted in clinical outcomes among people with CLBP.

Table 7. 10 Correlations between percentage changes in LMM characteristics and clinical outcomes in people with chronic low back pain (CLBP)

	Percentage change in total volume from baseline from the baseline					Percentage change in lean muscle volume from the baseline				
	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1
Percentage change in Pain-intensity from baseline	0.14	0.06	0.05	0.06	0.05	0.11	0.00	0.03	0.04	0.02
Percentage change in Disability	-0.19	-0.25	-0.22	-0.23	0.04	-0.23	-0.23	-0.24	-0.23	-0.06

*Significant correlations P<0.05

Regarding the LBP-related disability, the only significant correlation was found between the temporal change in PCS-R score and temporal change in LBP-related disability scores in participants with CLBP (Table 7.11).

Table 7. 11 Correlations between percentage changes in psychological variables, insomnia and clinical outcomes in people without chronic low back pain

	Percentage change in HADS-T from baseline	Percentage change in HADS-A from baseline	Percentage change in HADS-D from baseline	Percentage change in FAB-T from baseline	Percentage change in FAB-PA from baseline	Percentage change in FAB-W from baseline	Percentage change in PCS-T from baseline	Percentage change in PCS-H from baseline	Percentage change in PCS-M from baseline	Percentage change in PCS-R from baseline	Percentage change in ISI from baseline
Percent change in NPRS score from baseline	-0.02	0.01	-0.08	-0.06	-0.29	-0.07	0.56	0.43	0.45	0.64	-0.05
Percent change in RMDQ score from baseline	-0.07	-0.09	-0.24	-0.03	-0.29	-0.05	0.41	0.00	0.470	0.86*	0.18

FAB=fear-avoidance belief questionnaire; FAB-PA=fear-avoidance beliefs-physical activity; FAB-W=fear-avoidance beliefs questionnaire-work; HADS=hospital anxiety and depression scale; HADS-A=hospital anxiety and depression scale- anxiety; HADS-D=hospital anxiety and depression scale-depression; IQR= interquartile range; ISI=insomnia severity scale; NPRS=numeric pain rating scale; PCS-H=pain catastrophizing-helplessness; PCS-M= pain catastrophizing-magnification; PCS-R= pain catastrophizing-rumination; RMDQ=Rolland Morris Disability Questionnaire.
*Significant correlations $P<0.05$

Healthy participants demonstrated significant correlations between percentage change in LMM total volume at L3/4, L4/5 and L4-S1 and percentage change in pain over two-year period (Table 7.12).

	Percentage change in total volume from baseline from the baseline					Percentage change in lean muscle volume from the baseline				
	L3/4	L4/5	L5/S1	L4-S1	L3-S1	L3/4	L4/5	L5/S1	L4-S1	L3-S1
Percentage change in Pain-intensity from baseline	0.611*	0.737*	-0.171	0.566*	0.121	0.377	0.129	-0.023	-0.052	-0.055
Percentage change in Disability from baseline	0.155	0.019	0.158	0.008	0.023	0.181	-0.036	0.147	0.236	-0.007

Table 7. 12 Correlations between percentage changes in lumbar multifidus characteristics and clinical outcomes in asymptomatic participants

Asymptomatic participants demonstrated no significant percentage changes in psychological variables or clinical outcomes over the two-year period (Table 7.6). Therefore, no significant correlations were found between percentage changes in any psychological variables or ISI scores and pain intensity over a two-year period (Table 7.11). However, asymptomatic participants demonstrated significant temporal decreases in percentage of lean muscle volume at L3/4, L3-S1, and L4-S1, levels (Tables 7.7). Healthy participants demonstrated significant correlations between percentage changes in LMM total volume at L3/4, L4/5 and L4-S1 and percentage changes in pain over two-year period (Table 7.12). No significant correlations were found between percentage changes in LMM lean muscle volume at all the levels from L3-S1 levels and percentage changes in pain intensity/disability scores (Table 7.10). Further, the baseline LMM characteristics, psychological variables and insomnia scores could not predict the pain intensity or LBP-related disability at various follow-up time points (6 months, 12 months).

7.3.3 Baseline factors predicting LBP-intensity at the 2-year follow-up in participants with CLBP.

Baseline NPRS scores were significantly associated with baseline PCS-Total (ρ=0.29), PCS-Helplessness (PCS-H) (ρ=0.34), FABQ-Total (ρ=0.30), FABQ-Work (ρ=0.39), and ISI scores (ρ=0.44) in people with CLBP ($P<0.05$). These variables were included in the regression models. Three independent variables were eligible for the entry to the regression model for predicting LBP intensity (Baseline FAB-W, PCS-H, and ISI scores). FABQ-W scores predicted pain intensity at the two-year follow-up (approximately 19% of the variance) (R^2 = 0.189; adjusted R^2 = 0.166). (Table 7.13)

Table 7. 13 Summary of stepwise regression model predicting numeric pain rating scale scores at 2-year-Follow-Up

Model	**B**	**SE-B**	**β**
Constant	2.315	0.692	
FAB-W*****	0.083	0.029	0.435

FAB-W=Fear-avoidance beliefs questionnaire-work subscale; ISI=Insomnia severity index. B=regression coefficient; SE-B=standard error of B; β= standardized regression coefficient
Note: The dependent variable was numeric pain rating scale scores. $R^2 = 0.189$, Adjusted $R^2 = 0.166$. F (1,37) =8.39 *p<0.05.

7.3.4 Baseline factors predicting LBP-related disability at the 2-year follow-up in participants with CLBP.

Baseline RMDQ scores were significantly related to baseline HADS-total (ρ=0.26), HADS-Depression (ρ=0.28), PCS-total (ρ=0.29), FABQ-Total (ρ=0.34), FABQ-Physical activity (ρ=0.24), FABQ-Work (ρ=0.24), PCS-H (ρ=0.33) and ISI scores (ρ=0.24) (P<0.05). Baseline MC at L4/5 (point-biserial=0.26), FJD at L4/5 (point-biserial=0.30) and FJD at L4-S1 (point-biserial=0.28) were significantly correlated with disability scores at 2-year follow-up (P<0.05). HADS-D, FABQ-T, PCS-H, ISI, MC at L4/5, FJD at L4/5 and FJD at L4-S1 were entered into the regression model). Baseline PCS-H and ISI scores significantly predicted disability scores in people with CLBP at 2 years (accounting together for 12% of variance) (R^2 = 0.384; adjusted R^2 = 0.348) at the 2-year follow-up. (Table 7.14)

None of the asymptomatic participants' developed LBP at the 2-year follow-up

Table 7. 14 Summary of stepwise regression model predicting RMDQ scores at 2-year-Follow-Up

Model	**B**	**SE-B**	**β**
Constant	-1.195	1.492	
PCS-H*	0.411	0.153	0.381
ISI*	0.370	0.139	0.380

PCS-H=Pain Catastrophising scale- Helplessness; ISI=Insomnia severity index.
B=regression coefficient; SE-B=standard error of B; β= standardized regression coefficient
$R^2 = 0.384$, Adjusted $R^2 = 0.348$. F (2,36) =10.59 *p<0.001.
Note: The dependent variable was numeric pain rating scale scores

