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Greater Trochanteric Pain Syndrome
A comparison of exercise programmes and identification of subgroups

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Abstract

Greater trochanteric pain syndrome (GTPS) is a musculoskeletal condition for which exercise programmes are considered an essential part of management. Isometric exercise has been directly compared to isotonic exercise for other tendinopathies but the effectiveness of isometric exercise programmes for GTPS is currently unknown. A number of individuals with GTPS fail to experience clinical improvements following exercise programmes, which could be related to the presence of certain clinical characteristics, including health co-morbidities, co-existing physical symptoms and psychological factors. The prevalence of these clinical characteristics in GTPS populations is largely unknown. Subgroups based on such characteristics have yet to be defined. It is plausible that subgroups exist within GTPS populations who do not respond to current loading programmes.

Three studies were undertaken for this thesis. Firstly, a randomised controlled pilot study investigated whether there was any difference in clinical outcomes when 12 weeks of isometric exercise and isotonic exercise were compared. No difference was observed between both groups at 4 and 12-week follow-up. Secondly, a systematic review of 10 randomised controlled trials evaluated whether isometric exercise was superior to isotonic exercise or any other treatment in the management of tendinopathy. Isometric exercise did not appear to be superior in terms of immediate or short-term pain relief for any tendinopathy. Finally, an on-line survey of 261 individuals with GTPS was completed. Subgroups were defined for younger individuals (< 40 years) and older individuals (≥ 40 years) and sedentary and active individuals. The clinical characteristics identified in younger and older individuals were similar. Subgrouping based on physical activity level revealed that sedentary individuals had a greater number of health co-morbidities, co-existing physical symptoms and higher prevalence of psychological factors.

This thesis reports a number of important findings in relation to the effectiveness of isometric exercise in the management of GTPS and tendinopathy. For the first time subgroups of individuals with GTPS have been defined based on clinical characteristics which may guide future research.

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Clifford C, Paul L, Syme G, Millar NL. Isometric versus isotonic exercise for greater trochanteric pain syndrome: a randomised controlled pilot study. BMJ Open Sport Exerc Med. 2019 Sep 21;5(1):e000558.

Chapter 3:

Clifford C, Challoumas D, Paul L, Syme G, Millar NL. Effectiveness of isometric exercise in the management of tendinopathy: a systematic review and meta-analysis of randomised trials. BMJ Open Sport Exerc Med. 2020 Aug 4;6(1):e000760.

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Finally, to my wife Nancy and three children, Jack, Louisa and Harry. Louisa and Harry were born in 2017 and can't remember a time when Dad wasn't doing 'work stuff' in the evenings and weekends. Looking forward to more family time now this thesis is completed. Nancy, without your support I would never have achieved this.

Author's declaration

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

…… **Christopher Clifford**…….

Abbreviations

ACR:	American College of Rheumatology
BMI:	Body mass index
CI:	Confidence interval
CSI:	Corticosteroid injection
CSA:	Cross-sectional area
CNS:	Central nervous system
DASH	Disabilities of the Arm, Shoulder and Hand
EIH:	Exercise induced hypoalgesia
GMax:	Gluteus maximus
GMed:	Gluteus medius
GMin:	Gluteus minimus
GTPS:	Greater trochanteric pain syndrome
GROC:	Global rating of change
HADS:	Hospital anxiety and depression scale
HOOS:	Hip disability and osteoarthritis outcome score
HRT:	Hormone replacement therapy
HSR:	Heavy slow resistance
IPAQ:	International physical activity questionnaire
IFM:	Interfascicular matrix
ITB:	Iliotibial band
MeSH:	Medical Subject Headings
MCID:	Minimum clinically important difference
MHT:	Menopausal hormone therapy
MRI:	Magnetic resonance imaging
MSK:	Musculoskeletal
MVC:	Maximum voluntary contraction
NSAIDs:	Non-steroidal anti-inflammatory drugs
NPRS:	Numeric Pain Rating Scale
PRTEE	Patient-Rated Tennis Elbow Evaluation
PRP:	Platelet-rich plasma
QoL:	Quality of life
RCT:	Randomised controlled trial

ROM:	Range of movement
TFL:	Tensor fascia lata
TSK:	Tampa scale of kinesiophobia
TUT:	Time under tension
UoG:	University of Glasgow
URL:	Uniform resource locator
USS:	Ultra-sound scans
UTC:	Ultrasound tissue characterisation
VAS:	Visual Analogue Scale
WORC	Western Ontario Rotator Cuff Index
VISA-G:	Victorian Institute of Sport Assessment-Gluteal

Chapter 1

Introduction

1.1 Greater trochanteric pain syndrome (GTPS)

Greater trochanteric pain syndrome (GTPS) is a diagnostic term used to describe lateral hip pain over and around the greater trochanter. Pain in this location was first attributed to inflammation of the trochanteric bursa by Partridge (1846) and labelled as 'Trochanteric Bursitis' by Stegemann (1923). Almost 30 years later, Spear and Lipscomb (1952) asserted that the gluteal tendons should also be considered as a cause of lateral hip pain. Leonard (1958) agreed with this view and proposed the term 'trochanteric syndrome'. Gordon (1961) argued that the primary pathology occurs within the gluteal tendons due to microtrauma and degeneration and that bursal involvement was secondary. Later, Karpinski et al. (1985) proposed the term 'greater trochanteric pain syndrome', terminology that continues to be used in clinical and research settings.

Trochanteric bursitis and GTPS are diagnoses typically made following a clinical examination. With advances in radiological modalities, primarily magnetic resonance imaging (MRI) and ultrasound scans (USS), the evaluation and understanding of lateral hip anatomy and pathology have significantly improved. Pathology within the gluteal tendons, mainly gluteus medius (GMed) and gluteus minimus (GMin), include changes in collagen structure which can manifest as tendinosis, partial tears or complete rupture (Kingzett-Taylor et al. 1999). Fluid within the bursa, referred to as bursal distension, has also been observed and is thought to represent 'bursitis' (Bird et al. 2001). Kagan (1999) and Kingzett-Taylor et al. (1999) were among the first authors to describe MRI findings of gluteal tendon pathology with associated bursitis in patients with lateral hip pain. Subsequently, GMed tendon pathology was the most common observation on MRI, with isolated bursitis present in 8% of patients (Bird et al. 2001). Similarly, gluteal tendinopathy was the most frequent finding on USS with a low prevalence of isolated bursitis in 6-8% of individuals (Long et al. 2013, Ruta et al. 2015).

Histopathological analysis has provided additional insight into gluteal tendon and trochanteric bursal pathology. No evidence of acute or chronic inflammation was detected in the bursa of 25 patients with lateral hip pain (Board et al. 2014). The authors concluded that bursal inflammation has no role in lateral hip pain, casting doubt on the pathophysiology and terminology of this condition. This supports the earlier findings of Connell et al. (2003), Fearon et al. (2010) and Silva et al. (2008) who were also unable to identify acute or chronic inflammation in tendon or bursa. Thus far, Kingzett-Taylor et al.

(1999) are the only investigators to report inflammation of peritendinous tissue in patients with gluteal tendon tears. In all five studies, tissue samples were from patients with chronic symptoms, likely representing end-stage tendon disease. However, modern molecular techniques have identified the presence of inflammation in early tendinopathy (Millar et al. 2010). These observations were detected in the rotator cuff tendons but no studies have investigated whether inflammation is present in early gluteal tendinopathy. Overall, there is currently no clear evidence of inflammation within the gluteal tendons or trochanteric bursa in individuals with GTPS. In summary, gluteal tendon pathology is the most common radiological finding in individuals with lateral hip pain. Tendon involvement can occur in isolation but is often associated with bursal pathology. Bursitis/bursal distension in the absence of gluteal tendon pathology is rare.

For the remainder of this thesis, the term GTPS will be used to describe lateral hip pain that is present due to injury or pathology of the gluteus medius and/or gluteus minimus tendons and/or the associated trochanteric bursa.

1.2 Epidemiology

Musculoskeletal conditions are the leading cause of long-standing illness in Scotland and associated with a significant burden of disease (The Scottish Government 2016, GBD 2019 Diseases and Injuries Collaborators). Tendinopathy accounts for 30% of all musculoskeletal complaints seen in NHS general practice (McCormick et al 1995). However, this condition remains under recognised with two out of three cases believed to be unreported (Hopkins et al. 2016). As a consequence, the disease burden associated with tendinopathy is likely to be considerably greater than currently described. The impact of GTPS on society and health care usage has not been determined, however almost 30% of individuals continue to experience pain five years after symptom onset (Lievense et al. 2005).

Noordzij et al. (2010) defined prevalence as ‘the number of existing cases of a disease’ and incidence as ‘the number of new cases of a disease’. Connell et al. (2003) and Ruta et al. (2015) established that gluteal tendinopathy is the most common cause of lateral hip pain however, the exact prevalence and incidence in the United Kingdom (UK) has not been determined. In a Dutch primary care population, gluteal tendinopathy was the most common lower limb tendinopathy with a prevalence and incidence of 4.2 and 3.3 per 1000

person-years respectively (Albers et al. 2016). A cohort study of similar design reported a prevalence of 2.9 and an incidence of 1.6 per 1000 person-years for GTPS in Danish general practice (Riel et al. 2019). The prevalence of lower limb tendinopathy increases with age with older individuals (≥ 45 years) more frequently affected than younger individuals (< 45 years) (Albers et al. 2016, Riel et al. 2019). Participants with GTPS included in clinical trials are typically > 40 years. In the 'LEAP' randomised controlled trial, individuals diagnosed with gluteal tendinopathy were eligible for inclusion if aged 35-70 years (Mellor et al. 2018). Further studies only included post-menopausal women, a population that is predominantly middle-aged and older (Cowan et al. 2022, Ganderton et al. 2018). Rompe et al. (2009) did not report the age range of study participants, however the mean age was 46 years. GTPS is more prevalent in females with a female:male ratio of approximately 4:1 (Lievense et al. 2005, Riel et al. 2019). Although female gender and increasing age are associated with GTPS, there is currently a gap in the existing literature in relation to how this condition affects younger individuals < 40 years. The clinical characteristics of this age group will be investigated in Chapter 4 of this thesis.

1.3 Functional anatomy of the lateral hip

A number of muscles and bursa are located in the region of the lateral hip. The gluteal muscles attach via their tendons onto different facets of the greater trochanter. Dwek et al. (2005) identified four facets; anterior, lateral, posterior and superoposterior (Figure 1-1).

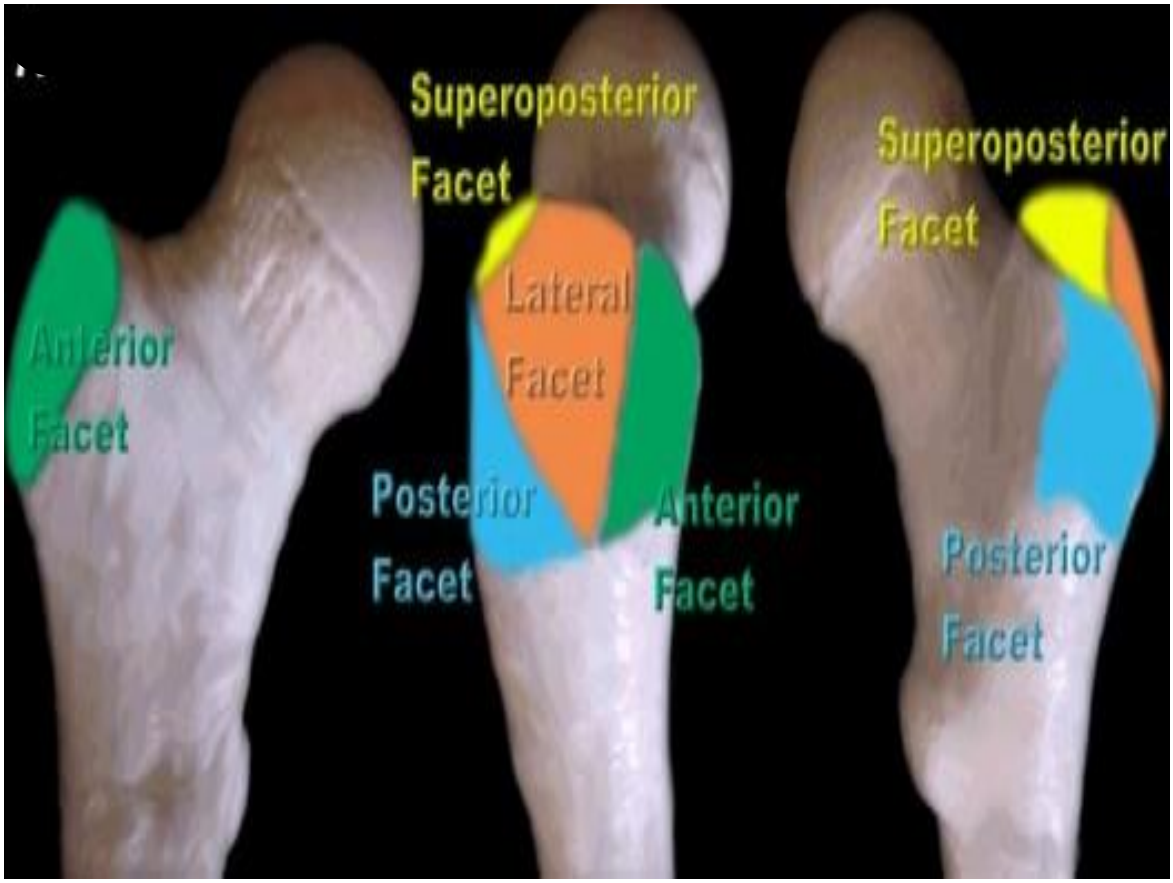

Figure 1-1. Facets of greater trochanter: anterior, lateral, posterior and superoposterior. Dwek et al. (2005) Reproduced with permission.

The four muscles most relevant to GTPS are:

- Gluteus medius
- Gluteus minimus
- Gluteus maximus
- Tensor fascia lata/Iliotibial band

Gluteus medius (GMed) arises from the outer surface of the ilium (Figure 1-2). The lateral facet of the greater trochanter is the attachment site for the anterior and middle fibres, while the posterior fibres attach to the superoposterior facet (Robertson et al. 2008). GMed is the primary abductor of the hip and has a secondary role in both internal and external rotation (Neumann et al. 2010). Eccentrically it controls hip adduction during single leg loading activities such as descending stairs (Lee et al. 2014).

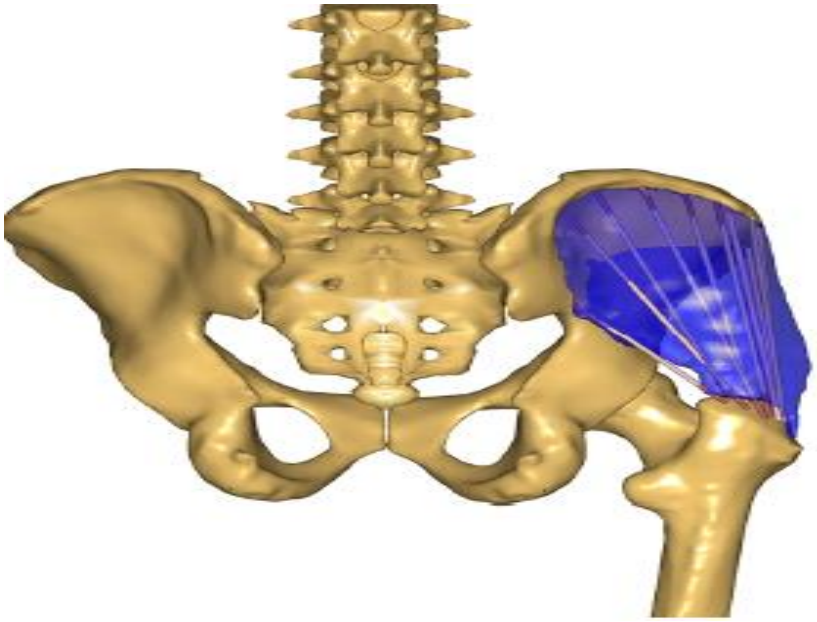

Figure 1-2. Right gluteus medius muscle. De Pieri et al. (2018).

Gluteus minimus (GMin) is the deepest of the gluteal muscles (Figure 1-3). Also arising from the outer surface of the ilium it is covered almost entirely by GMed (Beck et al. 2000). It attaches to both the anterior facet of the greater trochanter and the capsule of the hip joint. The line of action of gluteus minimus, running parallel to the femoral neck, indicates that its primarily role is to stabilise the femoral head in the acetabulum (Beck et al. 2000). It also contributes to hip abduction, flexion and both internal and external rotation (Neumann et al. 2010).

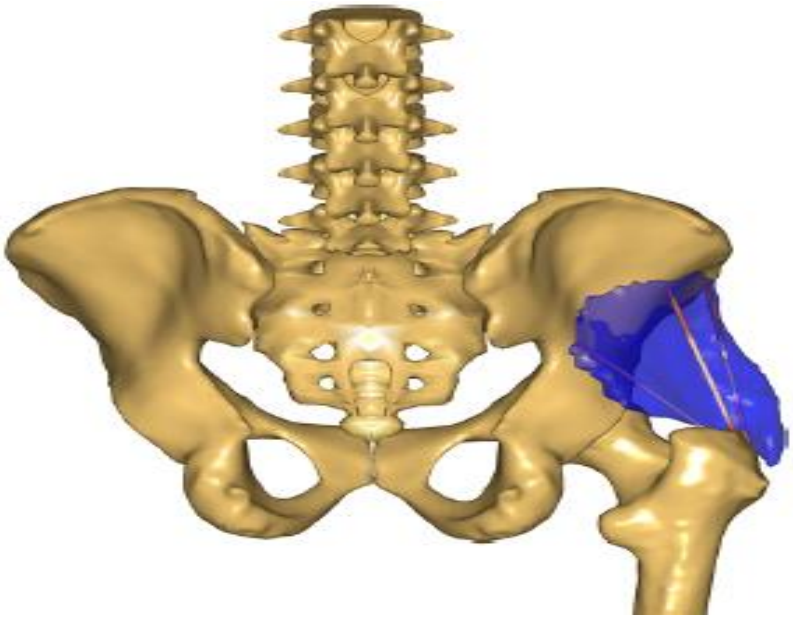

Figure 1-3. Right gluteus minimus muscle. De Pieri et al. (2018).

Gluteus Maximus (GMax) is a powerful extensor and external rotator of the hip (Figure 1-4). It also has a secondary role in hip adduction (Neumann et al. 2010). Reiman et al. (2012) reported that approximately 80% of this muscle inserts into the iliotibial band (ITB).

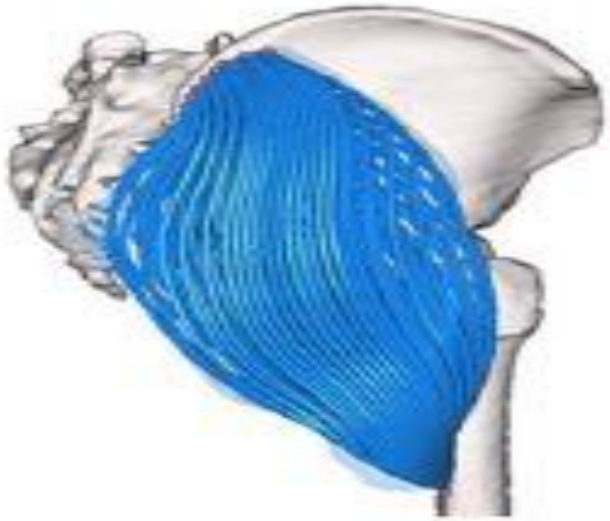

Figure 1-4. Right gluteus maximus muscle. Modenese and Kohout (2020).

Tensor fascia lata (TFL) arises from the anterior superior iliac spine (ASIS), mainly from the anterior and lateral borders, and blends distally with the ITB (Figure 1-5). The TFL functions in synergy with gluteus medius and minimus to abduct and internally rotate the hip, while also having a role as a hip flexor (Neumann et al. 2010).

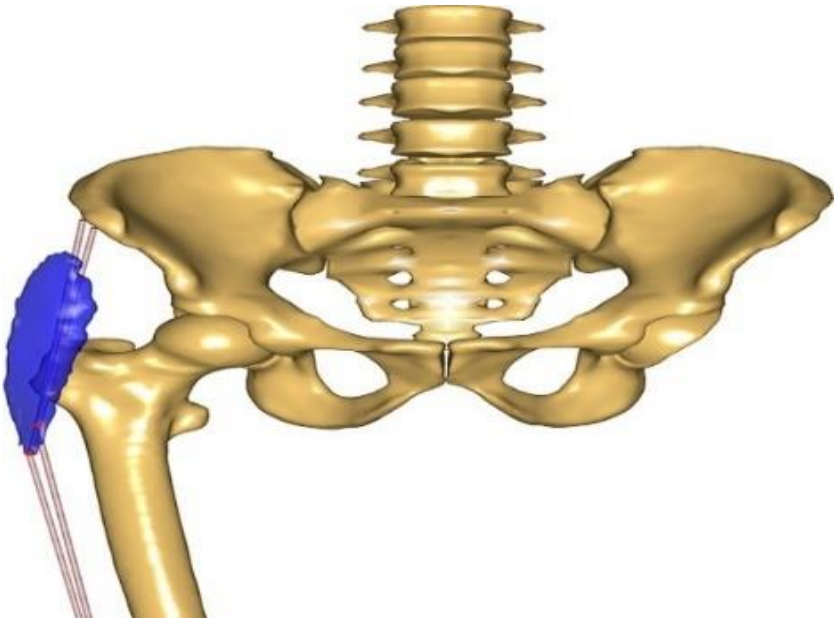

Figure 1-5. Right tensor fascia lata muscle. De Pieri et al. (2018)

Together, GMed, GMin and the TFL/ITB have a critical role during weight-bearing activities (Kumagai et al. 1997). During single leg standing and walking they contract to produce an abduction moment, stabilising the pelvis and balancing the adduction moment that occurs, thus preventing contralateral pelvic drop on the weight-bearing limb (Grimaldi 2011, Kumagai et al. 1997) (Figure 1-6).

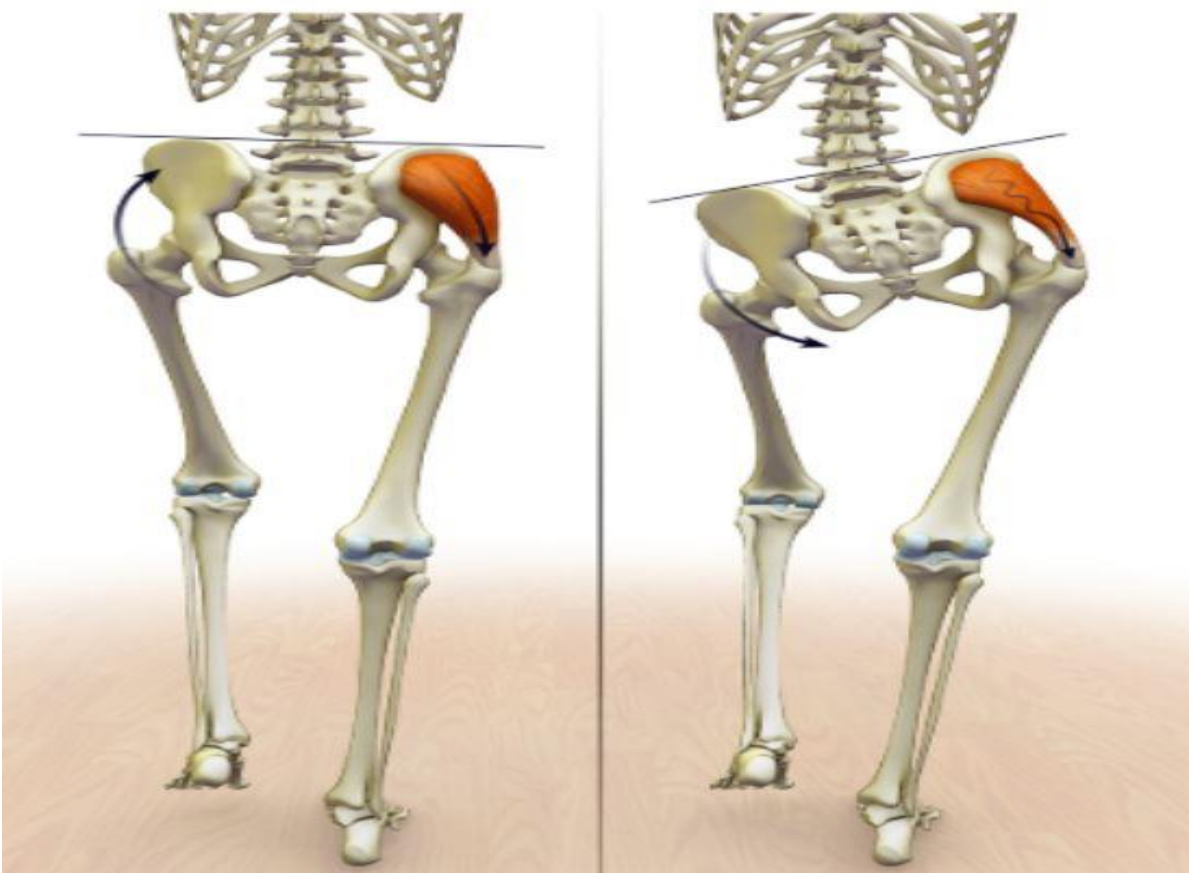

Figure 1-6. Gluteus medius function during single leg stance. Available at https://www.amitypt.com/ (Accessed 22 March 2022).

Bursa are fluid filled structures that reduce friction between tendon and underlying bone (Board et al. 2014). Reflecting that the trochanteric bursa were once considered to be the primary cause of lateral hip pain, numerous studies have investigated their precise location and number (Dunn et al. 2003, Gordon 1961, Pfirrmann et al. 2001, Woodley et al. 2008a). There is consensus that three trochanteric bursa are consistently present; subgluteus maximus, subgluteus medius and subgluteus minimus (Figure 1-7).

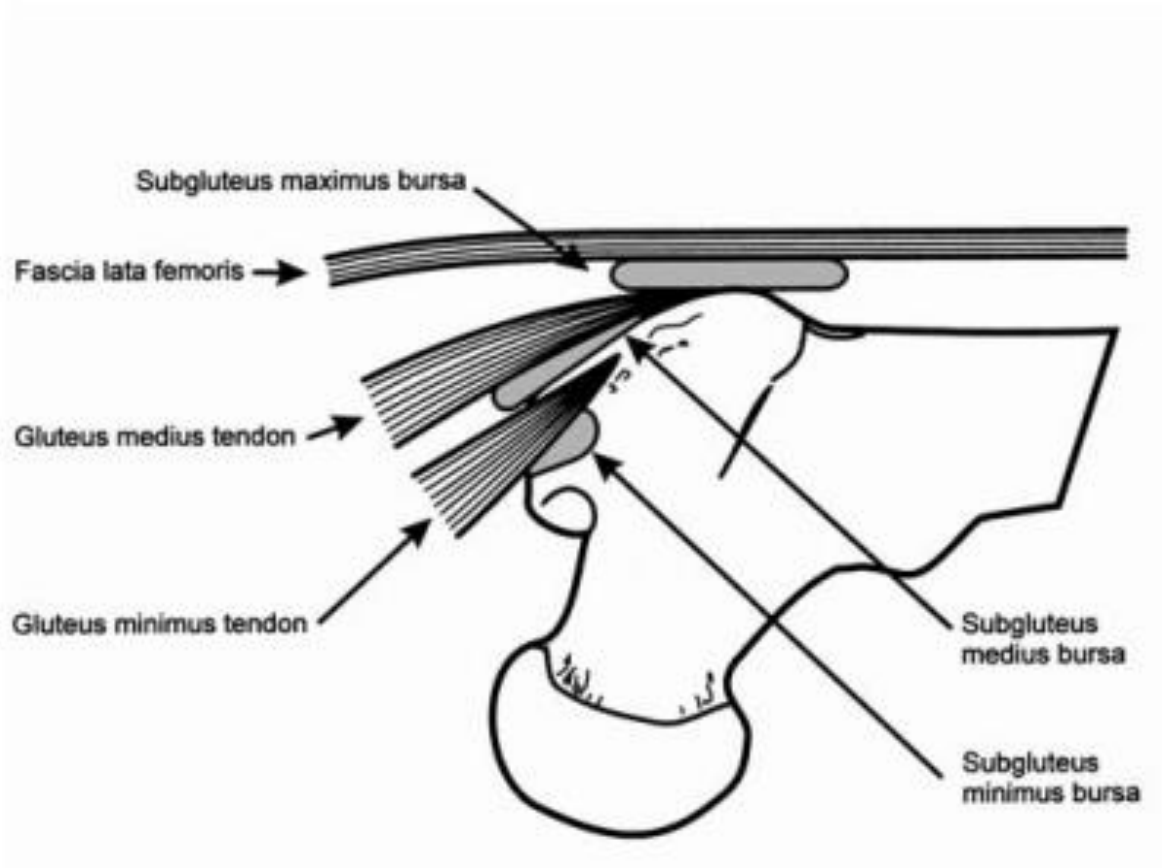

Figure 1-7. Location of trochanteric bursa. Connell et al. (2003). Reproduced with permission.

The subgluteus maximus bursa is the largest trochanteric bursa and positioned beneath the GMax and ITB, being separated from the greater trochanter by the GMed tendon (Leonard 1958, Pfirrmann et al. 2001, Woodley et al. 2008a). Located between the GMed tendon and the lateral surface of the greater trochanter is the subgluteus medius bursa (Pfirrmann et al. 2001). The subgluteus minimus bursa is situated deep to the GMin insertion on the anterior aspect of the greater trochanter (Pfirrmann et al. 2001). Cadaveric studies have identified that at least two bursa are located in proximity of each gluteal tendon (Woodley et al. 2008a). Branches of the inferior gluteal nerve can supply the subgluteus maximus bursa (Dunn et al. 2003).

1.4 GTPS clinical presentation and diagnostic tests

1.4.1 Symptoms

Individuals with tendinopathy typically complain of pain and loss of function (Scott et al. 2020). Pain is normally well localised to the site of pathology and provoked by activities which load the tendon (Cook and Purdam 2014). In GTPS, pain is located around the lateral hip, close to the insertion of gluteus medius and minimus (Gordon 1961, Mallow

and Nazarian 2014). Occasionally, there may also be diffuse spread into the lateral thigh and below the knee (Gordon 1961, Woodley et al. 2008b). The inferior gluteal nerve forms from the spinal nerves of L5-S2, which may explain the sensation of pain distal to the knee (Dunn et al. 2003). Activities of daily living including walking, going up stairs, prolonged standing and sitting will frequently aggravate pain (Bird et al. 2001, Karpinski et al. 1985, Lievense et al. 2005, Mallow and Nazarian 2014, Schapira et al. 1986, Silva et al. 2008, Strauss et al. 2010). Sleep disturbance is common as pain is often experienced while lying on the affected side (Bird et al. 2001, Connell et al. 2003, Stephens et al. 2020, Strauss et al. 2010). GTPS can also have a considerable impact on work and sport participation (Fearon et al. 2014a, Lievense et al. 2005). Unsurprisingly, quality of life can be significantly impaired and comparable to severe hip osteoarthritis (Fearon et al. 2014a).

1.4.2 Co-existing musculoskeletal pain

People with musculoskeletal conditions frequently report more than one site of pain (Kamaleri et al. 2008). Individuals with GTPS often complain of co-existing low back and/or hip joint pain (Gordon 1961, Collée et al.1990). The prevalence of low back pain with GTPS, ranges from 21% - 62% (Rompe et al. 2009, Stephens et al. 2020, Woodley et al. 2008b). Knee osteoarthritis has also been associated with GTPS and 15% of an NHS population reported lower limb osteoarthritis (Segal et al. 2007, Stephens et al. 2019a). Previous studies have reported that 20% - 50% of patients referred to a spinal clinic had symptoms consistent with GTPS (Tan et al. 2018, Tortolani et al. 2002). An accurate clinical diagnosis can therefore be challenging as GTPS may co-exist with low back and/or hip pain or be present secondary to referred pain from either region.

1.4.3 Clinical tests

Clinical tests that can improve the diagnostic accuracy of GTPS are essential, particularly in clinical and research settings when radiological imaging is not routinely available. Historically and prior to the use of MRI and USS in healthcare, a diagnosis of GTPS was based on clinical signs and symptoms. Pain on direct palpation around the greater trochanter was a consistent finding (Gordon 1961, Kagan 1999, Karpinski 1985 and Leonard 1958). Pain reproduced during resisted hip abduction and Patrick's test/FABER (Flexion, Abduction, External Rotation of the hip joint) have also been used in clinical settings for many years (Gordon 1961, Karpinski 1985). The diagnostic utility of a clinical test is determined by its sensitivity and specificity. Sensitivity refers to the ability of a test to correctly identify those patients with the condition whereas specificity refers to the

ability of a test to correctly identify patients without the condition (Lalkhen et al. 2008 pg.221). Sensitivity and specificity values of various diagnostic tests for GTPS have been calculated in a number of studies using MRI as the reference standard (Table 1-1).

Table 1-1. Clinical diagnostic tests for GTPS

Clinical test	Sensitivity	Specificity
1. Palpation around greater trochanter	80% (Grimaldi et al. 2017) 85.7% (Ganderton et al. 2017)	46.7% (Grimaldi et al. 2017) 61.1% (Ganderton et al. 2017)
2. Resisted hip abduction	72.7% (Bird et al. 2001) 47% (Woodley et al. 2008b) 50% (Ganderton et al. 2017	46.2% (Bird et al. 2001) 86% (Woodley et al. 2008b) 97.3% (Ganderton et al. 2017)
3. Trendelenburg	72.7% (Bird et al. 2001) 23% (Woodley et al. 2008b)	76.9% (Bird et al. 2001) 94% (Woodley et al. 2008b)
4. FABER	42% (Grimaldi et al. 2017) 50% (Ganderton et al. 2017)	80% (Grimaldi et al. 2017) 83% (Ganderton et al. 2017)
5. FADER	30% (Grimaldi et al. 2017) 44.4% (Ganderton et al. 2017)	86.7% (Grimaldi et al. 2017) 89.5% (Ganderton et al. 2017)
6. FADER-R	44% (Grimaldi et al. 2017) 39.2% (Ganderton et al. 2017)	93.3% (Grimaldi et al. 2017) 94.4% (Ganderton et al. 2017)
7. Resisted external derotation test	88% (Lequesne et al. 2008) 42.3% (Ganderton et al. 2017)	97.3% (Lequesne et al. 2008) 95% (Ganderton et al. 2017)
8. Resisted hip internal rotation	40.7% (Ganderton et al. 2017) 54.5% (Bird et al. 2001)	94.7% (Ganderton et al. 2017) 69.2% (Bird et al. 2001)
9. Single-leg stance (30s)	38% (Grimaldi et al. 2017) 100% (Lequesne et al. 2008) 45.4% (Ganderton et al. 2017)	100% (Grimaldi et al. 2017) 97.3% (Lequesne et al. 2008) 84.2% (Ganderton et al. 2017)
10. Passive hip adduction in side-lying	20% (Grimaldi et al. 2017) 12.5% (Ganderton et al. 2017)	86.7% (Grimaldi et al. 2017) 97.5% (Ganderton et al. 2017)
11. Passive hip adduction in side-lying with resisted abduction	38% (Grimaldi et al. 2017)	93.3% (Grimaldi et al. 2017)
Abbreviations: *FABER, Flexion Abduction External Rotation; FADER, Flexion Adduction External Rotation; FADER-R, Flexion Adduction External Rotation with resisted isometric hip internal rotation.*		

The purpose of each clinical test is to reproduce or provoke lateral hip pain. The exception is the Trendelenburg test, a functional test used to assess the strength of gluteus medius on the weight-bearing side (Figure 1-6). Although the performance of both the Trendelenburg and single leg stance test are identical, the latter is a provocation test to reproduce lateral hip pain within 30 seconds. Pain on direct palpation remains the most common examination finding and is often a requirement for inclusion in GTPS clinical trials. Given the sensitivity values identified in Table 1-1, at least 4 out of 5 individuals with pain on palpation would be expected to have gluteal tendon pathology on MRI. However, due to a specificity of 46.7% and 61.1%, pain on palpation is no longer recommended for use as a stand-alone test (Grimaldi et al. 2017). Moreover, caution has been advised when using any single test for the diagnosis of GTPS/gluteal tendinopathy owing to sensitivity and specificity values (Reiman et al. 2013). Instead, reproduction of lateral hip pain during a number of clinical tests rather than one stand-alone test has been used for study inclusion (Cowan et al. 2022, Ganderton et al. 2018, Mellor et al. 2018, Rompe et al. 2009). Pain on direct palpation and at least one other provocation test is advocated for a diagnosis of GTPS (Grimaldi et al. 2017). These criteria were also used for inclusion in the LEAP trial, the largest randomised controlled trial (RCT) to date for gluteal tendinopathy (Mellor et al. 2018).