7.4 DISCUSSION

Concurring with our findings at the analysis of baseline data, the spinal phenotypes or LMM characteristics were not correlated with LBP intensity nor LBP-related disability after considering various psychological factors. However, the prediction model revealed that only the baseline FABQ-work related scores in people with CLBP predicted their future LBP intensity after 2 years. Similarly, PCS-H and sleep disturbances predicted future RMDQ scores in participants with CLBP, At the two-year follow-up, participants with CLBP showed significantly higher percentage change in lean muscle volume only at L4/5 level as compared to healthy controls. There was a significant increase in LMM total volume at the L4/5 level in participants with CLBP over time, but no significant temporal change in percentage of LMM lean muscle volume was noted in individuals with CLBP at all the levels from L3-S1, from baseline. Conversely, there was a significant increase in the total volume of LMM at the L3/4 and L4/5 levels among asymptomatic participants over two years. Asymptomatic participants also demonstrated a significant decrease in percentage of LMM lean volume at L3/4, L4-S1 and L3-S1 levels from baseline to the two-year follow-up. Multiple reasons might explain these findings. Firstly, LBP intensity of participants with CLBP did not significantly increase from the baseline. Therefore, the predictors for LBP intensity/LBP-related disability at baseline remained to be the predictors at the follow-up. Secondly, only 9 out of 27 participants with CLBP had CLBP lasting for more than 3 years. Studies have reported atrophy of LMM in individuals with longer duration of LBP [168, 393]. For instance, positive correlation has been found between duration of symptoms and percentage decrease in the CSA of LMM in individuals with LBP [393]. At baseline, we found that people with CLBP for more than 3 years duration had significantly higher fatty infiltration of LMM as compared to people with CLBP for less than 3 years. Therefore, a longer follow-up period may be needed to see whether intramuscular fatty infiltration in LMM only predicts LBP at a

longer follow-up period. Additionally, a 2-year follow-up may not be long enough to observe significant temporal changes in the LMM in people with CLBP because LMM may degenerate over a long period. Future studies with a longer follow-up are warranted in the future.

While participants with CLBP showed significantly more intramuscular fatty infiltration of LMM than healthy controls at baseline, those with CLBP did not show significant increase in LMM fatty infiltration in the L3-S1 region over time when compared to healthy controls. This finding concurs with a prior systematic review and other studies that LMM morphometry do not seem to be reversed/changed over time [150, 394]. It is possible that some people are predisposed to have more fatty infiltration in skeletal muscle due to genetic traits [395]. However, intramuscular fatty infiltration in LMM is unrelated to the maintenance of LBP in people with CLBP. Likewise, although our findings like other studies [53, 396] found that people with CLBP had more IVD and FJD at the lower lumbar spine as compared to healthy individuals, these physical factors did not predict future CLBP intensity nor related disability in the 2-year follow-up. This observation either indicates that these factors might only be the cause or consequence of CLBP in the earlier stage, or the 2-year follow up was too short to reveal the predictive effect. Future studies with a longer follow-up are warranted to clarify whether certain spinal phenotypes or muscle changes can predict future CLBP in the long run.

Concurring with our findings at baseline, higher FABQ-W scores at baseline predict higher LBP intensity in the ensuing 2 years, while higher baseline PCS-H and insomnia predict higher LBP-related disability 2 years later. These results strongly support the psychosocial model of LBP [397, 398]. Conversely, the biomedical model of LBP appear to be less important based on the lack of correlation between spinal phenotypes/degenerative changes

and LBP clinical outcomes [398]. Pain is primarily attributed to structural pathology in the biomedical model, while biological, psychological, and social factors play a role in the biopsychosocial model [399]. Biopsychosocial models have a greater influence on LBP than biomedical models [398, 400, 401]. It could be due to the fact that psychological factors may have an influence on the perceived pain, behaviour and treatment outcomes [402]. For-instance, fear of pain might develop due to initial experience of pain caused by an injury which is considered as threatening, pain-catastrophizing and leading to fear-avoidance behaviours/beliefs followed by disuse, disability and depression [403].

PCS-Helplessness is characterized by an overemphasis on pain stimulus and a feeling of helplessness associated with pain, and by a relative inability to inhibit pain-related thoughts during or following painful experiences [404]. Our finding concurs with previous research that PCS-Helplessness scores could predict disability in people with CLBP [405]. Another study also found that when people with LBP were absence from work for more than 4 years, helplessness was the strongest predictor for pain-related disability [406]. A possible explanation for this was that patients with CLBP might pay more attention to pain and decrease their physical activities, which may eventually develop LBP-related disabilities and helplessness phenomena.

Sleep disturbances may be related to LBP-related disability because of the association between sleep disturbances and increased pro-inflammatory cytokines [334, 335]. These cytokines may cause sarcopenia (loss of muscle mass) and functional disability [334, 335, 407, 408]. Additionally, Impaired sleep may have had an indirect effect on disability. Research shows that poor sleep leads to a more painful day, rather than a more painful day leading to a poorer night's sleep.[409, 410] Further, impaired sleep may influence

nociceptive thresholds, resulting in increased pain sensitivity [411, 412], and leading to compromised activities of daily living in people with CLBP.[336]

Similar to our findings, a study found that higher baseline FAB-W scores in people with CLBP were associated with longer sick leave and persistent pain intensity/disability levels after 1 year [413]. Pain is significantly associated with FA beliefs, especially chronic pain [399]. Some people may pay constant attention to pain sensations after a back injury or LBP. The false belief that such painful sensation is an indication of reinjury, or disease progression may cause an individual to become intolerable to even low intensity of pain sensations. Such FABs may lead individuals to avoid activities that perceived to increase/exasperate pain/increase one's chances of reinjury during work or activities of daily living.[414] Such fear avoidance behaviors' may lead to general deconditioning, becoming a vicious cycle. Our findings on the FABQ, PCS and insomnia suggest that these factors should be considered to comprehensively evaluate people with CLBP.

Given the importance of psychosocial factors in predicting LBP, future studies should investigate the influence of personality traits on clinical outcomes in people with CLBP. Neuroticism has shown to be associated with FABs, anxiety and depression in people with CLBP [342]. A patient's personality traits could be assessed to determine whether there is a risk or protective factor for psychological distress, especially people with highly disabling CLBP [342]. The revised NEO personality inventory (NEO-PI-R) [415] could be used in future studies to evaluate the effects of personality traits on clinical outcomes of people with CLBP. Healthcare professionals play an important role in affecting attitudes of people experiencing LBP towards pain. Research has shown that clinicians' fear-avoidance beliefs may influence beliefs of people with LBP regarding their pain [416]. In addition to evaluating patients' fears fear-avoidance behaviours,, healthcare professionals should consider using

behavioural psychological interventions (e.g., cognitive-behaviour therapy [315] and acceptance and commitment therapy) [417] to reduce FABs in people with LBP, which has been proven to be more effective than routine treatments [313-315]. Clinicians can also consider referring indicated people to psychologists for further management [418], if necessary. Some less time-consuming approach, such as the Optimal Screening for Prediction of Referral and Outcome Yellow Flag screening tool [419], can may be used to help clinicians to screen negative coping (fear-avoidance and catastrophizing), positive affect, and self-efficacy of people with CLBP so that CLBP people with unfavourable psychological issues can be referred for multidisciplinary management.

The current study had some limitations. First, due to the COVID-19 pandemic, there was a high drop out. Many people preferred not to return for physical reassessments or MRI scans although different reminding strategies (e.g., phone calls and emails) were implemented. That said, those returned for reassessments or MRI scans did not have significant difference from those not returned for follow-up. Therefore, our findings might be generalized to those dropped out participants. However, future studies should validate our results. Second, as our participants were mainly working-age adults, our findings may not be generalized to older people with CLBP who may have other physical, psychological, and social concerns that may affect their pain development and maintenance. Third, our asymptomatic controls did not develop CLBP at the 2-year follow-up, which prevented us from identifying any risk factors for healthy individuals to develop CLBP in the future. Future large-scale longitudinal studies should determine whether a subgroup of healthy people with certain LMM characteristics (e.g., more intramuscular fatty infiltration) are more likely to develop LBP in long-term follow-ups after considering various psychosocial factors. Fourth, it is noteworthy that the trajectory of CLBP may vary among people with LBP [420-422] Our findings might just represent a subgroup of patients who are more influenced by psychosocial factors. Future

large-scale research with multiple follow-ups is warranted to investigate whether LMM characteristics or spinal phenotypes may play a role in predicting LBP in a subgroup of patients.