In summary, a series of clinical tests is currently recommended to improve the diagnostic accuracy of GTPS. Such tests are beneficial in both clinical practice and for inclusion in clinical trials when imaging modalities are not available. A number of these clinical tests were used as part of the inclusion criteria for participation in the randomised controlled trial in Chapter 2.

1.4.4 Clinical impairments

Patients with GTPS and participants in clinical trials commonly engage in exercise programmes that specifically target the hip abductor muscles (Mellor et al. 2018, Stephens et al. 2019b). This appears justified as hip abductor weakness and gluteal muscle atrophy have been previously identified in this population (Allison et al. 2016a, Chi et al. 2015, Fearon et. al). Muscle strength deficits in the hip adductor, external rotator and internal rotators were however not detected (Fearon et al. 2017). Differences in trunk and pelvic biomechanics have also been observed during functional tasks in people with gluteal tendinopathy. Specifically, an increase in hip adduction during walking, going up stairs and single leg standing (Allison et al. 2016b, Allison et al. 2016c, Allison et al. 2016d).

Due to the cross-sectional design of these studies a causal relationship cannot be established making it difficult to draw firm conclusions about cause and effect. However, these kinematic changes may be clinically relevant as compressive loading at the lateral hip increases during hip adduction (Birnbaum et al. 2004). Compression is also believed to be associated with the development of insertional tendinopathy and the persistence of pain (Cook and Purdam 2012). It is currently unclear whether these clinical impairments - muscle weakness and alterations in kinematics - contribute to the onset of GTPS or develop secondary to lateral hip pain and/or gluteal tendon pathology. Exercise programmes targeting the gluteal tendons alongside education to minimise compressive loading during activity have been used previously and could theoretically address these clinical impairments (Cowan et al. 2022, Ganderton et al. 2018, Mellor et al. 2018).

1.5 Tendon structure and function

Normal healthy tendon is mainly composed of type I collagen, accounting for approximately 60-85% of its dry weight (Kjaer 2004). The remaining constituents are a non-collagenous extracellular matrix (ECM) and cells. These resident cells are predominantly tenocytes which are responsible for producing the ECM, a complex structure containing collagen, proteoglycans and glycoproteins (Kjaer 2004, Bosman and Stamenkovic 2003).

The hierarchical structure of tendon consists of collagen fascicles, fibres and fibrils (Figure 1-8). Individual collagen fibrils are arranged into bundles of fibres which are tightly bound and arranged in parallel. These fibres form subunits called fascicles that are grouped together into fibre tertiary bundles and the tendon itself. Endotenon, also referred to as the interfascicular matrix (IFM), allows for sliding between fascicles (Thorpe et al. 2015a). The epitenon is a connective tissue sheath continuous with the endotenon and provides the tendon with its vascular and nerve supply (Sharma and Maffuli 2005). Sensory nerve fibres from the overlying superficial nerves or from nearby deep nerves are mostly afferent (Barr and Keimann 1998). There are four types of afferent receptors. Type I (Ruffini corpuscles) are pressure receptors that are extremely sensitive to stretch and adapt slowly. Type II (Vater-Pacini corpuscles) are activated by movement, Type III (Golgi Tendon Organ) are mechanoreceptors and type IV are free nerve endings that act as pain receptors (Jozsa and Kannus 1997). The paratenon facilitates movement of the tendon and is the outermost layer.

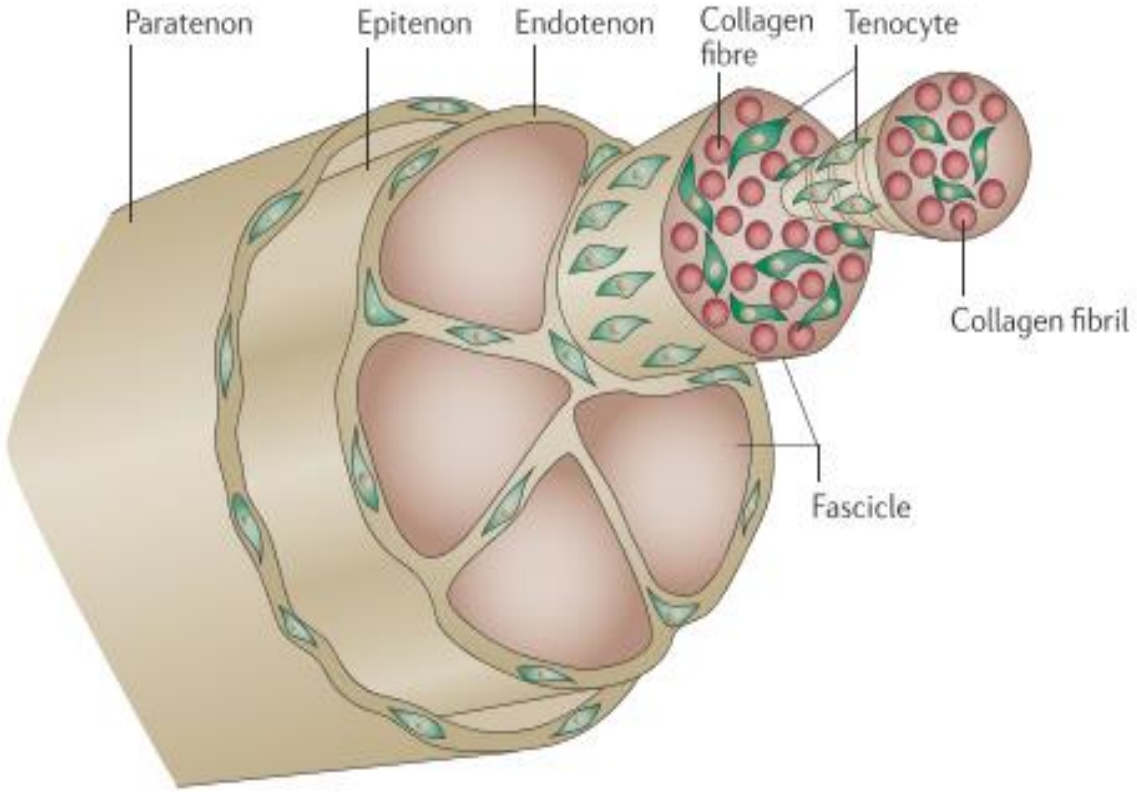

Figure 1-8. Normal hierarchical tendon structure. Millar et al. (2017). Reproduced with permission.

The primary function of tendon is to transmit force from muscle to bone (Nourissat et al. 2015). The organisation of collagen fibres in parallel is perfectly suited to this role, providing tendon with high tensile strength allowing it to absorb the significant stress that it can be subjected to during sporting and occupational activity (Bosman and Stamenkovic 2003). Within the ECM, proteoglycans are located between collagen fibres and are responsible for binding water and providing resistance to compressive forces (Yoon and Halper 2005).

The enthesis is a specialised region where tendon inserts directly to bone (Figure 1-9). The ECM composition of the enthesis is similar to the mid-portion but also contains additional collagens and an increased number of proteoglycans (Benjamin et al. 2006). A number of tendons, including gluteus medius and minimus, do not attach to bone in an isolated manner. Instead they fan out at the insertion site, allowing stress to be distributed over a larger area (Pfirrmann et al. 2001, Riley 2008). Four zones have been identified at the enthesis; pure dense fibrous connective tissue, uncalcified fibro-cartilage, calcified fibrocartilage and bone (Benjamin et al. 2002). As the enthesis is a transitional region, it is subjected to a high degree of stress and these zones are believed to balance and dissipate the load between tendon and bone (Benjamin et al. 2006). Fibrocartilage is formed in

tendon in response to compressive load or shear, an adaptive response that protects the tendon from damage (Riley 2008). Fibrocartilage is present in the enthesis of tendons that wrap around bone including the greater trochanter (Benjamin 1995). This site provides attachment for the tendons of gluteus medius and minimus and is exposed to high compressive forces during hip adduction (Birnbaum et al. 2004).

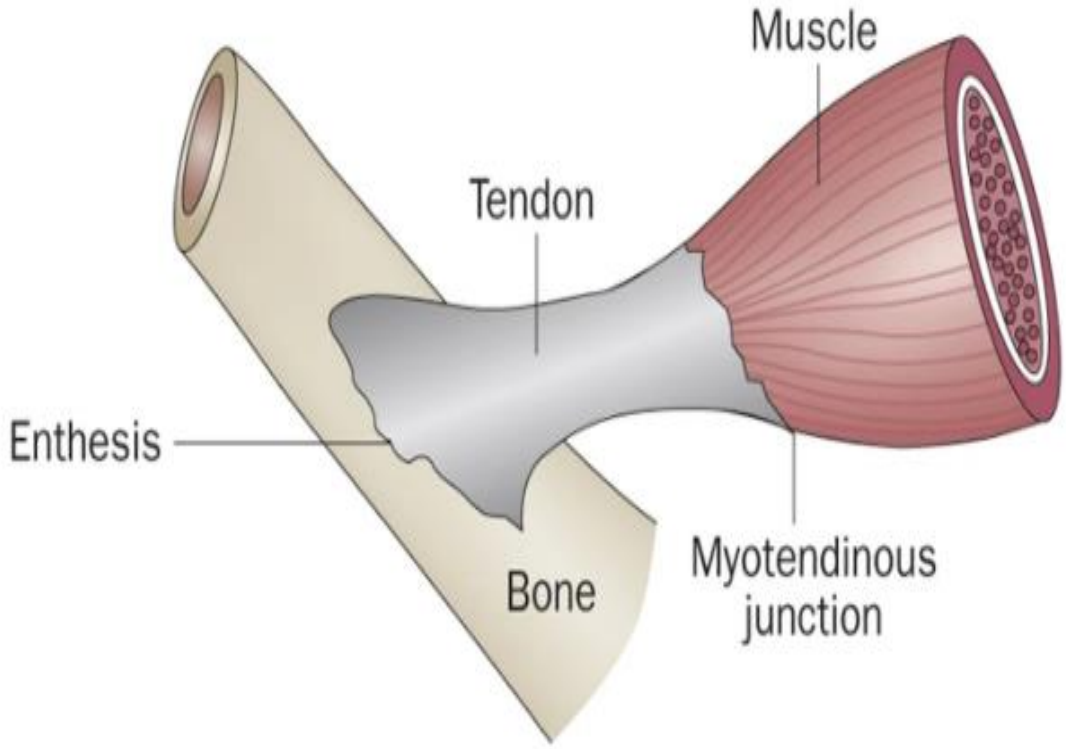

Figure 1-9. Tendon architecture. Nourissat et al. (2015). Reproduced with permission.

1.6 Tendon pathology

The diagnostic labelling of tendon disorders has changed over time. Historically the term 'tendonitis' was used for a condition believed to be secondary to inflammation. However, histological and surgical studies failed to identify any acute inflammatory cells (Astrom and Rausing 1995, Khan et al. 1996, Kraushaar and Nirschl 1999). Khan et al. (2000) proposed that the term 'tendinosis' would be more appropriate to reflect a degenerative pathology, devoid of inflammation. Subsequent microdialysis techniques provided further support that tendon pathology was not secondary to inflammation (Alfredson et al. 2000, Alfredson et al. 2001). However, it is probably an oversimplification to suggest that inflammation is not present (Rees et al. 2014). In recent years there have been advances in modern molecular techniques and inflammatory mediators have been identified in tendon (Dakin et al. 2015, Millar et al. 2010). The term 'tendinopathy' is now preferred to both

tendinitis and tendinosis as it considers pain and loss of function and makes no assumptions about the underlying pathology (Riley 2008).

1.6.1 Enthesopathy

An enthesopathy is defined as a pathological change at an enthesis (Benjamin et al. 2006). Enthesis are a site of high stress concentration and injuries secondary to overuse are common in this region (Benjamin et al. 2002, Riley 2008). Almost all tendinopathies, with the exception of mid-portion Achilles tendinopathy, occur at the enthesis and are recognised as insertional tendinopathies. When a tendon is subjected to tensile loading, force is transferred from muscle to the bone. The deep surface (joint side) of the tendon may also be subjected to compressive loading at the enthesis and develop pathologic changes (Almekinders et al. 2003). Such changes have been consistently observed in the deep surface of the tendon in both upper and lower limb tendinopathy (Carr et al. 2001, Connell et al. 2003, Connell et al. 2001, Factor and Dale 2014). However, it is the superficial portion that would be expected to demonstrate pathology as it is under higher stress being further from the joint axis of rotation (Orchard et al. 2004). These findings demonstrate that insertional tendinopathy is unlikely to be simply an 'overuse' injury secondary to tensile loading.

Cook and Purdam (2012) discussed the potential role of compression in the development and persistence of insertional tendinopathy, including gluteal tendinopathy (Figure 1-10).

Tendon	Anatomical site of compression	Position of compression
Achilles insertion	Superior calcaneus	Ankle dorsiflexion
Tibialis posterior	Medial malleolus	Anatomically permanent pivot
Biceps long head	Bicipital groove	Shoulder extension
Supraspinatus	Greater tuberosity	Shoulder adduction
Hamstring (upper)	Ischial tuberosity	Hip flexion
Gluteus medius and minimus	Greater trochanter	Hip adduction
Adductor longus/rectus abdominus	Pubic ramus	Hip abduction/extension
Peroneal tendons	Lateral malleolus	Anatomically permanent pivot
Quadriceps	Femoral condyle	Deep knee flexion
Pectorals	Humeral tuberosity	External rotation

Figure 1-10. Site and position of compression for insertional tendinopathy. Cook and Purdam (2012). Reproduced with permission.

The findings appear to have plausibility for gluteal tendinopathy as biomechanical modelling has revealed that compressive loading at the greater trochanter increases substantially with increasing hip adduction past neutral (0 degrees) (Birnbaum et al. 2004). Using an animal model, a combination of compressive and tensile loading has been shown to be more damaging than either compression or tensile loading alone (Soslowsky et al. 2002). The clinical diagnostic tests in Table 1-1 are theorised to reproduce lateral hip pain through tensile and/or compressive loading of the gluteal tendons and bursa. Moreover, an association between both tensile loading (walking, stair climbing) and compressive loading (increased hip adduction) has been identified in people with gluteal tendinopathy (Allison et al. 2016b, Allison et al. 2016c). Given that females tend to have wider pelvis' and therefore a greater hip adduction angle than males, the lateral hip region will likely be exposed to greater compression (Birnbaum et al. 2004). Taken together, this perhaps provides a biomechanical explanation as to why gluteal tendinopathy is more common in females.

1.6.2 Models of tendinopathy

Tendon homeostasis is a balance between cell death and regeneration. A failure in this physiological homeostasis can result in pathological changes and the clinical presentation of tendinopathy (Pingel et al. 2014). Pathology within the tendon at both the insertion and mid-portion is similar, at least in relation to the ECM (Cook and Purdam 2009). Collagen disorganisation is evident with a loss of parallel fibril structure, mainly due to an increase in type III collagen (Magnusson et al. 2010). Buckling of collagen fascicles in the ECM has also been observed (Pingel et al. 2014). Hypercellularity, vascular ingrowth and changes to tenocytes occur and the production of proteoglycans leads to accumulation of water and tendon thickening (Cook and Purdam 2009, Kjaer et al. 2013, Riley 2008). These cellular changes reduce the strength of tendon and may lead to the development of pain secondary to mechanical overload (Riley 2008).

Several models have been proposed to explain the pathogenesis of tendinopathy. These include i) failed healing ii) continuum and iii) inflammation. The **failed healing** model described by Fu et al. (2010) proposed that overuse may initiate the pathological process in some individuals with tendinopathy. However, in sedentary and non-athletic populations, systemic or lifestyle-related factors likely play a causative role. Three stages of failed healing are described, i) injury ii) failed healing and iii) clinical presentation (Figure 1-11). When injury occurs, there is a release of pro-inflammatory mediators. At this stage, tendon

healing is possible, however this may not occur and instead ‘failed healing’ ensues with the clinical presentation of tendon pain and mechanical weakness.

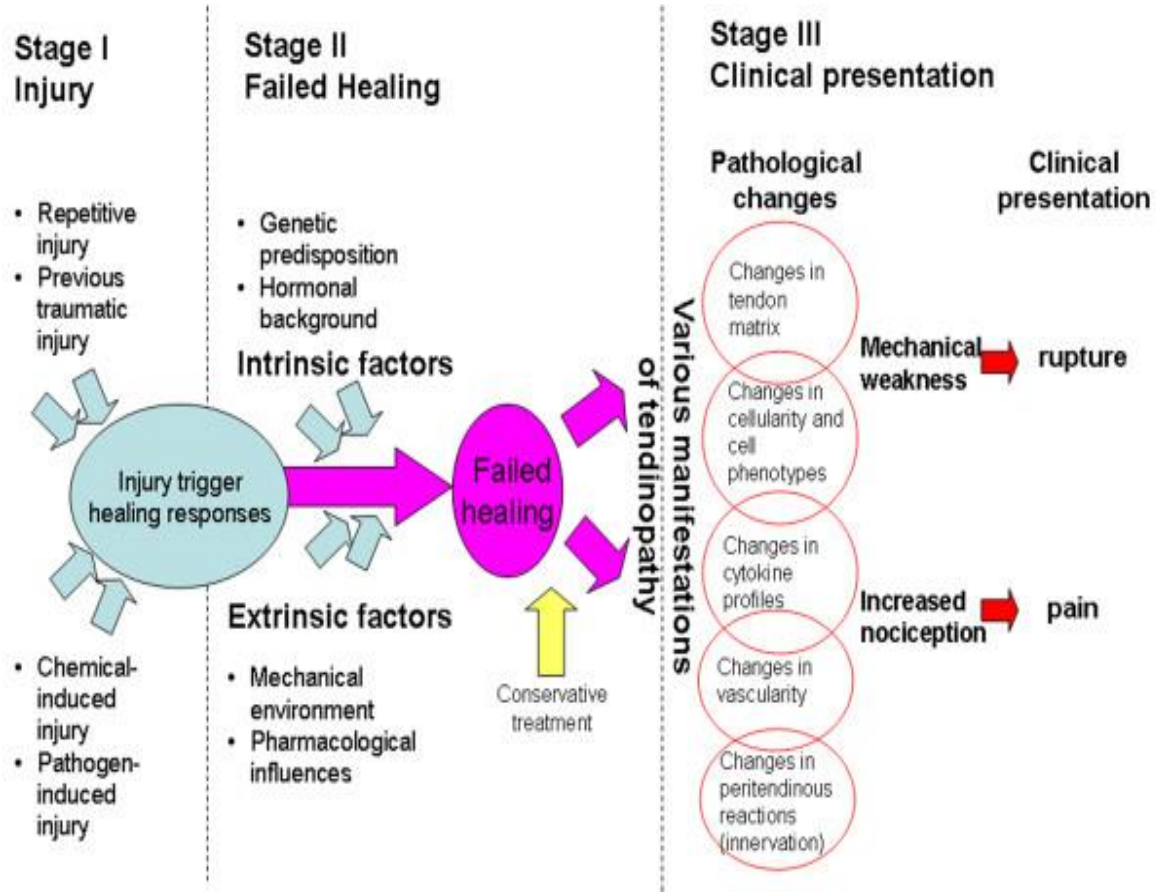

Figure 1-11. Failed healing theory. Fu et al. (2010). Reproduced with permission.

The **continuum model** consists of three stages of tendon pathology i) reactive ii) dysrepair and iii) degenerative (Cook and Purdam 2009) (Figure 1-12). During the reactive stage, and similar to the first stage of the ‘failed healing’ model, a normal healthy tendon is overloaded. In contrast however, the continuum model proposed that a non-inflammatory response follows. Tendon pathology is reversible at this stage if load is managed correctly. Without adequate load management, pathology can progress to dysrepair of the ECM and eventually irreversible degenerative tendon pathology and rupture (Cook and Purdam 2009).

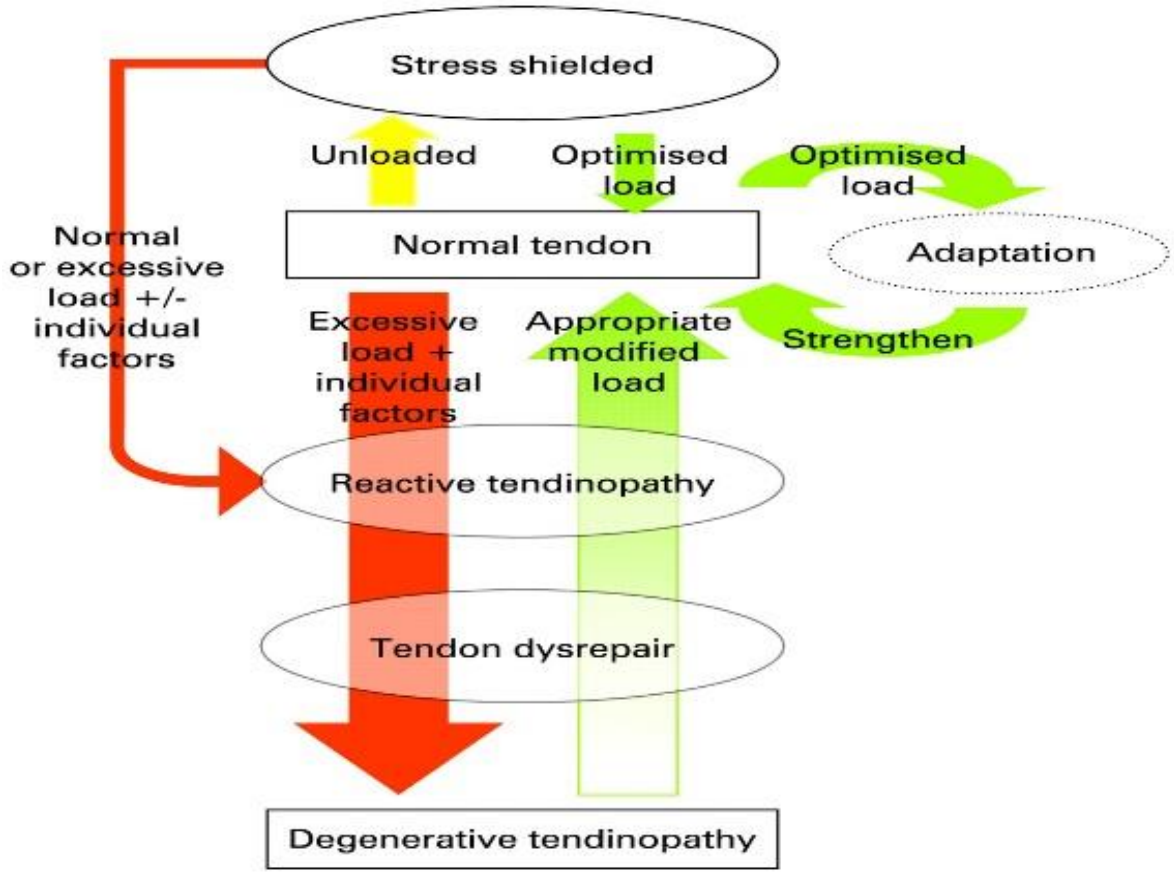

Figure 1-12. Continuum model of tendon pathology. Cook and Purdam (2009). Reproduced with permission.

The role of **inflammation** in the pathogenesis of tendinopathy remains highly debated. While it is well recognised that a classic inflammatory response occurs following tendon rupture, in tendinopathy it is still not fully understood (Millar et al. 2017). Traditional methods of detecting inflammation were based on the presence or absence of neutrophils or prostaglandins (Alfredson et al. 2000, Alfredson et al. 2001). Due to their absence, tendinopathy was believed to be primarily a degenerative condition (Khan et al. 2000). However, recent advances in modern molecular techniques and analysis support the contribution of inflammation in the development of tendinopathy (Dakin et al. 2015, Millar et al. 2010). Mechanical stress on a tendon cell releases numerous inflammatory mediators that can disrupt homeostasis and drive a tendon towards early tendinopathy (Millar et al. 2010) (Figure 1-13).

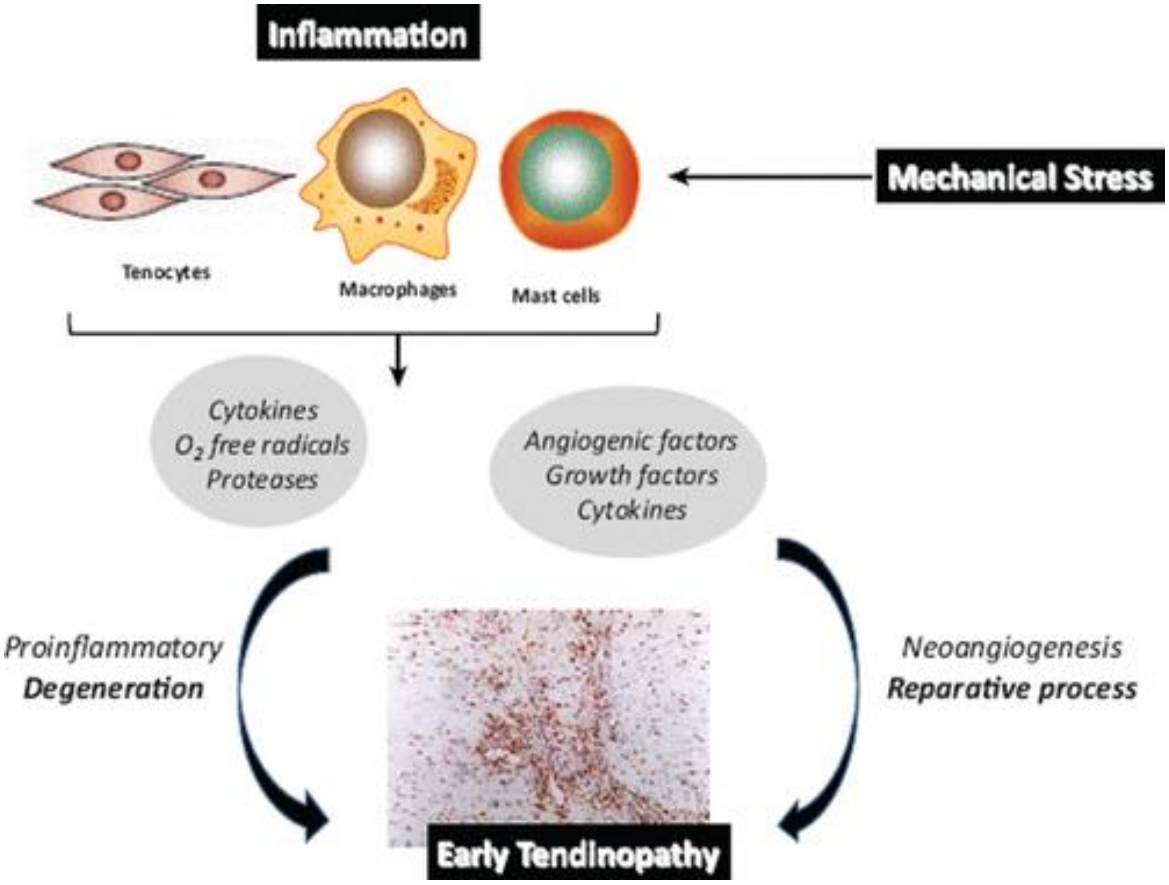

Figure 1-13. Early tendinopathy secondary to inflammation. Millar et al. (2010). Reproduced with permission.

Early tendinopathy contains an inflammatory cell infiltrate, including macrophages and mast cells, which play a crucial role in the inflammatory response (Dakin et al. 2015, Dean et al. 2016). Although the initial inflammatory response promotes healing, persistent inflammation may eventually lead to a dysregulated ECM (Crowe et al. 2019). Pro-inflammatory cytokines are involved in ECM turnover and appear to shift collagen production towards type III, which may be indicative of 'failed healing' (Millar et al. 2016). Inflammation is present in the early stages of tendinopathy but gradually subsides over time and degeneration takes over (Dakin et al. 2015, Millar et al. 2010). Evidence of ongoing inflammation has been identified in chronic Achilles and patellar tendinopathy (Dakin et al. 2018, Scott et al. 2008). Low-level inflammation in tendinopathy, either secondary to tissue overload or metabolic factors such as obesity and diabetes, may be a risk factor for a failed healing response and the persistence of symptoms (Chisari et al. 2019).

Although no agreed unifying model of tendon pathology currently exists, inflammation and degeneration are not mutually exclusive. Inflammation has a complex role in tendinopathy and contributes to all three stages of 'failed healing' (Fu et al. 2010). In contrast, both the

original and updated continuum models overlooked the contribution of inflammation (Cook and Purdam 2009, Cook et al. 2016), even in the early 'reactive stage' of the pathological process when inflammation has an important role in the initial cell response to tendon damage (Thorpe et al. 2015b). Loading and exercise are likely to be beneficial at all stages of tendinopathy due to the positive effect on tendon cells.

1.7 Loading in normal tendon

Tendons were previously considered inert tissue, however there is now clear evidence that both normal and pathological tendons are metabolically responsive to load (Magnusson et al. 2010). Mechanical load is required to maintain tendon homeostasis and can be either anabolic or catabolic (Thampatty and Wang 2018). Tenocytes are the primary cell type involved in homeostasis and regulate the synthesis and turnover of the ECM in response to loading (Langberg et al. 1999). Cellular changes occur almost immediately with an upregulation in collagen synthesis (Heinemeier et al. 2007, Miller et al. 2005), growth factors (Heinemeier et al. 2003, Proft et al. 2016), cytokines (Thorpe et al. 2015b) and vascular ingrowth (Proft et al. 2016). Adaptation of the ECM occurs between 6 and 24 hours after exercise and reduces over the next 72 hours (Heinemeier et al. 2007). Initially, an increase in type I collagen will improve tensile strength secondary to fibril reorganisation (Kjaer et al. 2005). Prolonged periods of loading (months to years) are required to increase cross-sectional area (CSA) as tendon hypertrophy is a slow process (Couppé et al. 2008, Magnusson et al. 2003, Wiesinger et al. 2015). This adaptation is mainly observed in athletic populations and would appear to be beneficial as the tendon will have a greater capacity to withstand loading prior to injury (Magnusson et al. 2003).

When a tendon is subjected to load (stress) it undergoes deformation (strain). Tendon stiffness relates to the resistance provided by the tissue to strain. Increased tendon stiffness occurs in response to strength training after 6-8 weeks due to changes in material properties and over longer periods due to the larger CSA (Wiesinger et al. 2015). Heavy loading at 90% of maximum voluntary contraction (MVC) leads to higher tendon strain than moderate loads (55% MVC) when volume is equal (Arampatzis et al. 2010). Furthermore, tendon strain is higher during longer duration contractions when compared to shorter duration contractions at a similar intensity (Arampatzis et al. 2007). Loading in a lengthened position is more effective than in a shortened position for tissue adaptation (McMahon et al. 2013). Since higher strain is required for tissue adaptation, longer

duration, higher intensity contractions in a lengthened position would be the optimal environment for tendon strain and adaptation to be achieved.

In relation to tissue adaptation, there appears to be age and gender differences. Tendon stiffness reduces with ageing and is associated with reduced force-capacity (Eriksen et al. 2018). However, strength training in older individuals can reverse this and significantly increase stiffness (Reeves et al. 2003). Females have a lower increase in collagen synthesis after exercise when compared to males (Miller et al. 2007). This may be secondary to hormonal changes, primarily a decrease in oestrogen levels (Kjaer et al. 2009). Older, post-menopausal females are more commonly affected by GTPS and this could be explained, at least in part, by a reduction in oestrogen and the effect of this change on tendon.

A muscle contraction can be classified as either isometric or isotonic. Isotonic contractions can be further divided into concentric (shortening) and eccentric (lengthening). During an isometric (static) muscle contraction, the muscle-tendon unit remains at a constant length (Oranchuk et al. 2019). For an isotonic contraction, typically a combination of muscle shortening and lengthening, the tension in the muscle remains constant despite a change in length (Oranchuk et al. 2019). Tendon is a passive structure that lengthens when load is applied and shortens when load is removed (Couppé et al. 2015). Therefore, while tendon cells are able to detect load, they are not able to differentiate between muscle contraction type. In the Achilles tendon, no difference in tendon force or deformation was observed when eccentric loading exercises were compared to concentric exercises (Rees et al. 2008). Furthermore, fluctuations in force were more apparent during eccentric loading and largely absent during concentric loading. The significance of this however is unclear and further studies are required. Overall, it would appear that loading magnitude rather than contraction type is most important for tissue adaptation (Bohm et al. 2015). Although performed in normal healthy tendon, these findings are frequently utilised in the design of exercise loading programmes for individuals with tendinopathy.

1.8 Loading in tendinopathy

1.8.1 Isotonic exercise programmes

Loading programmes are recommended as the first-line treatment for tendinopathy (Challoumas et al. 2019). Current loading paradigms have their origins in the work by Stanish et al. (1986), the first authors to describe the effectiveness of eccentric exercise in

the management of tendinopathy. In a prospective study of 200 patients with Achilles tendinopathy, a six-week programme of daily exercise consisting of 3 sets of 10 repetitions of concentric-eccentric exercise was investigated. Progressive loading was achieved by increasing contraction speed and adding weight when exercise could be performed without pain. Complete pain relief was reported in 44% of patients and marked improvement in a further 43% at long-term follow-up. Although introduced by Stanish and colleagues, eccentric exercise was popularised following the landmark study by Alfredson et al. (1998). Fifteen recreational athletes with mid-portion Achilles tendinopathy completed 12 weeks of isolated eccentric exercise. Two exercises, both 3 sets of 15 repetitions, were completed twice daily. Pain was allowed during exercise and progression was achieved by adding weight. After completion of the programme all 15 participants had returned to running. The positive results of this study encouraged a more active approach to tendinopathy management, focusing on rehabilitation and loading and shifting from passive strategies such as rest and NSAIDs which were previously advocated (Smart et al. 1980, Stanish et al. 1986). Eccentric exercise has also been shown to be superior to a 'wait and see' approach in Achilles tendinopathy (Rompe et al. 2007). Similar eccentric loading regimes, based on the original Alfredson protocol, have also demonstrated effectiveness in patellar tendinopathy (Jonsson et al. 2005). No studies to date have investigated isolated eccentric exercise for GTPS.

Eccentric exercise programmes remain the most widely utilised and researched management strategy for tendinopathy. However, there is limited evidence they are superior when directly compared to other loading regimes (Malliaras et al. 2013). Heavy slow resistance (HSR) exercise programmes have been compared to eccentric exercise in patellar and Achilles tendinopathy (Kongsgaard et al. 2009, Beyer et al. 2015). Three exercises, of 3-4 sets of 6 to 12 repetition maximum (RM) performed at a slow contraction speed (3-s concentric, 3-s eccentric) were completed three times per week. Despite the differences in loading parameters, programmes had a similar effect on pain and function in both studies after 12 weeks. In Achilles tendinopathy, Habets et al. (2021) recently compared the original Alfredson eccentric loading programme to the concentric-eccentric programme introduced by Silbernagel et al. (2007). Clinical symptoms improved in both groups and no differences were identified between programmes, providing further evidence that different loading programmes provide similar outcomes in tendinopathy.

The pain monitoring model, first used in patellofemoral pain by Thomeé et al. (1997) has been modified for Achilles tendinopathy (Figure 1-14) (Silbernagel et al. 2001, Silbernagel et al. 2015). Participants using the pain monitoring model were not required to rest from sport and activity and pain during a loading programme was also permitted. Importantly, use of the pain monitoring model did not negatively affect clinical outcome. Indeed, painful exercise has been reported to provide significant short-term benefits for pain and function when compared to pain free exercise in chronic musculoskeletal conditions (Smith et al. 2017).