7.5 CONCLUSIONS

Taken together, this is the first study to evaluate the role of LMM characteristics in predicting LBP intensity and disability in people with CLBP at the 2-year follow-up after considering the potential influence of demographic factors, spinal phenotypes, and psychosocial factors. Our results highlight that FABQ-W at baseline predict CLBP intensity in 2 -year, while baseline PCS-H and insomnia predict LBP-related disability at the 2-year follow-up. Future large-scale prospective studies with multiple long-term follow-ups are warranted to clarify whether LMM characteristics have a role in predicting LBP in the long run in both people with and without CLBP.

Chapter 8. General Discussion and Conclusion

Being a major paraspinal muscle, lumber multifidus muscle (LMM) has been suggested to stabilize and control the lumbar spine, and to endure compressive loading [7, 40, 140]. It has been hypothesized that structural/functional deficits of LMM may influence low back pain (LBP) development or maintenance. Although individual cross-sectional studies found that LMM cross-sectional area in people with LBP was smaller than that in asymptomatic controls [17, 18, 53, 142, 423], these studies were limited by the cross-sectional study design, and lack of consideration of potential confounders (e.g., physical inactivity, or depression) for LBP clinical outcomes. Therefore, the causal relationships between aberrant LMM morphometry or function and the corresponding LBP intensity or LBP-related disability remain uncertain. Although prior systematic reviews attempted to summarize evidence regarding the association between baseline LMM morphometry and future LBP intensity or LBP-related disability, or the temporal associations between changes in LMM morphometry and the corresponding changes in LBP-related clinical outcomes, the quality of evidence was low due to limited number of relevant studies.

Other characteristics beyond LMM that could be related to non-specific CLBP include spinal degenerative changes in the facet joint (FJD) [424] or intervertebral discs (IVD) [425]. A functional spinal unit is composed of a pair of posterior facet joints and an anteriorly located intervertebral disc (IVD), which form the lumbar three-joint complex joints to support the load on the lumbar spine [426]. By sharing the load and protecting the IVD from excessive shear and rotational forces, facet joints play a crucial role in maintaining the stability of the lumbar spine [427]. Likewise, an IVD bear the compressive and shear forces to the spine during various physiological movements. Degeneration in any of the three joints may affect the loading in other structures, resulting in a heightened risk of tissue damage and LBP.

Given the above, this PhD project aimed to clarify if:

1) Literature suggests that conservative treatments can modify LMM morphometry and whether improved LMM morphometry is associated with improved LBP symptoms or LBP-related disability.
2) There are differences in proprioception between people with and without LBP.
3) Morphometric and Biomechanical Characteristics of LM are associated with clinical outcomes in people with CLBP after accounting for various psychological factors or Insomnia.
4) After accounting for spinal degenerative features and psychosocial confounders, changes in some LMM characteristics are associated with LBP outcomes.
5) Baseline LMM characteristics predicts future LBP outcomes after adjusting for various spinal degenerative features and psychosocial confounders.

8.1 OVERARCHING SUMMARY OF RESEARCH FINDINGS

8.1.1 Findings of Systematic Review (Study 1)

Given that structural/functional deficits of LMM in people with LBP may be restored by exercises, this project involved the conduction of a systematic review to summarize evidence regarding the effectiveness of motor control exercise (MCE) in improving LMM morphology and LBP or LBP-related disability in people with LBP. MCE was chosen because it targeted deep trunk muscle activation [428]. The results from nine included randomized controlled trials (RCTs) showed that MCE might not be superior to other interventions in restoring LMM morphometry or reducing pain intensity among people with LBP. Although low-quality evidence supported that MCE was significantly better than McKenzie exercise or analgesics in increasing contracted LMM thickness in these people, such post-MCE temporal changes in the morphometry or functions of LMM were unrelated to the corresponding changes in clinical outcomes among people with LBP. The main finding of the review is that changes in LMM characteristics following MCE appear to explain little improvement in pain

and disability, thus, raising the possibility that shifts in other factors that may explain improvement. The findings highlight the importance of conducting research to determine the cross-sectional and causal relationship between LMM characteristics and LBP or LBP-related disability after considering various confounding factors.

8.1.2 Age-related changes in proprioception of LMM in people with and without CLBP (Study 2)

Proprioception tests revealed that compared to healthy young people, the proprioceptive reweighting capacity of young adults with CLBP, middle-aged adults with and without CLBP was inferior. This is the first study to reveal that middle-aged adults with and without CLBP show no significant difference in LMM proprioception, which may be attributed to age-related impairment in central and peripheral lumbar proprioceptive transmission. The age wise subgroup analysis in my study revealed no significant differences in percentage of LMM lean volume between young/middle-aged individuals with and without CLBP.

8.1.3 Cross-sectional associations between various LMM parameters, psychological parameters, or sleep disturbances and LBP intensity or LBP-related disability in people with CLBP (Study 3)

The baseline data found that people with CLBP showed significantly higher pain intensity, disability (Roland Morris score), Hospital Anxiety and Depression Scale (HADS), Fear Avoidance Beliefs Questionnaire (FABQ), Pain Catastrophising Scale (PCS), and Insomnia Severity Index (ISI) scores than healthy participants. The results also revealed that the presence of fear-avoidance beliefs (FABs) or insomnia in people with CLBP were more likely to be associated with greater LBP intensity and/or LBP-related disability. Additionally, people having fearful beliefs about their LBP and about activity/movement, hold the potential to upregulate the sensitivity of the nervous system and make that activity hurt more. The B-mode ultrasonography results showed that the LMM thickness change at the L4/5 level

during submaximal contraction was significantly smaller in people with CLBP than in healthy individuals. There were no significant differences in LMM resting thickness, contracted thickness, or LMM resting stiffness at both levels between people with and without CLBP. Although people with CLBP demonstrated aberrant LMM morphometry/function as compared to healthy age- and gender-matched controls, there was no cross-sectional correlation between LMM characteristics and LBP intensity or LBP-related disability after considering psychological factors (e.g., FABs and insomnia). These findings suggest that clinicians should consider screening for FABs and sleep issues in people with CLBP in order to better manage these people.

8.1.4 Differential characteristics of LMM parameters and spinal phenotypes in people with CLBP and healthy participants at baseline (Study 4)

Our baseline lumbar magnetic resonance images (MRI) findings revealed that people with CLBP had a relatively greater percentage of fatty infiltration and a smaller volume of lean LMM muscle over the L3-S1 region than age-matched healthy controls. Similarly, our results revealed that people with CLBP had more severe IVD and FJD at L3/4, L4/5 and L5/S1 levels, and FT at L5/S1 than age-matched asymptomatic people. This finding substantiated the concept that IVDs and facet joints are closely related. The LMM morphometric parameters in individuals with CLBP were not related to LBP intensity or LBP-related disability after considering other spinal phenotypes (FJD and MC), fear avoidance beliefs, and insomnia. Although speculative, it is possible that NSCLBP may lead to non-specific structural changes of LMM due to disuse/deconditioning [429].