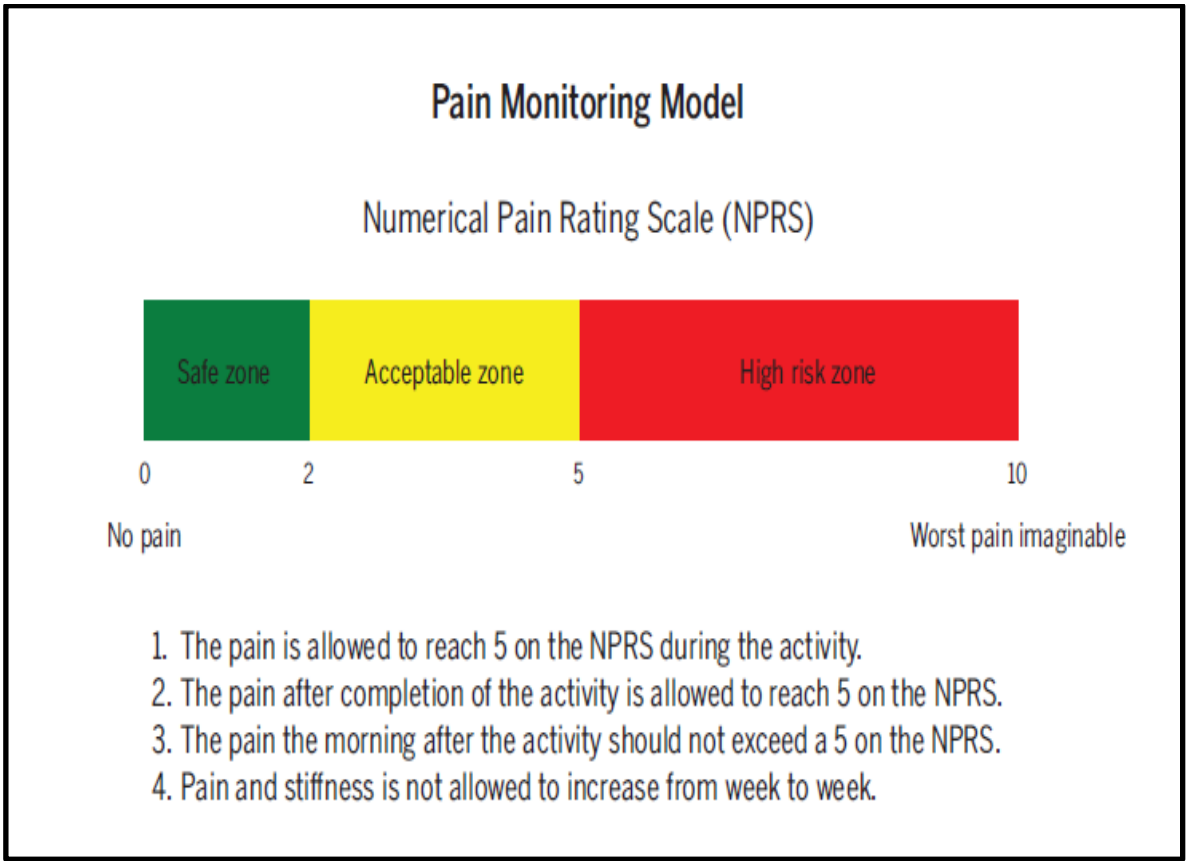

Figure 1-14. Pain monitoring model. Silbernagel et al. (2015). Reproduced with permission.

1.8.2 Isometric exercise programmes

There has been considerable interest in isometric exercise for tendinopathy following the randomised controlled trial by Rio et al. (2015). In this small study (n=6) of volleyball players with patellar tendinopathy, improvements in pain were reported during a single leg squat on a visual analogue scale (VAS) immediately following a single session of either isometric exercise or isotonic exercise. Both groups achieved a pain reduction by the minimally clinically important difference (MCID) of at least two points on the VAS but the improvement in pain was greater following isometric exercise (mean=6.8 points) compared

to isotonic exercise (mean=2.5 points). A further study measured the immediate effect of isometric and isotonic exercise after each session for four weeks in patellar tendinopathy (Rio et al. 2017). Pain and function improved in both groups, but isometric exercise resulted in greater pain relief. The total amount of time the muscle-tendon unit was under load or time under tension (TUT) was identical for both groups in both studies. A further RCT for patellar tendinopathy, utilising an identical loading protocol to Rio et al. (2015) but with a larger population (n=20), reported a smaller reduction in pain following isometric exercise (mean=0.8 points) and isotonic exercise (mean=1.1 points) (Holden et al. 2020). Pearson et al. (2020) compared long-duration (6 x 40s), and short-duration isometric holds (24 x 10s) for patellar tendinopathy. A similar pain reduction (mean =1.7 points) was observed in both groups. In both studies neither group achieved the MCID following isometric exercise, which contrasts to the findings if Rio et al. (2015) The immediate response to isometric exercise has also been investigated in other tendinopathies with variable results. For Achilles tendinopathy, 45s isometric holds resulted in an immediate reduction in pain of one point in some participants whereas others reported an immediate increase in pain (O'Neill et al. 2019). In lateral elbow tendinopathy, the response to isometric exercise was also variable with an immediate increase in pain intensity reported following isometric exercise above an individual's pain free threshold (Coombes et al. 2016). To date, no studies have examined the immediate effect of isometric or isotonic exercise for pain relief in GTPS and this will not be specifically investigated in this thesis.

One RCT has compared the short-term effect of isometric exercise to isotonic exercise in patellar tendinopathy (van Ark et al. 2016). In jumping athletes with patellar tendinopathy, four sessions per week of isometric exercise (5 x 45s holds) were compared to isotonic exercise (4 x 8 repetitions). After four weeks both programmes were similarly effective in reducing pain and improving function when TUT was identical. The results of this study raise the possibility that isometric exercise could be used, not only for immediate pain relief, but also as part of a rehabilitation programme to improve function and aid recovery for individuals with tendinopathy. No previous clinical trials have compared the short-term effect of isometric and isotonic exercise in GTPS.

When directly compared, different loading programmes appear to produce similar outcomes in tendinopathy. Isometric exercise has been reported to relieve tendon pain and was recommended for use at the start of a rehabilitation programme (Cardoso et al. 2019, Malliaras et al. 2015). However, this recommendation appears to be based solely on earlier

patellar tendinopathy studies. Due to the magnitude of pain reduction following isometric exercise, the study by Rio et al. (2015) made a significant clinical and research impact. However, subsequent studies have reported smaller reductions in pain and the immediate pain response following isometric exercise appears to be highly variable both within and across different tendinopathy populations (Holden et al. 2020, O'Neill et al. 2019). It is unclear whether isometric exercise programmes are more effective at reducing pain and improving function when directly compared to isotonic exercise or any other treatment for tendinopathy, including GTPS. It is also unknown whether the short-term benefits of both isometric exercise and isotonic exercise observed in one patellar tendinopathy study would be replicated in GTPS. Chapters 2 and 3 of this thesis will attempt to answer these questions.

1.9 Pain in tendinopathy

1.9.1 Pain mechanisms

Many questions remain about the identity of the nociceptive driver(s) in tendinopathy and gluteal tendinopathy. The presence of neovascularisation has been well established in various tendinopathies, a process associated with the ingrowth of abnormal sensory nerve endings and blood vessels into the tendon. (Wheeler 20220) In addition, to these 'neovessels', higher levels of several neurochemicals directly associated with pain including glutamate and substance P have been detected (Alfredson et al. 1999, Merkel et al. 2021). A recent review however by Ackermann et al. (2022) highlighted that there is no correlation between tendon degeneration, collagen disruption, neovascularisation and chronic tendon pain. Although there are numerous structural and cellular changes associated with tendinopathy, the mechanism by which pain is produced remains unclear.

1.9.2 Pain relief due to loading

The mechanism by which loading relieves pain in tendinopathy is not fully understood (Kjaer et al. 2009). Mechanotransduction describes the process through which cells sense mechanical force and translate it into biological responses (Gracey et al. 2020). Importantly, mechanical loading affects not only the tendon but also the contracting muscle and central nervous system (CNS). Several hypotheses have been proposed to explain how loading and exercise may reduce pain in tendinopathy, including an

improvement in collagen tissue structure, changes within the CNS and a reduction in systemic inflammation.

A pathological tendon has reduced load-bearing capacity (Scott et al. 2015a). Loading programmes targeting the muscle-tendon unit are intended to improve function and reduce pain (Cook and Docking 2015). Currently, regenerative treatments such as platelet-rich plasma (PRP) are reported to improve tendon structure and 'heal' the pathological area of tendon (Krogh et al. 2016). However, there is no strong evidence that this can be achieved with loading. Docking and Cook (2016) used the analogy of a doughnut to describe a pathological tendon. The doughnut represents the aligned collagen fibrils in the normal portion of tendon which surround the 'hole', the disorganised collagen in the degenerative portion (Figure 1-15). Although normalising tendon structure may not be possible with loading, it also may not be required for pain relief. Improvements in pain following eccentric exercise could not be attributed to changes in tendon structure as visualised on ultrasound tissue characterisation (UTC), MRI or USS (Drew et al. 2014). Pain reduction was reported in the absence of structural change after four weeks of either isometric and isotonic exercise in patellar tendinopathy (van Ark et al. 2018). Conversely, increased collagen synthesis and improvement in collagen fibril morphology have been reported in patellar tendinopathy following 12 weeks of HSR loading (Kongsgaard et al. 2009, Kongsgaard et al. 2010). Tendon biopsies were visualised using an electron microscope and production of new collagen fibrils was observed (Kongsgaard et al. 2010). This was a small study (n=8), so caution is advised when interpreting the results. However, it raises the possibility that UTC, MRI and USS are not sensitive enough to detect changes in collagen fibril structure that occur in response to loading. In some instances, pain relief in tendinopathy may be associated with a positive change in collagen structure.

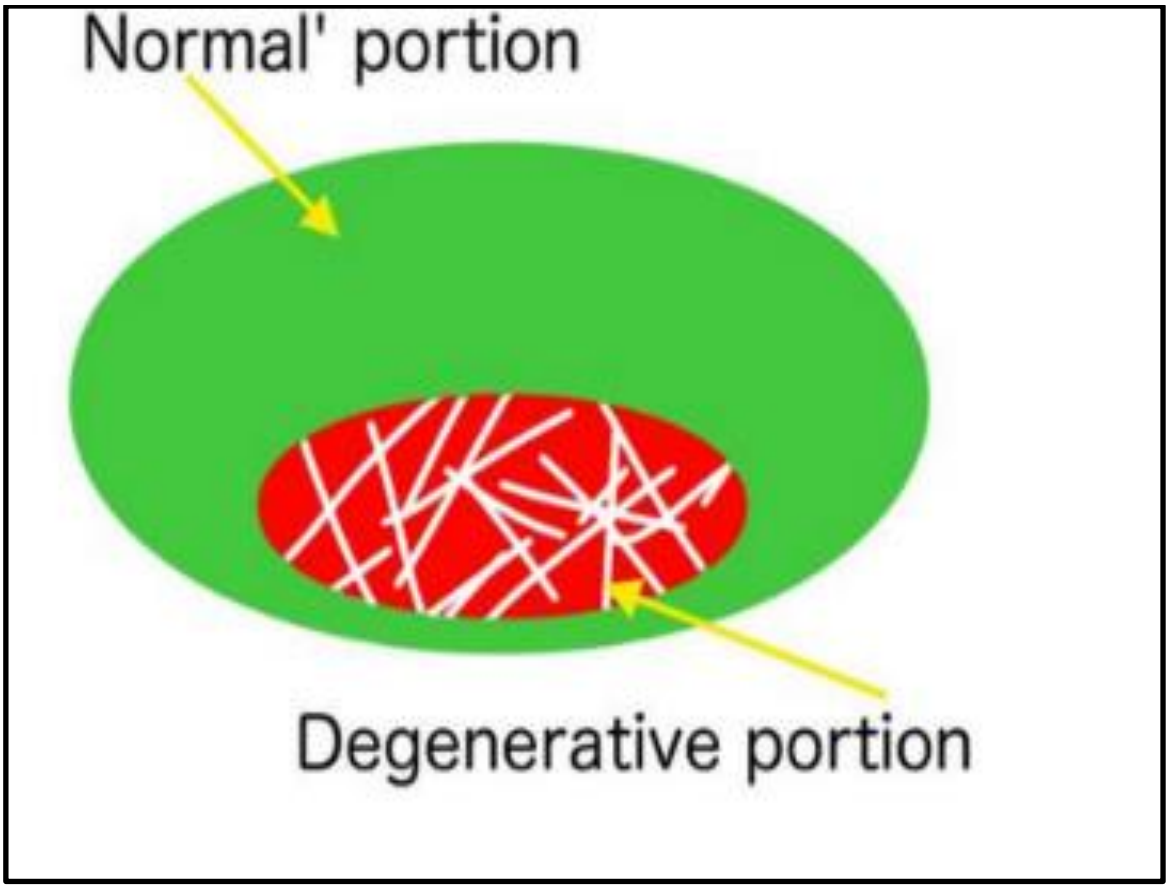

Figure 1-15. Normal and degenerative portion of tendon. Cook et al. (2016). Reproduced with permission.

Exercise-induced hypoalgesia (EIH) occurs in response to exercise in pain free individuals (Naugle et al. 2012). The mechanisms are not fully understood but are thought to occur via the CNS and descending pain inhibition (Koltyn and Umeda et al. 2007). EIH has been demonstrated in asymptomatic populations in response to both aerobic and resistance exercise, including isometric exercise (Bonello et al. 2021). In contrast, isometric exercise has not consistently induced EIH in people with chronic musculoskeletal pain (Bonello et al. 2021, Rice et al. 2019, Wewege et al. 2021). Isometric exercise produces hyperalgesia in individuals with widespread pain, secondary to a deficiency of central inhibition (Naugle et al. 2012, Staud et al. 2005). If pain relief in tendinopathy is related to the CNS and the descending inhibition associated with exercise, the act of engaging in exercise is perhaps more important than the exercise type. This would be supported by studies in patellar tendinopathy that reported similar pain reduction regardless of muscle contraction type (Holden et al. 2020, van Ark et al. 2016). Impaired or complete absence of EIH in some individuals with tendinopathy may partly explain the variable response to loading observed both within and across different tendinopathy populations.

Exercise has systemic anti-inflammatory effects which can positively influence tendon healing by altering the local inflammatory environment (Chisari et al. 2019). An increased number of pro-inflammatory cytokines have been identified in tendinopathy (Millar 2017). However, regular physical activity and exercise can shift the balance towards an anti-inflammatory state in chronic musculoskeletal pain (Sluka et al. 2018). Management strategies that target low-level inflammation such as weight loss and aerobic exercise may have a role in tendinopathy management in addition to, or instead of, loading programmes. This would have plausibility in tendinopathy populations who have a metabolic contribution, especially obesity. Interestingly, the greatest systemic anti-inflammatory benefit was achieved when aerobic exercise was combined with resistance exercise for asymptomatic individuals with diabetes (Nimmo et al. 2013). It is currently unknown whether loading programmes have a similar effect in tendinopathy.

Overall, loading reduces pain in some individuals with tendinopathy and GTPS, but the mechanism for pain relief remains unclear. Tendinopathy is a complex musculoskeletal condition and it is possible that the mechanism for pain relief is variable between individuals. Sedentary individuals with a metabolic contribution may achieve a reduction in pain by reducing low-level systemic inflammation. In active populations with overuse tendinopathy, loading may help via the CNS or secondary to positive changes in the structure of tendon.

1.10 Management of GTPS

Historically, management strategies for GTPS have primarily focused on reducing pain and inflammation associated with trochanteric bursitis. Despite the absence of inflammation, the trochanteric bursa can be a source of pain (Fearon et al. 2014b). Corticosteroid injection (CSI) delivered into the most painful area around the greater trochanter was the mainstay of treatment for many years, often providing significant pain relief (Gordon 1961, Sayegh et al. 2004, Schapira et al. 1986, Shbeeb et al. 1996). However, the analgesic effect was often short-term with the benefits of CSI reducing over time (Bolton et al. 2018, Shbeeb et al. 1996). When compared to analgesics as required, or placebo injection, improvements in pain were not superior at long-term follow-up following CSI (Brinks et al. 2011, Nissen et al. 2019). However, one study did report that CSI resulted in a 2.5-fold increased chance of recovery after five years when compared to no injection (Lievense et al. 2005). The associated risks of CSI on tendon are well documented. Corticosteroid

negatively affects the mechanical properties of tendon with a reduction in collagen synthesis and increased collagen disorganisation (Dean et al. 2014). This may lead to a tendon that is 'weaker' and more susceptible to injury and could explain the high recurrence of symptoms often observed following CSI (Coombes et al. 2010). Exercise programmes targeting the muscle-tendon unit are intended to improve function and reduce pain (Cook and Docking 2015). This should result in a 'stronger' tendon that is able to tolerate greater loads prior to injury.

Four clinical trials have investigated exercise for GTPS (Cowan et al. 2022, Ganderton et al. 2018, Mellor et al. 2018, Rompe et al. 2009). A 12-week programme of hip stretching and strengthening exercises was compared to shockwave therapy and CSI (Rompe et al. 2009). Participants rated their recovery on a six-point Likert scale, with 'completely recovered' or 'much improved' rated as treatment success. After one month, 7% of participants in the exercise group had improved, compared to 13% for shockwave and 75% for CSI. At 4-month follow up success rates in the exercise group were 41% compared to 68% for shockwave and 51% for CSI. After 15 months exercise was superior to both shockwave and CSI with 80% reporting improvement compared to 74% for shockwave and 48% for CSI. This study provided further evidence that the short-term benefits of CSI in GTPS reduce over time. The benefits of a 12-week exercise programme should be apparent after four months but in this trial almost 60% of participants had not improved. A number of factors could explain these results. Firstly, the inclusion of ITB stretching exercises encouraged sustained periods of hip adduction and compressive loading. Furthermore, advice on load management was not provided and the strengthening exercises were not progressive and not specific to the hip abductor muscles. It is noteworthy, however, that this study was designed prior to the study by Cook and Purdam (2012), which highlighted the importance of minimising compressive loading in tendinopathy.