8.1.5 Findings at the 2-year follow-up

The results of the prediction model showed that higher FABQ-W at baseline predicted LBP intensity at the 2 -year follow-up in people with CLBP. Higher baseline PCS-H and insomnia also predicted LBP-related disability at the 2-year follow-up. Conversely, LMM

morphometry/function and spinal phenotypes were not significantly correlated with the clinical outcomes (pain intensity and disability) of people with CLBP. Likewise, temporal changes in LMM characteristics were unrelated to the corresponding changes in LBP intensity or LBP-related disability after accounting for other confounders. Interestingly, none of the healthy controls developed LBP at the 2-year-follow-up. Therefore, risk factors for developing CLBP were not identified in our healthy participants.

The current thesis has some new findings that have not been reported before. First, lumbar proprioceptive changes start to occur after middle-age. Second, fear avoidance beliefs and sleep disturbance are important predictors of LBP and LBP-related disability at baseline and at the two-year follow-up after considering LMM morphometry, spinal phenotypes, and other demographic variables.

Age related Proprioceptive Changes

The proprioceptive deficits in both middle-aged individuals with and without CLBP could be attributed to age-related changes in the peripheral or central nervous systems. Muscle atrophy and increased fatty infiltration of LMM has been confirmed in middle-aged adults, which may affect muscle spindles in LMM [230, 430]. Studies on human aging have demonstrated that intrafusal muscle fibres decrease and become denervated as people age [431]. Other than peripheral changes mentioned above, changes in central nervous system of middle-aged adults may also affect proprioceptive processing. A number of cortical areas participate in proprioceptive processing, including the primary motor cortex, primary and secondary somatosensory cortex, and supplementary motor cortex [432-434]. As people age, cortical thinning begins due to cellular shrinkage and dendrite branching declines [435]. Further, decreases in frontal white matter and gray matter occurs in middle-aged people [436, 437]. Additionally, there is significant evidence that middle-aged adults have significantly lower levels of neurotransmitters in the frontal and sensorimotor cortices compared to young adults

(e.g., N-acetyl-aspartate, g-aminobutyric acid, and glutamate) [438]. These age-related brain changes may lead to altered proprioceptive processing even without the presence of CLBP.

Associations between Fear Avoidance Beliefs or Insomnia and LBP

Fear-avoidance beliefs might be related to pain intensity or LBP-related disability among people with CLBP. The reason for this relationship could be attributed to the fact that some individuals experiencing pain may decrease their physical activity/movement of the spine fearing that these movements might increase their pain intensity [439]. The association between insomnia/sleep disturbances and pain intensity/LBP-related disability among people with CLBP could be attributed to multiple reasons. For instance, sleep deprivation may increase pain sensitivity by affecting the descending inhibitory pain pathways and/or causing an increase in inflammatory cytokines [440, 441]. Similarly, people with CLBP may experience changes in their pain modulation due to insomnia [442].

Additionally, the current thesis also provides some empirical data to support the presence of aberrant morphometric changes in LMM, and more degeneration of IVD, and facet joints among people with CLBP as compared to asymptomatic counterparts.

Possible reasons for increased fatty infiltration and decreased lean muscle volume of LMM in people with CLBP compared to asymptomatic participants.

Although speculative, we postulate that these LMM changes may be attributed to FJD and IVD degeneration. A common cause of lumbar facet joint and IVD degeneration is the result of aging and tissue wear-and-tear [443, 444]. Depending on the severity of IVD degeneration, such degeneration may lead to increased translational range of motion or decreased joint space in the segmental facet joints, which may increase the loading/compressive force and degeneration of the facet joint cartilage [445]. Studies have demonstrated that the range of motion of lumbar flexion, extension and lateral bending are reduced due to both IVD degeneration and FJD [446, 447]. These decreased movements in the lumbar spine may lead

to disuse/deconditioning of LMM. In people with CLBP, the disuse of back muscles may cause intramuscular fatty infiltration/atrophy of LMM due to reduced fatty acid oxidation [189]. Since fat is a noncontractile tissue, increased intramuscular fatty infiltration may impair the contractility of LMM [13, 448]. The weakened LMM may compromise spinal stability during spinal movement and accelerate the degeneration of IVD. Likewise, IVD degeneration may reduce the disc height and hydrostatic pressure, which in turn may increase the shear forces on the vertebral endplates, causing micro-traumas and leading to Modic changes (MCs) in adjacent lumbar vertebrae over time [116]. Specifically, small fissures formed in the endplates allow IVD materials to leak into the vertebra, causing inflammation. The basivertebral nerve located within the vertebral endplates may be irritated by the damaged endplates and related inflammation [116], resulting in transmission of pain signals to the brain [370-372]. In my study, most of the participants with CLBP showed MC type 1, and the presence of MC type 1 at L4 was significantly related to LBP intensity among those with CLBP. These findings concur with prior research [121].

Possible reasons for the associations between IVD or FJD and CLBP

Approximately 40% of CLBP cases are associated with IVD problems [449]. IVD degeneration is a chronic multifactorial process characterized by damages to the disc structure resulting in loss of the extracellular matrix, loss of differentiation between annulus fibrosus and nucleus pulposus of a disc, and tear or bulge in the annulus, or reduced disc height [450]. These changes may eventually result in the infiltration of peripheral inflammatory cells and the production of pro-inflammatory cytokines (tumour necrosis factor-α, interleukin-1α, interleukin -1β, and vascular and nerve growth factors) in the IVD [451]. These increased cytokines stimulate microvascular blood flow and nerve growth, which causes pain and tissue degradation. This may cause an individual to be sensitive to chemical and/or mechanical stimuli, resulting in back pain [452].

Likewise, around 45% of people with CLBP have facet joint degeneration (FJD) as the source of their pain [424]. In asymptomatic individuals, bilateral facet joints bear roughly 30% of the overall spinal load, while IVDs carry the rest of the loading. However, in severely degenerated IVDs, loadings on facet joint may increase up to 70% [130]. Increased mechanical forces to the facet joint architecture (joint capsule, and ligaments) may cause damage and activate nociceptors [130]. The outer capsule surrounding the facet joint or the surfaces of the facet joint can also be the source of pain [453]. This hypothesis is substantiated by the fact that the injection of isotonic saline into an asymptomatic facet joint would increase the joint pressure and cause pain [454]. Further, FJD can also cause inflammation and damage to the surrounding tissues, and activate nociceptors and/or increase pain sensitivity in the joint [373]. Research has revealed that degenerated facet joints generate high levels of inflammatory cytokines and cells within the joint, as well as increased capsular vascularization [455, 456], which cause pain.

The incidence of facet tropism is higher at L4-5 and L5-S1 levels in people with LBP [457]. FT refers to the asymmetry between the right and left facet joint angles, with one joint being oriented more sagittal than the other [458]. FJD and FT are known to be the risk factors for the CLBP [369]. FT can cause or contribute to FJD by inducing abnormal force loadings to facet joints. FJD and FT have also been suggested to be risk factors for the development of IVD degeneration [443, 458]. Although, no significant association was found between FT and pain intensity and/ disability among people with CLBP in my study, people with CLBP had significantly higher FT at L5-S1 level compared with asymptomatic individuals. This result substantiated the findings of the study by Noren et al, that reported higher prevalence of FT in people with degenerated lumbar discs diseases than those with asymptomatic participants [458], may be resulted from the abnormality in any of the three joints, (e.g., overloaded facet joints and/or IVD, accelerated IVD degeneration, FJD, or FT).