Exercise in post-menopausal females with GTPS has been investigated in two studies. The 'GLoBE' study compared 12 weeks of lower limb exercise to sham exercise (Ganderton et al. 2018). The four-stage programme targeted the gluteal, quadriceps and calf muscles. The sham programme included lower limb exercises all deemed unlikely to specifically load the gluteal tendons. Education on load management was provided to both groups with advice on minimising postures and activities that could increase compressive loading. Disability was measured using the Victoria Institute of Sports Assessment-gluteal (VISA-G) and improvements were detected in both groups. However, no between-group

difference was observed with approximately 50% of participants not improving at one-year follow up. After 12 weeks only 50% of participants in the GLoBE treatment group were able to progress to stage four of the programme. In comparison to males, females have a lower rate of collagen synthesis and tendon adaptation following exercise, which may be secondary to reduced oestrogen levels (Magnusson et al. 2010, Oliva et al 2016). Therefore, loading programmes of longer than 12 weeks duration may be required for improvements to be observed in some post-menopausal females. Cowan et al. (2022) compared the GLoBE exercise protocol or sham exercise combined with either menopausal hormone therapy (MHT) cream or placebo cream. VISA-G scores improved in all four groups, but superior outcomes were observed in women with a body mass index (BMI) < 25 who were administered MHT cream in conjunction with either exercise protocol. The authors speculated that reduced absorption of the MHT cream in overweight or obese individuals may be secondary to excess local adipose tissue. Perhaps the beneficial effects of HRT are not enough to 'offset' the low-grade inflammatory contribution which may contribute to pain in overweight or obese individuals (Abate 2014). The results of this study imply that increased levels of oestrogen may improve pain when combined with exercise in post-menopausal females with GTPS.

In the LEAP trial, 204 participants with gluteal tendinopathy were randomised into three groups (Mellor et al. 2018). Eight weeks of progressive exercise targeting the hip abductors was combined with education and compared to either a single ultrasound guided CSI or a 'wait and see' control group. The pain monitoring model was used to guide exercise progression. After four weeks, similar results were observed for both exercise plus education and CSI with 58% of participants reporting an improvement in a global rating of change (GROC) scale. After eight weeks, exercise plus education (77%) was more effective than both CSI (58%) and a 'wait and see' approach (29%). At one-year follow-up improvement was maintained for both exercise plus education (78%) and CSI (57%). This contrasts with previous studies where the short-term benefits of CSI reduce over time (Bolton et al. 2018, Shbeeb et al. 1996). Improved clinical outcomes were reported after eight weeks in the exercise plus education group and associated with an increase in hip abductor muscle strength. Interestingly, similar improvements in hip abductor muscle strength were also observed in the CSI group. This infers that another mechanism, aside from muscle strength changes, could be responsible for symptom improvement in GTPS, at least in the short-term.

In summary, exercise appears to be essential in the management of GTPS. Programmes which specifically target the hip abductor muscles are currently the most commonly prescribed treatment for this condition. In the LEAP trial, exercise combined with education on load management reported higher success rates at long-term follow-up than all other clinical trials, which investigated exercise. However, further studies are required as 20 - 50% of individuals do not improve with current exercise regimes and continue to experience chronic pain and disability. For this reason, investigating alternative loading programmes such as isometric exercise for GTPS appears justified and will be investigated in Chapter 2.

1.11 Clinical characteristics in tendinopathy

Current loading programmes are not a panacea for GTPS with effectiveness of 50 - 80% (Ganderton et al. 2018, Mellor et al. 2018). The reason for poor response in some individuals remains unclear but may be associated with the presence of certain clinical characteristics (McAuliffe et al. 2021). The importance of measuring and reporting clinical characteristics including health co-morbidities and co-existing physical symptoms in tendinopathy research has been recognised (Rio et al. 2020). Psychological factors should also be considered and may contribute to a suboptimal outcome in tendinopathy (Mallows et al. 2017). Health co-morbidities, co-existing physical symptoms and psychological characteristics are however not routinely recorded in tendinopathy research (McAuliffe et al. 2021).

Patients with GTPS attending NHS physiotherapy clinics frequently have multiple health co-morbidities (Stephens et al. 2019a). Individuals with GTPS are typically overweight (BMI 25-30) or obese (BMI > 30) (Minetto et al. 2020, Plinsinga et al. 2020). An association between BMI and GTPS has also been established (Plinsinga et al. 2019). Obesity is characterised by chronic low-grade inflammation and associated with an increased risk of developing tendinopathy (Abate 2014, Macchi et al. 2020). Tendon health can also be affected by elevated blood glucose, leading to an alteration in collagen structure and loss of tissue viscoelasticity (Oliva et al. 2016, Scott et. al 2015b). Ranger et al. (2016) reported a higher prevalence of tendinopathy in individuals with diabetes and an association has been observed between diabetes and GTPS (Albers et al. 2016). Hormonal changes which occur during the menopause can affect the mechanical properties of tendon (Ganderton et al. 2016). Specifically, decreasing oestrogen levels may lead to a reduction

in collagen tensile strength and increase the risk of tendon injury (Frizziero et al. 2014, Hansen et al. 2009). Metabolic factors may reduce tissue capacity and increase the likelihood of developing pain, even in the absence of a clear history of overuse.

Single site pain is uncommon in chronic musculoskeletal disorders (Carnes et al. 2007). Individuals with GTPS often report co-existing low back and/or hip joint pain (Gordon 1961, Collée et al.1990). An association has also been identified with knee osteoarthritis (Segal et al. 2007). The total number of pain sites reported by individuals with tendinopathy could be a prognostic indicator as multi-site pain has been associated with poorer outcome in other musculoskeletal conditions (Hott et al. 2020, Kamaleri et al. 2008, Mallen et al. 2007). Pain localised to the site of the involved tendon is a common prerequisite for inclusion in tendinopathy clinical trials. However, additional pain sites are often not reported and participants with multi-site pain are frequently excluded from GTPS research studies. In one study, individuals who reported either bilateral GTPS or lower limb osteoarthritis were not eligible for inclusion (Rompe et al. 2009). Moreover, the total number of pain sites has not been specifically measured in all other trials that have investigated the effectiveness of exercise in GTPS (Cowan et al. 2022, Ganderton et al. 2018, Mellor et al. 2018). Additional pain sites could partly explain the poor response observed in some participants following loading programmes. Measuring and reporting the total number of pain sites in a GTPS population would therefore be of value and will be outlined in Chapter 4 of this thesis.

Psychological factors have been identified as one of the core domains for tendinopathy (Vicenzino et al. 2020). However, they have been poorly reported in tendon research and measured in only 4% of Achilles tendinopathy studies (Silbernagel et al. 2022). Kinesiophobia (fear of movement and reinjury), depression and anxiety have been associated with tendinopathy and may have a role in the persistence of musculoskeletal pain (Mallows et al. 2017, Martinez-Calderon et al. 2020). In the study by Plinsinga et al. (2020), 57% of individuals exhibited kinesiophobia, 25% were classified as having anxiety and 5% with depression. Mest et al. (2020) identified kinesiophobia in more than 50% of patients attending a physiotherapy clinic with gluteal tendinopathy. Kinesiophobia may affect adherence to a loading programme and contributed to a suboptimal outcome in Achilles tendinopathy (Silbernagel et al. 2011). Anxiety and depression were associated with higher levels of disability in gluteal tendinopathy (Plinsinga et al. 2018). To date, only a small number of studies have measured kinesiophobia, anxiety and depression in GTPS.

Establishing the prevalence of these psychological factors will also be investigated in Chapter 4.

Tendinopathy is a complex musculoskeletal condition with variable clinical presentations. Dividing individuals into subgroups based on specific clinical characteristics has recently been explored in Achilles tendinopathy. Hanlon et al. (2021) identified three distinct subgroups; i) younger/activity related, ii) psychosocial and iii) older with obesity. No previous studies have attempted to define subgroups in GTPS but a number of unidentified subgroups may exist. Identifying the prevalence of specific clinical characteristics within GTPS populations may allow subgroups to be identified.

The prevalence of lower limb tendinopathy increases with age, with older individuals more frequently affected than younger individuals (Albers et al. 2016, Riel et al. 2019). The majority of data from clinical and research settings has been gathered from older individuals with GTPS. Patients attending NHS physiotherapy clinics are typically older than 40 years (Stephens et al. 2019a). Participants in the LEAP trial were only eligible for inclusion if aged 35-70 years (Mellor et al. 2018). Further studies only included post-menopausal females, a population that is almost exclusively middle-aged and older (Cowan et. al 2022, Ganderton et al. 2018). However younger adults, particularly running athletes, are also reported to develop this condition (Anderson et al. 2001). Currently, clinical data are lacking for younger individuals (< 40 years) when compared to older individuals ($\geq$ 40 years) in GTPS. The prevalence of specific clinical characteristics, including health co-morbidities, co-existing physical symptoms and psychological factors in younger and older age groups is currently unknown.

Tendinopathy is not solely related to activity with less than 30% of people with lower limb tendinopathy in a primary care population participating in sport (Albers et al. 2016). Active individuals typically develop tendinopathy secondary to overuse (Millar et al. 2021). However, a metabolic contribution is believed to play an important role in the development of symptoms in sedentary individuals (Tilley et al. 2015) (Figure 1-16). In GTPS, active and sedentary populations are known to be affected (Blank et al. 2012, Plinsinga et al. 2018, Plinsinga et al. 2020, Rompe et al. 2009). Interestingly, inactive people with Achilles tendinopathy do not respond as favourably to eccentric exercise when compared to athletic counterparts (Sayana and Maffuli 2007). This raises the possibility that a sedentary lifestyle may be a confounder to successful treatment outcome in tendinopathy. The prevalence of health co-morbidities, co-existing physical symptoms and psychological

factors is also unknown in active and sedentary populations with GTPS. It is plausible that subgroups based on i) age group and ii) physical activity level may exist for GTPS. A comparison between younger (< 40 years) and older (≥ 40 years) subgroups and sedentary and active subgroups has yet to undertaken and represents a gap in the current literature worthy of further investigation.

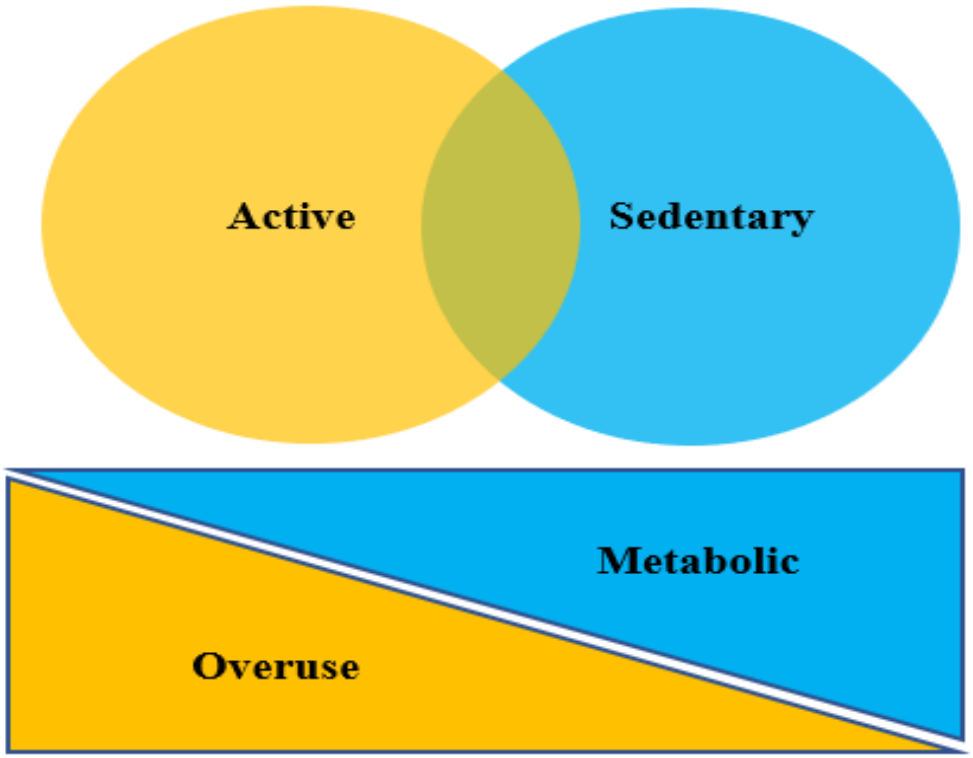

Figure 1-16. Proposed contribution to development of symptoms in active and sedentary populations

1.12 Aims of thesis

The introduction chapter provided an overview of the current understanding of greater trochanteric pain syndrome including gluteal tendon pathology, loading programmes and the clinical characteristics which may be present in individuals with this condition. The overarching aim of this thesis was to explore the clinical presentation of individuals with GTPS and to investigate the effectiveness of isometric exercise in the management of tendinopathy, with a focus on GTPS. The remainder of this thesis will discuss the findings of three studies.

In **Chapter 2** the primary aim of this randomised controlled pilot study was to determine whether a 12-week exercise programme of progressive isometric or progressive isotonic exercise was more effective for improving function in GTPS. The secondary aim was to determine whether either exercise programme was more effective in reducing pain intensity, pain catastrophising, improving quality of life and physical activity. Outcome measures were assessed after 4 and 12 weeks. This was the first randomised controlled trial to compare isometric and isotonic exercise for GTPS.

In **Chapter 3** a systematic review of randomised clinical trials was conducted, using meta-analysis where appropriate. The aim of this systematic review was to evaluate the effectiveness of isometric exercise compared with other treatment strategies or no treatment in the management of all tendinopathies, including GTPS. Pain was the primary outcome measure. Functional disability, range of movement (ROM), muscle strength, quality of life, satisfaction, structural integrity and cortical inhibition were secondary outcome measures.

In **Chapter 4** the results of an on-line survey completed by 261 individuals with GTPS were analysed and discussed. The first aim of this study was to compare the clinical characteristics, including health co-morbidities, co-existing physical symptoms (number of pain sites, sleep disturbance, pain intensity during activity), disability and psychological factors (kinesiophobia, anxiety and depression) between i) younger individuals (< 40 years) and older individuals (≥ 40 years) and ii) sedentary and active individuals with GTPS. The second aim was to identify if any clinical characteristics were associated with and able to predict disability, kinesiophobia, anxiety or depression in GTPS.

Chapter 2

Isometric versus isotonic exercise for greater trochanteric pain syndrome: a randomised controlled pilot study

Content of this chapter has been published in the following manuscript:

Clifford C, Paul L, Syme G, Millar NL. Isometric versus isotonic exercise for greater trochanteric pain syndrome: a randomised controlled pilot study. BMJ Open Sport Exerc Med. 2019 Sep 21;5(1):e000558.

2.1 Aims and introduction

This chapter presents the first study in the thesis, a randomised controlled pilot study comparing 12 weeks of isometric exercise and isotonic exercise for greater trochanteric pain syndrome.

Greater trochanteric pain syndrome encompasses a number of conditions characterised by pain in the region of the greater trochanter (Williams and Cohen 2009). The pathology primarily involves the tendons of GMed and GMin and less frequently the trochanteric bursa (Connell et al. 2003, Ruta et al. 2015). This condition is more prevalent in females with a female:male ratio of approximately 4:1 (Lievense et al. 2005, Riel et al. 2019). Chronic symptoms are common with 36% of individuals continuing to experience pain after one year and 29% after five years following symptom onset (Lievense et al. 2005). Pain associated with GTPS can affect an individual's ability to perform basic activities of daily living while also having a negative impact on sleep, work and participation in sport (Stephens et al. 2019a).

Despite its prevalence and impact on quality of life, only a small number of studies have investigated the effectiveness of exercise in the management of GTPS (Cowan et al. 2022, Ganderton et al. 2018, Mellor et al. 2018, Rompe et al. 2009). Isometric exercise programmes gained popularity in the management of tendinopathy following the randomised controlled trial by Rio et al. (2015). Subsequently, four weeks of isometric exercise and isotonic exercise were compared in patella tendinopathy (van Ark et al. 2016). Time under tension was identical in both groups. Both programmes were equally effective in reducing pain and improving function with no significant difference between groups. The results of this study imply that muscle contraction type may not be the critical factor in clinical improvement in tendinopathy.

Exercise programmes are normally the first-line treatment for tendinopathy and at least 12 weeks of progressive muscle-tendon loading is recommended (Challoumas et. al 2019). Daily exercise for 12 weeks has resulted in positive clinical outcomes in lower limb tendinopathy (Alfredson et al. 1998, Bahr et al. 2006, Silbernagel et al. 2007). In more recent studies, improvements have also been observed after only four weeks of exercise (Mellor et al. 2018, van Ark et al. 2016). Thus far, isometric and isotonic exercise programmes have not been directly compared for GTPS and it is unclear whether the

improvements observed after four weeks in a single study for patellar tendinopathy would be replicated in GTPS. It is also unclear whether 12 weeks of progressive isometric loading will be effective in this population. This was the first randomised controlled trial to compare isometric exercise and isotonic exercise for individuals with GTPS and the only study which has investigated the effectiveness of progressive isometric exercise of longer than four weeks for any tendinopathy.

The primary aim of this randomised controlled pilot study was to determine whether a 12-week exercise programme of progressive isometric or progressive isotonic exercise was more effective for improving function in GTPS. The secondary aim was to determine whether either exercise programme was more effective in reducing pain intensity, pain catastrophising, improving quality of life and physical activity.

2.2 Methods

2.2.1 Ethics

Ethical approval for this study was granted by the West of Scotland Research Ethics Service (REC reference: 17/WS/0110) (Appendix 1). The Consolidated Standards of Reporting Trials 2010 checklist was used to report the study (Eldridge et al. 2010).The trial was prospectively registered at www.clinicaltrials.gov/ct2/show/NCT03145233.

2.2.2 Participants

Thirty participants were recruited from musculoskeletal physiotherapy waiting lists in NHS Greater Glasgow and Clyde between August 2017 and March 2018 (Figure 2-1). As this was a pilot study no formal sample size calculation was performed. The sample size of 30 was decided pragmatically based on the number of patients referred to physiotherapy each month with GTPS.