8.2 STRENGTHS AND IMPLICATIONS OF THIS DISSERTATION

8.2.1 MCE on improving LMM dimension and the effect on clinical outcomes.

My systematic review has important implications for research and clinical practice. As mentioned earlier, MCE is not significantly better than other interventions in reducing LBP or improving LMM morphometry as measured by B-mode ultrasonography in people with CLBP. Although low-quality evidence supported that MCE is better than McKenzie exercise in increasing contracted LMM thickness in people with CLBP, such changes may not be clinically relevant. However, my systematic review only found a few included studies that investigated the temporal relationship between post intervention changes in LMM morphometry and the corresponding clinical outcomes. These studies found no correlation between post-MCE changes in LMM morphometry and LBP/LBP-related disability (low-quality evidence). My

study also found that changes in LMM morphometry/function were not significantly correlated with clinical outcomes (pain intensity and disability) among people with CLBP. Given the limited evidence, future studies are warranted to clarify whether temporal morphometric changes in LMM as measured on MR images (including LMM volume and/or fatty infiltration) are related to LBP outcomes in people with CLBP.

8.2.2 Differences in LMM characteristics, psychology, insomnia, pain intensity and disability between people with and without CLBP

While my study did not find significant differences in baseline resting LMM thickness, contracted LMM thickness or LMM resting stiffness between people with and without CLBP, the absolute mean resting LMM thickness and stiffness values in people with CLBP were higher than those in healthy people. These findings are consistent with previous trials that used B-mode ultrasonography to measure these LMM parameters [146, 288, 294]. As expected, pain intensity and disability had higher scores among people with CLBP than

healthy participants. Percentage thickness change during contraction at the L4/5 level was significantly higher in healthy participants than people with CLBP, indicating that healthy people have better LMM contraction than people with CLBP. However, it is noteworthy that this LMM thickness changes during contraction in people with CLBP were unrelated to LBP intensity or LBP-related disability after controlling for psychological factors. Given these observations, it is conceivable that although the contractility of LMM is decreased in people with CLBP, it has no significant associations with clinical outcomes. Given that B-mode ultrasonography only creates 2-dimensional images, future studies can use more sensitive LMM measurements (e.g., surface electromyography, multivoxel magnetic resonance spectroscopy, or diffusion magnetic resonance imaging) to detect subtle differences in LMM characteristics between people with and without CLBP.

8.2.3 Relationship of LMM morphometry/function with CLBP

While the current project found that compared to healthy participants at baseline, participants with CLBP had a significantly smaller percentage of lean muscle volume and a higher percentage of intramuscular fatty infiltration in LMM over the L3-S1 region, there was no significant correlation between LMM lean muscle volume and pain intensity/disability. The lack of association might be ascribed to various reasons. Firstly, the fact that the median age of participants in the current project was around 46 years in both groups, they might have shown sign degeneration in paraspinal muscles due to aging [459]. Research has shown that physical inactivity is related to a higher risk of more fat infiltration in LMM [460], while sedentary lifestyle is inversely related to pain and disability in individuals with CLBP [461-463]. Future studies should investigate the correlation between deficits in LMM morphology and LBP/LBP-related disability after controlling for physical activity level, psychological variables (HADS, PCS, and FABQ), and sleep factors. Secondly, The LMM degeneration

might hold more importance in the initial transition from acute to chronic LBP and after it is chronic, they contribute little to the overall pain/disability experience.

8.2.4 The necessity of measuring LMM cross-sectional area (CSA) or LMM volume

While many previous studies measured LMM CSA, one may argue that muscle CSA may not be as good as muscle volume to assessing muscle morphometry. My results showed that the CSA of LMM was strongly correlated with LMM volume at any given level between L3 and S1 region in both people with and without CLBP. My results substantiate that the measurement of LMM CSA is an adequate and less time-consuming measurement of LMM morphometry in clinical research. Future studies should use machine learning algorithms to measure LMM morphometry to further enhance the efficiency of measurement [464].

8.3 FUTURE DIRECTIONS

While the self-reported questionnaires used in the current study (HADS, FABQ and PCS) were validated screening tools for various psychological problems related to chronic pain, they were time-consuming to complete. Recently, the Optimal Screening for Prediction of Referral and Outcome Yellow Flag screening tool [419] has been developed to comprehensively assess multiple domains of psychological issues in one questionnaire. This questionnaire has three versions with 17, 10, and 7 items [419]. It provides continuous data on 11 psychological constructs, 3 domains, and a summary score. It also provides dichotomous data (yellow flags are present or absent for 11 constructs).

It includes 3 psychosocial domains [negative coping (fear-avoidance and catastrophizing), positive affect, and self-efficacy). The total duration for completing this questionnaire is 2 to 3 minutes [465]. It could be an efficient yellow flags screening tool for people with CLBP. This questionnaire has demonstrated high test-retest reliability, internal consistency for each domain, and good validity to evaluate pain related psychological distress in people with

musculoskeletal disorders [465]. Given the close correlation between psychological factors and/or sleep disturbance and CLBP reported in prior and current research, clinicians should routinely screen for psychological risk factors and insomnia in people with CLBP. Since CLBP is multifactorial [466], physiotherapists should triage people with LBP based on their presence of yellow flags. If yellow flags are present in these patients, trained physiotherapist can provide psychological interventions like cognitive-behaviour therapy [315] and/or acceptance and commitment therapy [417] alongside physiotherapy interventions to manage unhelpful thoughts and improve clinical outcomes in people with CLBP. Physiotherapists should also refer people with LBP to psychologists or psychiatrists for timely intervention, if necessary.

While the current project suggests a potential interrelation among degenerative spinal changes, psychological factors, insomnia, and clinical outcomes, we did not adjust for neuroticism, which is a common personality trait among people with CLBP [342]. There is a paucity of research specifically examining the personality–pain–coping relationship in people with CLBP [467, 468]. Future works are warranted to investigate the influence of psychological factors, sleep disturbances, LMM dysfunctions and spinal degenerative changes on pain intensity and LBP-related disability in people having CLBP with neuroticism. Overall, the current findings regarding the influence of psychological factors on pain intensity and LBP-related disability in people with CLBP corroborates with the biopsychosocial in nature of CLBP. According to the biopsychosocial model, cognitive, emotional, psychological, behavioural, physical, and social factors are interrelated factors that perpetuate pain [399, 469]. This model incorporates a wide variety of factors (such as cultural considerations and complex family situations that are not usually considered in the assessments or treatments of CLBP) that may affect CLBP prognosis [470]. Future studies should incorporate more biopsychosocial factors as confounding factors in investigating the

association between LMM morphometry/function with pain intensity and LBP-related disability in people with CLBP.

8.5 CONCLUSIONS

In summary, although motor control exercises may change LMM morphometry, these changes are unrelated to clinical outcomes. The current dissertation is the biggest study by far to compare LMM characteristics between people with and without CLBP using ultrasonography and MRI. It is also the first study to evaluate both the cross-sectional and temporal associations between LMM characteristics and clinical outcomes in people with and without CLBP after adjusting for various potential confounders for LBP or LBP-related disability. The results demonstrated that baseline LMM characteristics were unrelated to clinical outcomes (pain intensity and LBP-related disability) at baseline or at the two-year follow-up in people with CLBP after adjusting for fear avoidance beliefs or insomnia. Our findings challenge the thought that LMM characteristics are likely to be related to clinical outcomes. Interestingly, people with CLBP are more likely to experience LBP pain in the following two years if they have fear-avoidance beliefs at baseline. Additionally, higher baseline Pain Catastrophizing-Helplessness scores and ISI scores will carry a greater risk of future LBP-related disability. Given the above, it is important for clinicians to routinely screen people with CLBP for these psychological factors in order to identify high-risk individuals with CLBP to ensure proper treatment or referral in a timely manner.