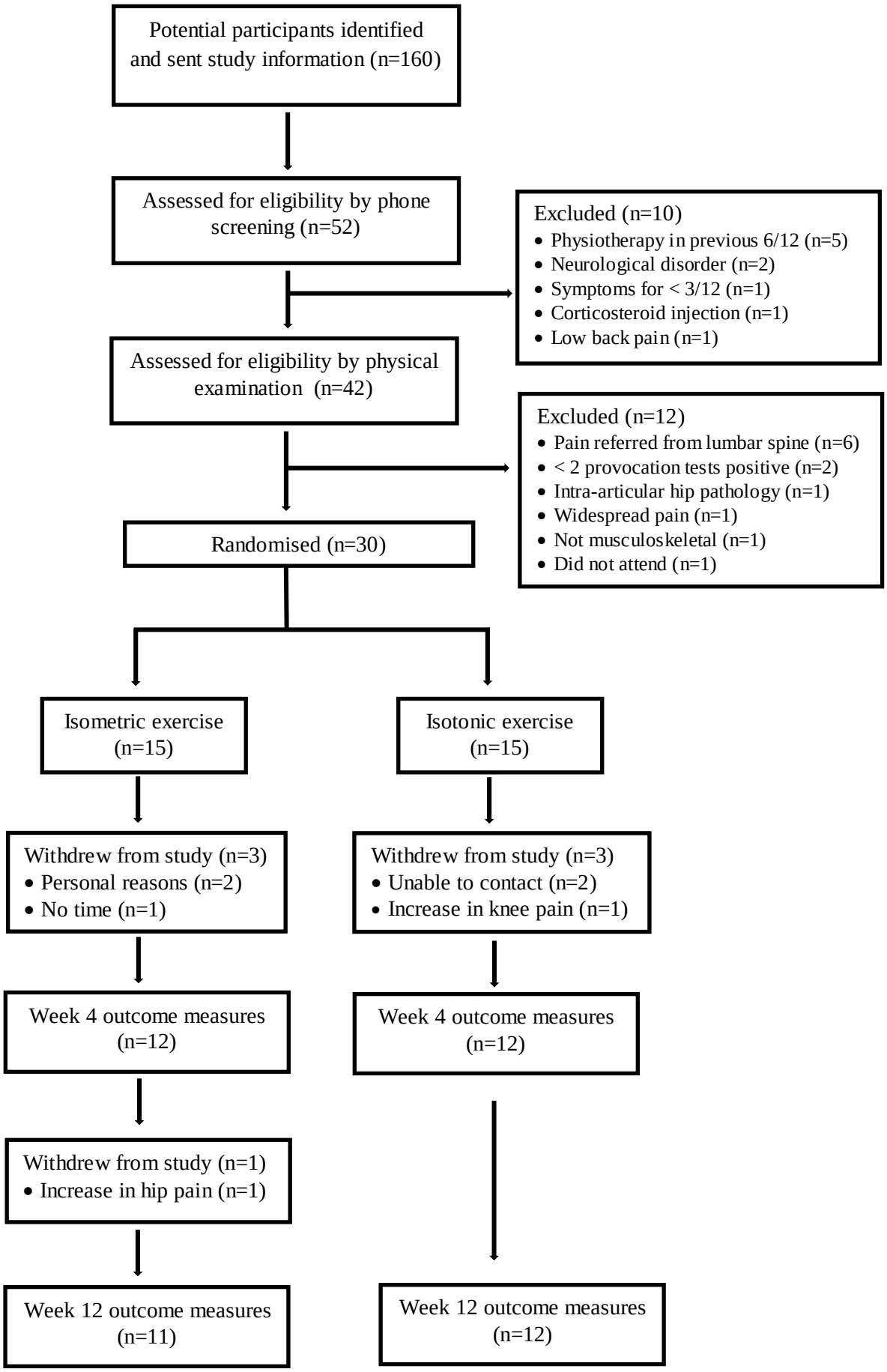

Figure 2-1. Flowchart of participants through study

Patients referred to physiotherapy with lateral hip pain or a provisional diagnosis of gluteal tendinopathy, GTPS or trochanteric bursitis were identified. An invitation letter was posted to each potential study participant (Appendix 2). Written information about the purpose of the study was enclosed (Appendix 3). Individuals interested in study participation were asked to contact the PhD student (CC) directly. Telephone screening was performed and a series of questions were asked to determine suitability for inclusion into the study (Appendix 4). If GTPS was suspected, the individual attended for a physical examination to confirm a clinical diagnosis of GTPS and to exclude other possible causes of lateral hip pain (Appendix 5). For inclusion in the study each participant required to have lateral hip pain on direct palpation around the greater trochanter with pain also reproduced in at least one other of five pain provocation tests (Grimaldi et al. 2017). Each of these six tests are capable of reproducing lateral hip pain through tensile and/or compressive loading of the gluteal tendons and/or trochanteric bursa (Figure 2-2). If indicated, a pelvis x-ray was requested to exclude possible hip joint pathology. Individuals that satisfied the eligibility criteria and agreed to participate in the study were asked to give written informed consent (Appendix 6). A letter was sent to each participant's general practitioner informing them of study inclusion (Appendix 7). This study was not advertised to the general public and all participants were actively seeking treatment for their condition. The full eligibility criteria are displayed in Table 2-1.

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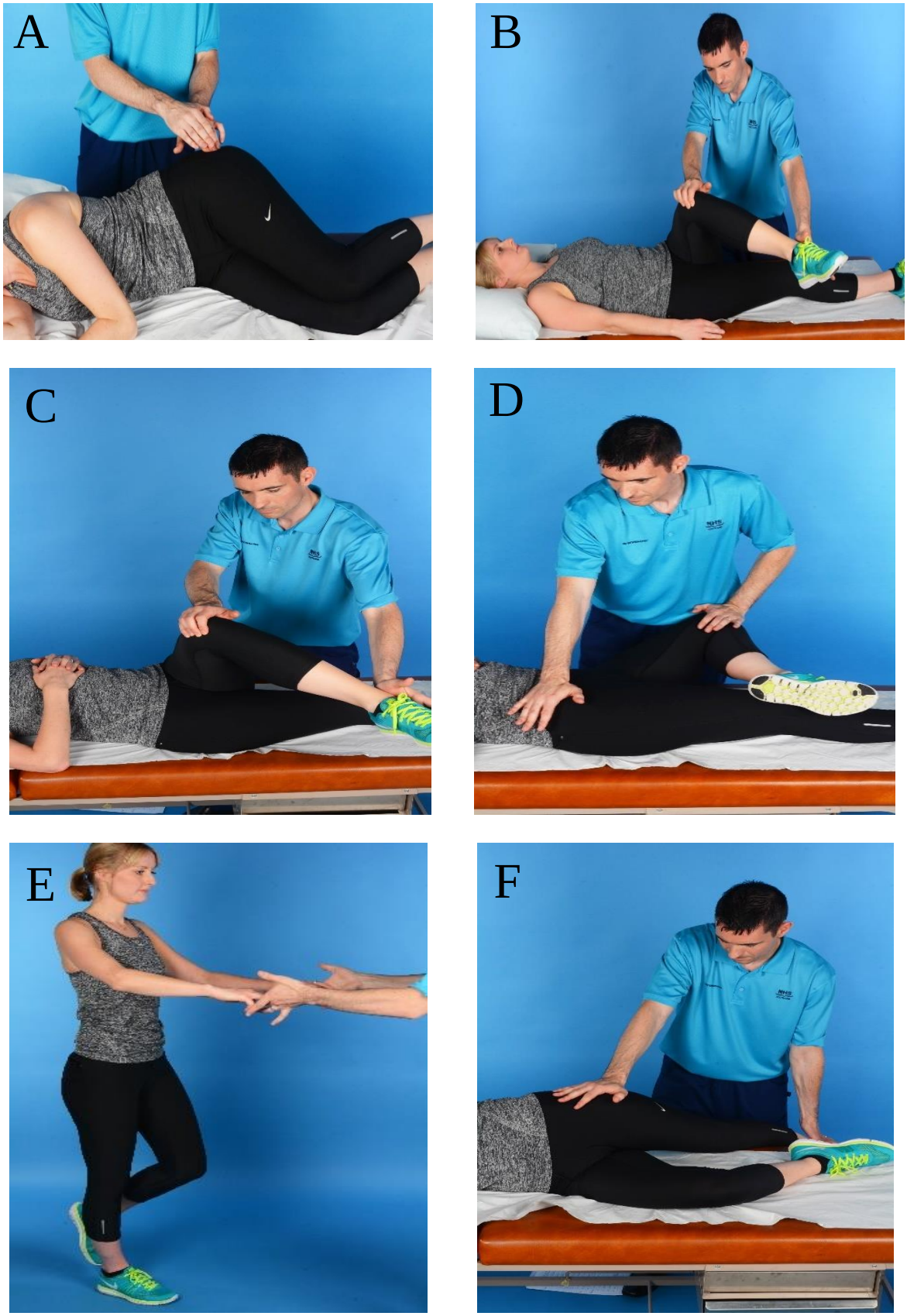

Figure 2-2. Pain provocation tests. (A) Pain on direct palpation, (B) FADER, (C) FADER-R, (D) FABER, (E) Single leg stance held for 30s, (F) Passive hip adduction with resisted hip abduction

Table 2-1. Eligibility criteria for study participation

Inclusion criteria	Exclusion criteria
1. Aged ≥ 18 years 2. Lateral hip pain for > 3 months 3. Lateral hip pain reproduced on direct palpation around greater trochanter 4. Lateral hip pain provoked in at least one other of five pain provocation tests: i) FADER ii) FADER-R iii) FABER iii) Single leg stance (30-s) iv) Passive hip adduction in side-lying with resisted abduction	1. Physiotherapy treatment for lateral hip pain in the previous 6 months 2. Corticosteroid injection for lateral hip pain in the previous 3 months 3. Inability to actively abduct the affected hip in side-lying, suggestive of a full-thickness gluteal tendon tear or rupture 4. Lateral hip pain reproduced with flexion, adduction and internal rotation of the hip with concurrent hip osteoarthritis on anterior posterior pelvis radiographs defined as Kellgren-Lawrence > grade 2 (mild) 5. Previous hip or lumbar spine surgery in the previous 12 months 6. Inflammatory joint disease 7. Unstable diabetes or cardiovascular disease 8. Known neurological disorders 9. Widespread chronic pain or fibromyalgia 10. Pregnancy 11. Participants unable or unwilling to give informed consent 12. Participants who are unable to write, read or comprehend English.

Abbreviations: *FADER, Flexion Adduction External Rotation; FADER-R, Flexion Adduction External Rotation with resisted isometric hip internal rotation; FABER, Flexion Abduction External Rotation.*

2.2.3 Randomisation

Participants were randomly assigned to either the isometric exercise group or isotonic exercise group. Each consecutive participant selected a sealed opaque envelope from a box which contained all of the envelopes, 15 envelopes contained labels inside with the word ‘isometric’ and 15 the word ‘isotonic’.

2.2.4 Interventions

Both programmes consisted of daily exercise for 12 weeks. A maximum of 5/10 on the Numeric Pain Rating Scale (NPRS) was permitted, provided this eased following completion of the exercises and did not increase in the subsequent 24 hours (Figure 1-14). The exercises in both programmes specifically targeted the hip abductor muscles. No external resistance was used initially. Progressive muscle and tendon loading were achieved through the introduction of therapeutic elastic bands ranging from low to high resistance. Progression with the resistance bands was individualised and based on each participant’s ability to complete the exercises without increasing their pain beyond 5/10. All bands were 100 cm in length and attached around both ankles.

Following randomisation and during the first session, the respective exercise programme was explained to each participant and they had the opportunity to practice both exercises to ensure correct technique. An exercise booklet was provided to each participant in the isometric exercise group (Appendix 8) and isotonic exercise group (Appendix 9). Each booklet contained the exercise programme with load management advice on activity modification and advice on reducing tendon compression. An exercise diary was used to record the number of repetitions completed and the individual pain score elicited (0-10) during each exercise. Exercise adherence was also monitored by reviewing the diary at each session. Eighty per cent adherence has been suggested to be a reasonable threshold in exercise intervention studies (Bailey et al. 2020). Participants attended eight individual appointments during the 12-week programme, weekly for the first two weeks and thereafter for a further five sessions over the next 10 weeks for exercise progression. All appointments were with the PhD student. Participants were encouraged to remain physically active within their limits of pain. Simple analgesia was permitted, but participants were asked to refrain from seeking other forms of treatment during the study.

2.2.4.1 Isometric exercise programme

The isometric exercise programme consisted of two exercises, completed once per day (Figure 2-3).

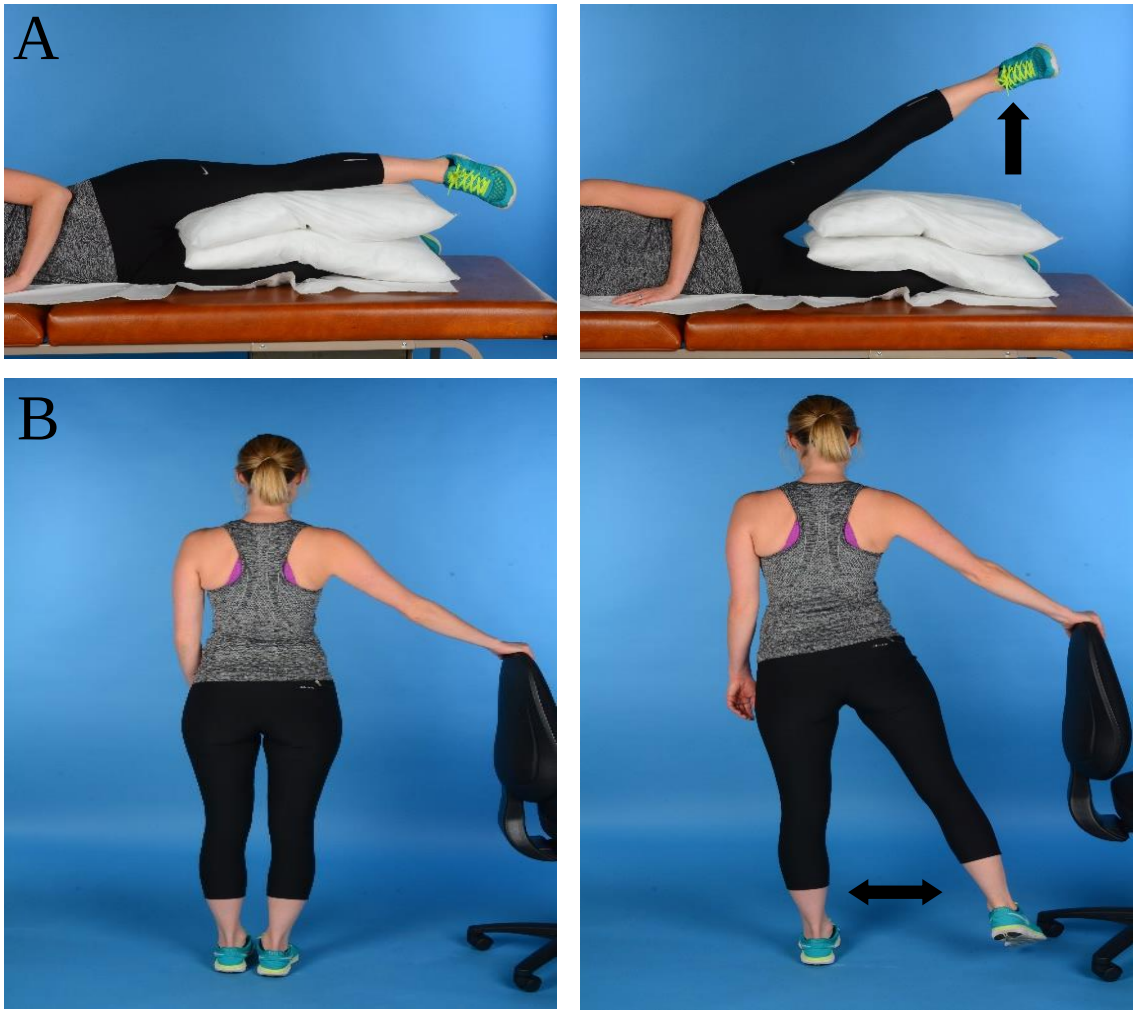

Figure 2-3. Isometric exercise programme. (A) Hip abduction hold (B) Weight-bearing gluteal contraction. The left leg is the affected side.

Hip abduction hold (A) was completed while lying on the non-affected side with pillows between both knees. The affected hip was abducted to approximately 30 degrees in mid-line abduction and held in this position for 30-s. This exercise was completed six times with 60-s rest between each repetition. During the weight-bearing gluteal contraction exercise (B), while holding onto a chair for support the unaffected hip moved into abduction and adduction, achieving an isometric gluteal contraction of the weight-bearing leg. Each repetition was 6-s duration (3-s abduction, 3-s adduction). Three sets of 10 repetitions were completed with 60-s rest between each set. Time under tension was six minutes daily.

2.2.4.2 Isotonic exercise programme

The isotonic exercise programme also consisted of two exercises completed once per day (Figure 2-4).

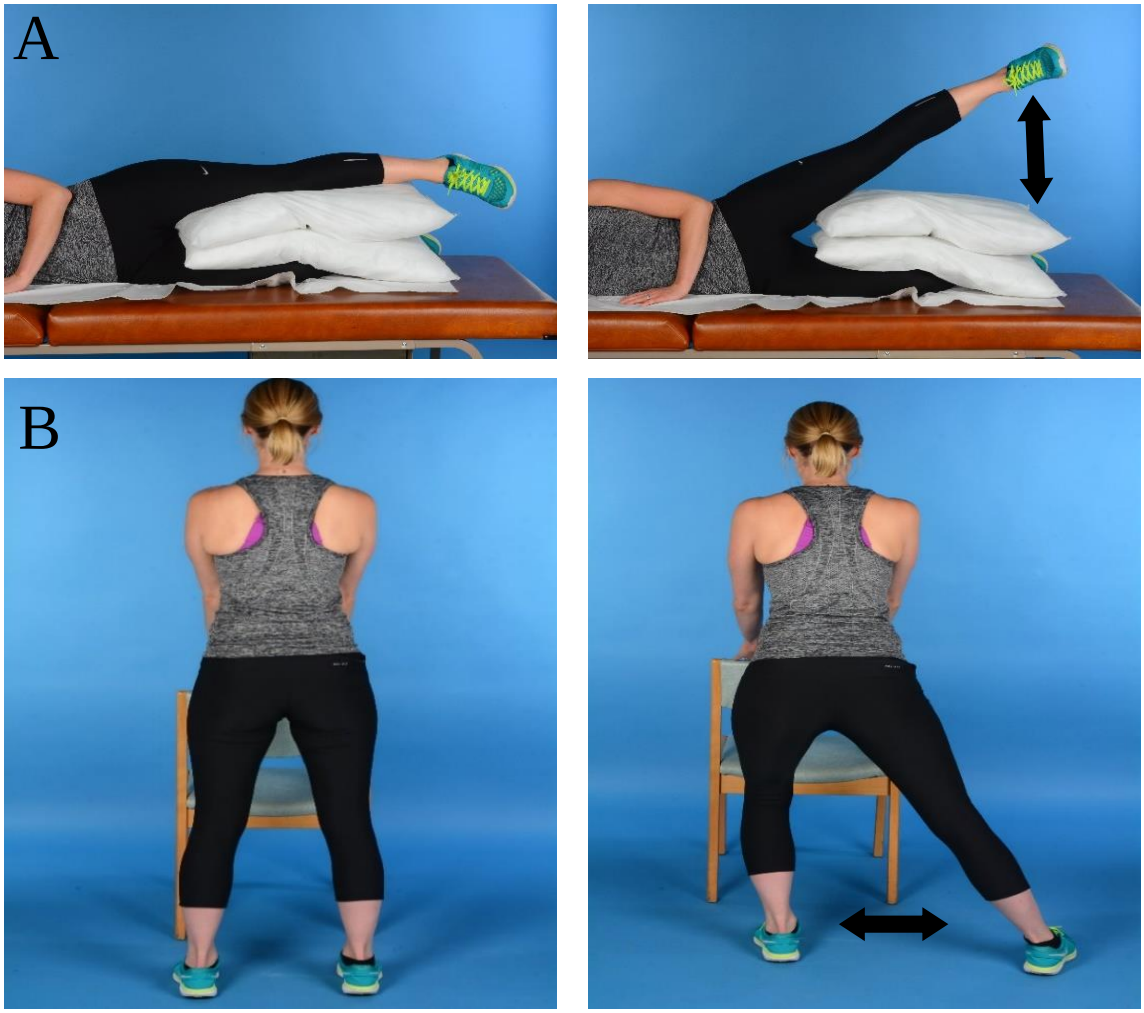

Figure 2-4. Isotonic exercise programme. (A) Side lying hip abduction (B) Hip abduction slide

Side lying hip abduction (A) was completed while lying on the non-affected side with pillows between both knees. The affected hip was abducted to approximately 30 degrees in mid-line abduction and then lowered. Each repetition was 6 s duration (3-s concentric, 3-s eccentric). The hip abduction slide (B) was completed in upright standing with both hands supported on a chair. The affected leg moved into hip abduction while maintaining foot contact with the floor. The knee on the affected side was extended but the non-affected hip and knee were permitted to bend to around 45 degrees. The abducted hip then returned to the starting position. Both exercises were completed for 3 sets of 10 repetitions with 60-s rest between each set. Time under tension was six minutes daily.