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APPENDICES

Appendix 2. 1 Pfirrmann grading system for the assessment of lumbar disc degeneration for Chapter 2 [471]

Grade	**Criteria**
Grade I	The structure of the disc is homogeneous, with a bright hyperintense white signal intensity and a normal disc height.
Grade II	The structure of the disc is inhomogeneous, with a hyperintense white signal. The distinction between nucleus and anulus is clear, and the disc height is normal, with or without horizontal gray bands.
Grade III	The structure of the disc is inhomogeneous, with an intermediate gray signal intensity. The distinction between nucleus and anulus is unclear, and the disc height is normal or slightly decreased.
Grade IV	The structure of the disc is inhomogeneous, with an hypointense dark gray signal intensity. The distinction between nucleus and anulus is lost, and the disc height is normal or moderately decreased.
Grade V	The structure of the disc is inhomogeneous, with a hypointense black signal intensity. The distinction between nucleus and anulus is lost, and the disc space is collapsed

Appendix 2. 2 Classification of Modic changes for Chapter 2 [466]

Classification	**Criteria**
Modic type I	Subchondral signal abnormalities and high signal intensity on T2 and low signal intensity on T1
Modic type 2	Changes adjacent to endplates and high signal intensity on T1 and T2 images
Modic type 3	Sclerosis of vertebral body, low signal intensity on T1 and T2 images

Appendix 2. 3 HIZ classification for Chapter 2 [467]

Classification	**Criteria**
Posterior round type	Concentric or oval cavity
Posterior fissure type	Parallel and transverse layer to the adjacent endplate
Posterior vertical type	Vertical layer to the adjacent endplate
Anterior round type	Concentric or oval cavity
Anterior rim type	Oblique radiating layer from the adjacent endplate
Anterior enlarged type	Greater concentric area than typical round HIZ
Posterior	HIZ located in the posterior annulus fibrosus
Anterior	HIZ located in the anterior annulus fibrosus

Appendix 2. 4 Grading of Facet joint degeneration for Chapter 2 [468]

Grade	**Criteria**
Grade 0	Normal facet joint space (2±4 mm width)
Grade 1	Narrowing of the facet joint space (< 2 mm)/small osteophytes/mild hypertrophy of the articular process
Grade 2	Narrowing of the facet joint space/moderate osteophytes/moderate hypertrophy of the articular process or mild subarticular bone erosions
Grade 3	Narrowing of the facet joint space/large osteophytes/severe hypertrophy of the articular process/severe subarticular bone erosions/subchondral cysts

Appendix 3. 1 Search strategies for Chapter 3

MEDLINE

#	Searches
1	Lumbar Vertebrae OR Lumbo* OR Lumbar OR Lumbopelvic OR Lumbosacral OR Sacrum OR Sacral OR Sacroiliac OR Back OR Coccyx OR Low back OR Lower back OR Trunk OR Torso OR iliac OR ilium OR Spine
2	Muscle OR Muscul* OR paraspinal OR Musculoskeletal OR Back Muscle OR back extensor OR Multifid* OR LM OR LMM OR Lumbar Multifidus
3	S1 and S2
4	Pain OR agony
5	S1 AND S4
6	Back pain OR Low back pain OR LBP OR Sciatica OR lumbago OR dorsalgia OR Lumbar pain OR Pelvic Pain OR lumbalgia OR backache* OR backache* OR Coccydynia
7	S5 OR S6
8	Therap* OR Therapeutic OR Exercise* OR Treatment* OR Rehabilitation OR Treatment effects OR Treatment efficacy OR Conservative* OR non-surgical OR Intervention* OR stabilizing* OR spinal stabilization OR Core stabilization OR Physiotherapy OR Physical therapy OR Physical rehabilitation OR Muscle strengthening OR Electric stimulation OR muscle stimulation OR Resistance exercise* OR Motor control Training OR Motor control exercise
9	Randomized Controlled Trial* OR Randomised controlled trial* OR Randomization OR Randomized Controlled OR Random OR RCT OR Clinical trials
10	S3 AND S7 AND S8 AND S9

Embase

#	Searches
1	'lumbar vertebrae'/exp OR 'lumbar vertebrae' OR (lumbar AND vertebrae) OR lumbo* OR lumbar OR lumbopelvic OR lumbosacral OR 'sacrum'/exp OR sacrum OR sacral OR sacroiliac OR 'back'/exp OR back OR 'coccyx'/exp OR coccyx OR 'low back' OR (low AND ('back'/exp OR back)) OR 'lower back' OR (lower AND ('back'/exp OR back)) OR 'trunk'/exp OR trunk OR 'torso'/exp OR torso OR iliac OR 'ilium'/exp OR ilium OR 'spine'/exp OR spine
2	'muscle'/exp OR muscle OR muscul* OR paraspinal OR musculoskeletal OR 'back muscle'/exp OR 'back muscle' OR (('back'/exp OR back) AND ('muscle'/exp OR muscle)) OR 'back extensor' OR (('back'/exp OR back) AND extensor) OR multifid* OR lm OR lmm OR 'lumbar multifidus'/exp OR 'lumbar multifidus' OR (lumbar AND multifidus)
3	#1 AND #2
4	'pain'/exp OR pain OR 'agony'/exp OR agony

5	#1 AND #4
6	'back pain'/exp OR 'back pain' OR (('back'/exp OR back) AND ('pain'/exp OR pain)) OR 'low back pain'/exp OR 'low back pain' OR (low AND ('back'/exp OR back) AND ('pain'/exp OR pain)) OR lbp OR 'sciatica'/exp OR sciatica OR 'lumbago'/exp OR lumbago OR 'dorsalgia'/exp OR dorsalgia OR 'lumbar pain'/exp OR 'lumbar pain' OR (lumbar AND ('pain'/exp OR pain)) OR 'pelvic pain'/exp OR 'pelvic pain' OR (('pelvic'/exp OR pelvic) AND ('pain'/exp OR pain)) OR 'lumbalgia'/exp OR lumbalgia OR backache* OR 'coccydynia'/exp OR coccydynia
7	#5 OR #6
8	(therap* OR therapeutic OR exercise* OR treatment* OR 'rehabilitation'/exp OR rehabilitation OR 'treatment effects' OR (('treatment'/exp OR treatment) AND effects) OR 'treatment efficacy'/exp OR 'treatment efficacy' OR (('treatment'/exp OR treatment) AND ('efficacy'/exp OR efficacy)) OR conservative* OR 'nonsurgical' OR intervention* OR stabilizing* OR 'spinal stabilization'/exp OR 'spinal stabilization' OR (spinal AND ('stabilization'/exp OR stabilization)) OR 'core stabilization' OR (core AND ('stabilization'/exp OR stabilization)) OR 'physiotherapy'/exp OR physiotherapy OR 'physical therapy'/exp OR 'physical therapy' OR (physical AND ('therapy'/exp OR therapy)) OR 'physical rehabilitation'/exp OR 'physical rehabilitation' OR (physical AND ('rehabilitation'/exp OR rehabilitation)) OR 'muscle strengthening'/exp OR 'muscle strengthening' OR (('muscle'/exp OR muscle) AND strengthening) OR 'electric stimulation'/exp OR 'electric stimulation' OR (electric AND ('stimulation'/exp OR stimulation)) OR 'muscle stimulation'/exp OR 'muscle stimulation' OR (('muscle'/exp OR muscle) AND ('stimulation'/exp OR stimulation)) OR 'resistance'/exp OR resistance) AND exercise* OR 'motor control training' OR (('motor'/exp OR motor) AND ('control'/exp OR control) AND ('training'/exp OR training)) OR 'motor control exercise' OR (('motor'/exp OR motor) AND ('control'/exp OR control) AND ('exercise'/exp OR exercise))
9	randomized AND controlled AND trial* OR 'randomised controlled' OR (randomised AND controlled AND trial*) OR 'randomization'/exp OR randomization OR 'randomized controlled'OR (randomized AND controlled) OR random OR rct OR 'clinical trials'/exp OR 'clinical trials' OR (('clinical'/exp OR clinical) AND trials)
10	#3 AND #7 AND #8 AND #9

SPORTDiscus

#	Searches
1	Lumbar Vertebrae OR Lumbo* OR Lumbar OR Lumbopelvic OR Lumbosacral OR Sacrum OR Sacral OR Sacroiliac OR Back OR Coccyx OR Low back OR Lower back OR Trunk OR Torso OR iliac OR ilium OR Spine
2	Muscle OR Muscul* OR paraspinal OR Musculoskeletal OR Back Muscle OR back extensor OR Multifid* OR LM OR LMM OR Lumbar Multifidus
3	S1 and S2
4	Pain OR agony
5	S1 AND S4
6	Back pain OR Low back pain OR LBP OR Sciatica OR lumbago OR dorsalgia OR Lumbar pain OR Pelvic Pain OR lumbalgia OR backache* OR backache* OR Coccydynia
7	S5 OR S6
8	Therap* OR Therapeutic OR Exercise* OR Treatment* OR Rehabilitation OR Treatment effects OR Treatment efficacy OR Conservative* OR non-surgical OR Intervention* OR stabilizing* OR spinal stabilization OR Core stabilization OR Physiotherapy OR Physical therapy OR Physical rehabilitation OR Muscle strengthening OR Electric stimulation OR muscle stimulation OR Resistance exercise* OR Motor control Training OR Motor control exercise
9	Randomized Controlled Trial* OR Randomised controlled trial* OR Randomization OR Randomized Controlled OR Random OR RCT OR Clinical trials
10	S3 AND S7 AND S8 AND S9

CINAHL

#	Searches
1	Lumbar Vertebrae OR Lumbo* OR Lumbar OR Lumbopelvic OR Lumbosacral OR Sacrum OR Sacral OR Sacroiliac OR Back OR Coccyx OR Low back OR Lower back OR Trunk OR Torso OR iliac OR ilium OR Spine
2	Muscle OR Muscul* OR paraspinal OR Musculoskeletal OR Back Muscle OR back extensor OR Multifid* OR LM OR LMM OR Lumbar Multifidus
3	S1 and S2
4	Pain OR agony
5	S1 AND S4
6	Back pain OR Low back pain OR LBP OR Sciatica OR lumbago OR dorsalgia OR Lumbar pain OR Pelvic Pain OR lumbalgia OR backache* OR backache* OR Coccydynia
7	S5 OR S6
8	Therap* OR Therapeutic OR Exercise* OR Treatment* OR Rehabilitation OR Treatment effects OR Treatment efficacy OR Conservative* OR non-surgical OR Intervention* OR stabilizing* OR spinal stabilization OR Core stabilization OR Physiotherapy OR Physical therapy OR Physical rehabilitation OR Muscle strengthening OR Electric stimulation OR muscle stimulation OR Resistance exercise* OR Motor control Training OR Motor control exercise
9	Randomized Controlled Trial* OR Randomised controlled trial* OR Randomization OR Randomized Controlled OR Random OR RCT OR Clinical trials
10	S3 AND S7 AND S8 AND S9

Other search strategies for PEDro and Cochrane Library:

(Lumbar spine OR sacro-iliac joint OR pelvis OR low back pain OR lower back pain OR backache OR LBP OR lumbar multifidus OR LM OR treatment OR motor control training OR exercise OR Stabilisation OR stabilization OR stimulation OR RCT OR randomized controlled trial OR randomised controlled trial OR clinical trial).

Appendix 3.2 Measurement methods for various morphological parameters of lumbar multifidus muscle for Chapter 3

Category	Definition	Measurement methods
Resting lumbar Multifidus thickness	The distance between the thoracolumbar fascia and the facet joint at rest[472]	Ultrasonography
Contracted lumbar multifidus thickness	The distance between the thoracolumbar fascia and the facet joint during multifidus contraction when the participant is performing a contralateral arm lift maneuver[472]	Ultrasonography
Contracted Multifidus thickness with resistance	The distance between the thoracolumbar fascia and the facet joint during contraction, when the participant is performing a contralateral arm lift maneuver by holding a weight[76, 472]	Ultrasonography
Percent thickness change during multifidus contraction	Thickness change = (Contracted thickness – resting thickness)/Resting thickness x 100[473]	Ultrasonography
Cross-sectional area of multifidus	The cross-sectional area of lumbar multifidus at a target vertebral level is measured from a transverse ultrasound image,[151] or The cross-sectional area is measured from a trans-axial view of CT image. The outlines of the multifidus is identified by a cursor on the computer screen at different lumbar levels.[154]	Ultrasonography or computerized tomography
Fatty infiltration of multifidus	Hyperintense regions within the multifidus muscle observed on T2 axial view of MR images is considered as fatty infiltration/replacement of multifidus muscle tissue by fat.[144] Fatty infiltration of multifidus muscle is determined by the difference between the total cross-sectional area and functional cross-sectional area (lean muscle mass/the area of muscle which is free from fat).[474, 475] Low-density regions within the multifidus muscle observed on trans-axial view of CT image is considered as fatty infiltration of multifidus muscle.[476] Trans-axial CT images are used to estimate the mean density of multifidus muscle which is measured in Hounsfield unit.[362]	Magnetic Resonance Imaging or Computerized tomography
Total volume of lumbar multifidus	A software is used to trace around the multifidus muscle on both right and left side on a T2 axial view and the muscle area is calculated. Total volume of lumbar multifidus from 1st to 5th vertebral level is calculated.[172]	Magnetic Resonance Imaging or Computerized tomography

Appendix 3. 3 Reasons for excluding studies for Chapter 3

Reasons for exclusion	**Excluded studies.**
Healthy participants	Belavy et al 2010,[477] Belavy et al 2008,[478] Hides et al 2012,[479] Holt et al 2016,[480] Rostami et al 2014,[481] Herbert, Heiss, and Basso, 2008[482]
Healthy controls	Lariviere et al 2018,[483] Kliziene et al 2015,[484] Zhang et al 2018[264]
Ineligible study design/intervention	Huang et al 2013,[152] Huang et al 2014,[153] Azadinia et al 2019,[472] Longo et al 2016,[485] Minetto et al 2018,[486] Chung et al 2013,[150] Danneels et al 2001,[154] Sipaviciene et al 2018,[151] Sokunbi et al 2008[174]
Ineligible outcome measures	Jackson, Shepherd, and Kell 2011,[487] Jeong at al 2015,[488] Ko et al 2018,[489] Mayer et al 2016,[490] Smith et al 2011,[491] Alrwaily 2017,[492] Storheim et al 2003[493]
Thesis	Sions, 2012.[494]
Conference proceedings	Thomas. A, 2015,[495] Barut, Tastaban, and Sendu 2018[496]
Poster Presentation	Vincent et al 2014[497]
Other than English	Mannion et al 2001,[498] Dalichau et al 2005[499]

Appendix 3. 4 Details of various physiotherapy treatments in the included studies for Chapter 3

Publications	Types of treatment	Details
MOTOR CONTROL EXERCISE		
Akbari et al, 2008[74]	MCE	At the first stage, exercises causing low-load activation of the stabilizing muscles (transversus abdominis and lumbar multifidus) introduced in supine, sitting, standing and 4-point kneeling positions). Participants were taught to contract these stabilizing muscles. Gradually, the holding time of these muscles was increased to the extent where participants were able to perform 10 contractions with a 10-second hold. Accordingly, the dynamic exercises were introduced at the second stage. The activation of transversus abdominis and LMM was ensured by observing the drawing-in maneuver of lower abdomen and bulging of LMM under therapist's finger placed on spinous process of L4-L5, respectively. MCE were specified for each stage.
Berglund et al, 2017[75]	MCE	The exercises were tailor-made for individual participants' impairment and muscle activation pattern. Initially, the exercises were targeted to maintain the lumbar spine in neutral position in supine, sitting, four-point kneeling, and standing. Later, they learned to control movements in their lumbar spine with minimal efforts while moving their arms or legs in similar positions. Finally, the difficulty level of exercises was increased by introducing various activities which caused dynamic movements of the lumbar spine.
Hides et al, 1996[500]	MCE	In standing position, participants performed an active, isometric LMM contraction with the lumbar spine in neutral position.
Hosseinifar et al, 2013[76]	MCE	The MCE was performed in 6 steps: Exercise 1 - MCE with focus on training isolated contraction of the TrA, LMM, and pelvic floor muscles. Exercise 2 - MCE with focus on co-contractions of the TrA, LMM, and pelvic floor muscles in the prone, supine, and 4-point kneeling positions. Exercise 3 - Closed kinematic chain SCE. Exercise 4 - MCE with low load by adding leverage of the limbs during open chain exercises; Exercise 5- MCE in functional activities. Exercise 6- co-contraction of the TrA and LMM muscles with an external load, complex movements, increased loading to the lumbar spine in neutral position, co-contraction of TrA and LMM during light aerobic activities such as walking, and activities that aggravate the symptoms
Kehinde et al, 2014[169]	MCE	Details of exercise were not reported.
Kim and Kim, 2013[170]	MCE using sling	MCE using sling – 1st week - In prone, MCE and in supine position bridging exercise were introduced. 2nd & 3rd week - In prone, MCE and in supine position bridging, pelvic lift and hip abduction exercises was introduced. 4 to 6 weeks - In prone, MCE and in supine position bridging, pelvic lift, and hip abduction. In side-lying position hip abduction and adduction.
Nabavi et al, 2018[138]	MCE	Exercises were represented through images in the article and details were not provided
Motor control exercise on a gymnastic ball		
Lee et al, 2011[171]	MCE on a gymnastic ball	Warm-up for 5 mins: stretching. Exercises on the ball for 30-35 mins: push-up, alternate superman pose, roll out, side crunch, bridging, reverse bridging, crunch-legs elevated, sit up, back extension, alternate arm-leg extension. Cool-down for 5 mins: stretching
MOTOR CONTROL EXERCISE WITH OTHER INTERVENTIONS		
Kehinde et al, 2014[169]	MCE + TENS MCE + massage	Details of interventions were not provided
Kim and Kim, 2013[170]	MCE using sling+ Push-ups	MCE in Quadrupedal position during 1-week, MCE in prone position for weeks 2-3, MCE in standing position for weeks 4-6. Details of the exercises were not provided
Tagliaferri et al, 2020[172]	MCE + manual therapy	MCE which caused activation of TrA, LMM and pelvic floor muscles were performed in non-weight bearing activities. MCE were performed in functional activities (e.g., walking) if it was a part of participants goals. Depending on the level of pain, exercises were progressed. Manual therapy: Spinal manipulations were provided in antero-posterior and transverse direction to mobilize lumbar spine along with cognitive-behavioural education
General Physiotherapy		

Kim and Kim, 2013[170]	GPT	Hot pack application (80ºC) for 10 mins, intermittent/continuous traction (2,000-2,500Hz) for 15 mins and US (0.8-1MHz) for 5 mins.
Lee et al, 2011[171]	GPT	Moist heat treatment (20-25mins), US (5 mins, 1.5W/cm2) and TENS (20 mins at 4Hz) and strength of recognizable muscle contraction.
Nabavi et al, 2018[138]	GPT	Warmup exercises, routine exercises, 5 mins of therapeutic US, 15 mins of continuous TENS, and infrared radiation
General exercises		
Akbari et al, 2008[74]	GE	Exercises that would activate paravertebral and abdominal muscles.
Other interventions		
Berglund et al, 2017[75]	High load lifting	Participants were instructed to maintain a neutral position of the low back and activate the lumbar stabilizing muscles during lifting and lowering the barbell from the floor. First few sessions were aimed at starting a proper technique at 3 to 5 sets of 10 repetitions with low loads (10-20 kg). Progression was done by increasing the number of 5 - 8 sets per session while the repetitions were reduced to 3 to 5 per set with increased weight on the bar.
Hides et al,1996[500]	Drugs	Analgesics aspirin, paracetamol (8 mg codeine tablets), combinations of low doses of codeine and aspirin (8 tablets per day), non-steroidal anti-inflammatory drugs (Digesic and Capadex) and Valium
Hosseinifar et al, 2013[76]	McKenzie	Six exercises were performed: In prone, four extension-type exercises were performed and standing, while two flexion-type exercises were performed in supine and sitting. Participants needed to maintain at the end position of each exercise for 10 seconds
Kehinde et al, 2014[169]	Drugs	Analgesics (details of drugs were not provided)
Tagliaferri et al, 2020 [172]	GSA	Aerobic exercise: (running/walking on a treadmill- 65%-85% of HR max for 20 mins) Strengthening exercises: Exercises like squatting, deadlifts, push-ups, trunk flexion and extension

Abbreviations: ADLs, activities of daily living; C, Celsius; exs, exercise; GE, general exercises; Gp, group; GPT, general physiotherapy; GSA, general strengthening and aerobic exercises; LMM, lumbar multifidus muscle; MCE, motor control exercise; mins, minutes; TENS, transcutaneous electrical nerve stimulation; TrA, transversus abdominis; US, therapeutic ultrasound therapy.

Appendix 3. 5 Summary of Findings and Quality of Evidence Assessment for Chapter 3

Quality assessment						Quality
No of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	
Volume						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
Cross-sectional area						
MCE + drugs vs Drugs only						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
GPT vs MCE using sling + GPT vs MCE using sling + GPT + pushups						
1	RCT	very serious [a]	not serious	not serious	serious [b]	⊕◯◯◯ VERY LOW
MCE on a gymnastic ball vs GPT						
1	RCT	very serious [a]	not serious	not serious	serious [b]	⊕◯◯◯ VERY LOW
MCE + GPT vs GE + GPT						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE + manual therapy vs GSA						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
Resting thickness						
MCE vs GE						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE vs HLL						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE vs McKenzie exercise						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE + GPT vs GE + GPT						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
Contracted Thickness						
MCE vs McKenzie exercise						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE vs MCE + TENS vs MCE + massage vs analgesics						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
Pain						
MCE vs GE						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE vs HLL						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯

						LOW
MCE vs McKenzie exercise						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE + drugs vs Drugs only						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE on a gymnastic ball vs GPT						
1	RCT	very serious [a]	not serious	not serious	serious [b]	⊕◯◯◯ VERY LOW
MCE + GPT vs GE + GPT						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW
MCE + manual therapy vs GSA						
1	RCT	serious [a]	not serious	not serious	serious [b]	⊕⊕◯◯ LOW

Explanations:

The Risk of Bias among included studies was assessed using the Cochrane collaboration's Tool (RoB 2.0) which included 5 domains of potential bias: Randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, and selective reporting.

a. The quality of evidence was downgraded if:

- There was a 'high' risk of bias in any domain (by one level)
- There was a 'high' risk of bias in half or more of the domains (by two levels)

Note: The risk of bias in all studies was evaluated using the using the Cochrane collaboration RoB Tool (RoB 2.0).

The quality of evidence was downgraded by one level if:

b. There was only one study.