2.2.5 Outcome measures

2.2.5.1 Primary outcome

The VISA-G was the primary outcome measure used in this study (Appendix 10). It is currently the preferred option to capture the disability associated with GTPS and has been validated for use in this condition (Fearon et al. 2015, Nasser et al. 2021). Previous GTPS exercise trials have also used the VISA-G as the primary outcome measure (Cowan et al. 2022, Ganderton et al. 2018). It consists of eight questions with total scores ranging from 0 to 100. Higher scores indicate less pain and better function.

2.2.5.2 Secondary outcomes

The NPRS is a unidimensional measure of the average pain intensity in the previous week (Farrar et al. 2001). Pain was measured on an 11-point scale between 0 (no pain) and 10 (worst pain imaginable) (Appendix 11). The MCID for musculoskeletal pain has been reported as two points (Salaffi et al. 2004).

The Global Rating of Change (GROC) scale was used to assess perceived overall change in lateral hip pain (Appendix 12). An 11-point Likert scale ranging from ‘very much worse’ to ‘completely recovered’ was used. The MCID for GROC has been previously reported as two points (Kamper et al. 2009)

The Pain Catastrophising Scale (PCS) is a 13-item self-report scale measuring pain catastrophizing (Sullivan et al. 2009). Participants indicated on a five-point scale the degree to which they had certain thoughts and feelings when experiencing lateral hip pain (Appendix 13). A rating of 0 (not at all) to 4 (all the time) can be given. Total scores range from 0 to 52 with higher scores indicating higher levels of pain catastrophising. A score $\geq$ 30 is clinically significant and indicative of catastrophising (Sullivan et al. 2009).

The Hip Disability and Osteoarthritis Outcome Score (HOOS) is used for individuals with hip pain and disability (Klässbo et al. 2003). It consists of five subscales: i) symptoms and stiffness, ii) pain, iii) function in activities of daily living, iv) function in sport and recreation and v) quality of life (Appendix 14). Each question has five possible answers, each scored from 0 to 4. A total score of 0 indicates a severe problem and a score of 100 no hip problem.

The Euro Qol (EQ-5D-5L) is a five-dimension questionnaire and a standardised instrument for measuring generic health status (Preedy and Watson 2010). Health status is measured in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Appendix 15). Each of these five dimensions has five statements and each participant was asked to tick one of these five boxes for each dimension. An index value (0-1) is calculated from five separate questions. A score of 1 is the highest score. Each participant also evaluated their current overall health status using a visual analogue scale with a score of 0 indicating the worst imaginable health and a score of 100 the best imaginable health.

The International Physical Activity Questionnaire Short Form (IPAQ-SF) comprises seven items measuring different physical activity intensities (Craig et al. 2003). The seven questions relate to the amount of time each participant was physically active during the previous week (Appendix 16). Results were reported as either low, moderate or high physical activity levels.

2.2.6 Statistical analysis

Statistical analysis was performed using Minitab (version 18). Data were found to be normally distributed. Descriptive statistics were used to describe the sample and the trends in the data over time for both groups. Comparisons between and within groups were measured at baseline, 4 and 12-weeks using means, standard deviations (SD) and 95% confidence intervals (CIs). Cohen's d effect sizes were calculated for the VISA-G using a threshold of 0.2 (small), 0.5 (medium) and 0.8 (large) (Cohen 1988). Per-protocol analysis was undertaken, and statistical significance taken as $p < 0.05$.

2.3 Results

2.3.1 Participants

Thirty participants with GTPS were randomised into isometric and isotonic groups. Group characteristics were found to be comparable at baseline (Table 2-2) Twenty-three participants were included in the final analysis. A total of seven participants did not complete the study. One participant in the isometric group and one participant in the isotonic group withdrew due to an increase in hip and knee pain respectively. The other five withdrawals were due to reasons unrelated to the study.

Table 2-2. Participant characteristics (mean (SD) unless otherwise stated)

Characteristics	Isometric (n=15)	Isotonic (n=15)
Age (years)	57.5 (16.8)	61.1 (15.2)
Female	13	14
Height (cm)	164.4 (7.0)	159.1 (8.9)
Body mass index (kg/m^2)	27.7 (4.1)	29.6 (4.8)
Duration of symptoms (months)	23 (21.4)	22.9 (28.3)
Unilateral symptoms	13	13
Previous CSI	7	2
Low back pain	8	10
Groin pain	3	4
Diabetes	2	3
Abbreviations: *CSI, Corticosteroid injection.*		

2.3.2 Outcomes

VISA-G

Both groups had similar improvements in VISA-G scores at 4 and 12 weeks (Figure 2-5). The isometric exercise group increased from 54.6 +/- 23.1 points (Week 0) to 59.2 +/- 21.0 (week 4) to 65.0 +/- 22.6 (week 12). The isotonic exercise group scored a mean of 61.9 +/- 16.1 (week 0), 60.8 +/- 12.8 (week 4) and 72.4 +/- 13.3 (week 12). At week 4 between group differences were 5.5 points (95% CI −3.5 to 14.4) and −0.1 points (95% CI −13.8.to 13.5) at week 12. Effect sizes at week 12 were d=0.45 (isometric) and d=0.71 (isotonic).

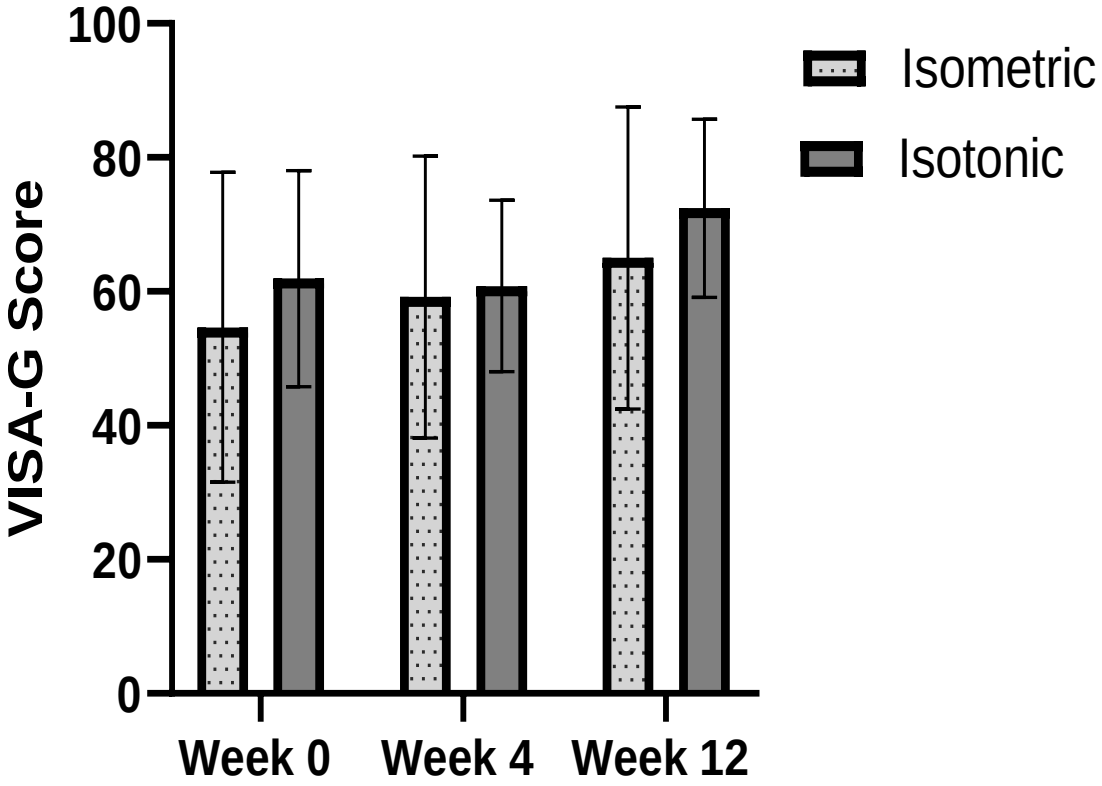

Figure 2-5. Mean (SD) Victorian Institute of Sport Assessment-Gluteal (VISA-G) scores at 0, 4 and 12 weeks

Numeric Pain Rating Scale

At week 4, 5/11 (45%) of the isometric exercise group had achieved a pain reduction of at least 2 points (Figure 2-6) compared with 7/12 (58%) of the isotonic exercise group (Figure 2-7). At week 12, 6/11 (55%) of the isometric exercise group and 7/12 (58%) of the isotonic exercise group had achieved the MCID.

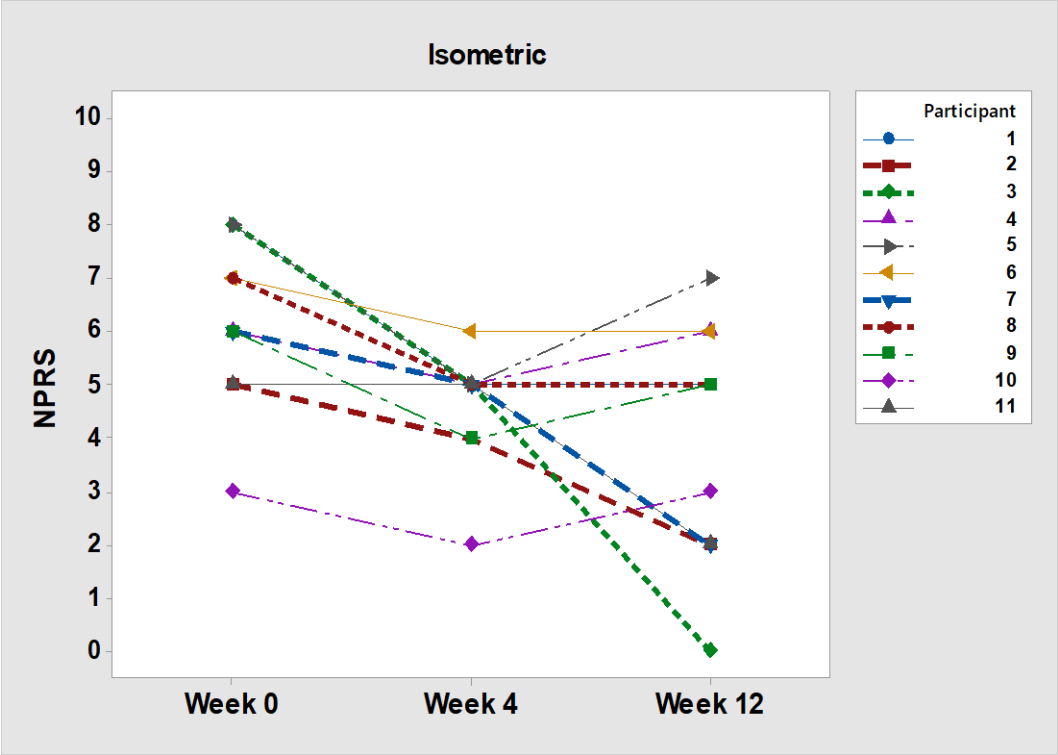

Figure 2-6. Individual Numeric Pain Rating Scale (NPRS) for isometric exercise. Note: due to the same scores reported for different participants, some lines overlap.

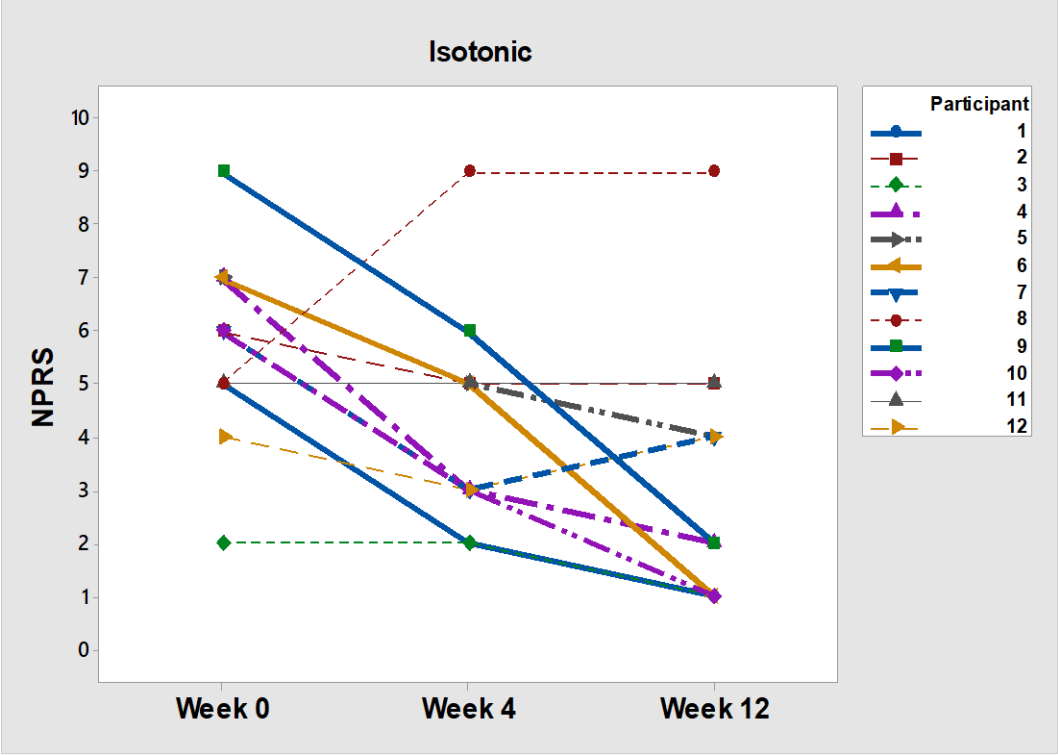

Figure 2-7. Individual Numeric Pain Rating Scale (NPRS) for isotonic exercise. Note: due to the same scores reported for different participants, some lines overlap.

Global Rating of Change

At week 4, 5/11 (45%) of participants in both groups had improved by the MCID of two points (Figures 2-8 and 2-9). At week 12, 7/11 (64%) of the isometric group and 9/12 (75%) of the isotonic group reported a meaningful change.

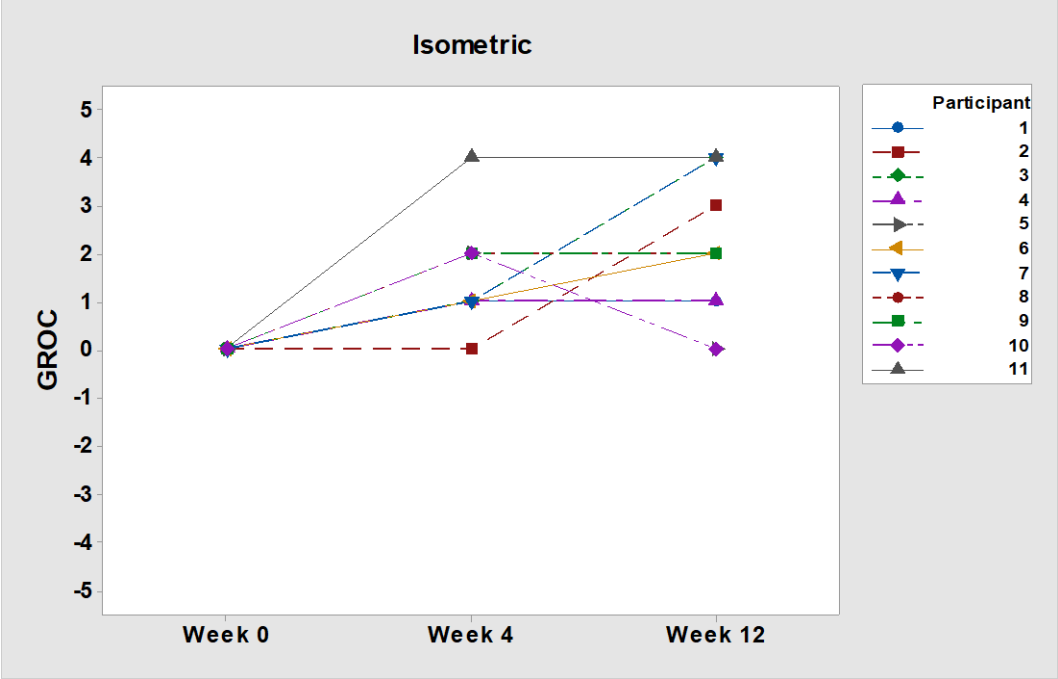

Figure 2-8. Global Rating of Change (GROC) scale for isometric exercise. Note: due to the same scores reported for different participants, some lines overlap.

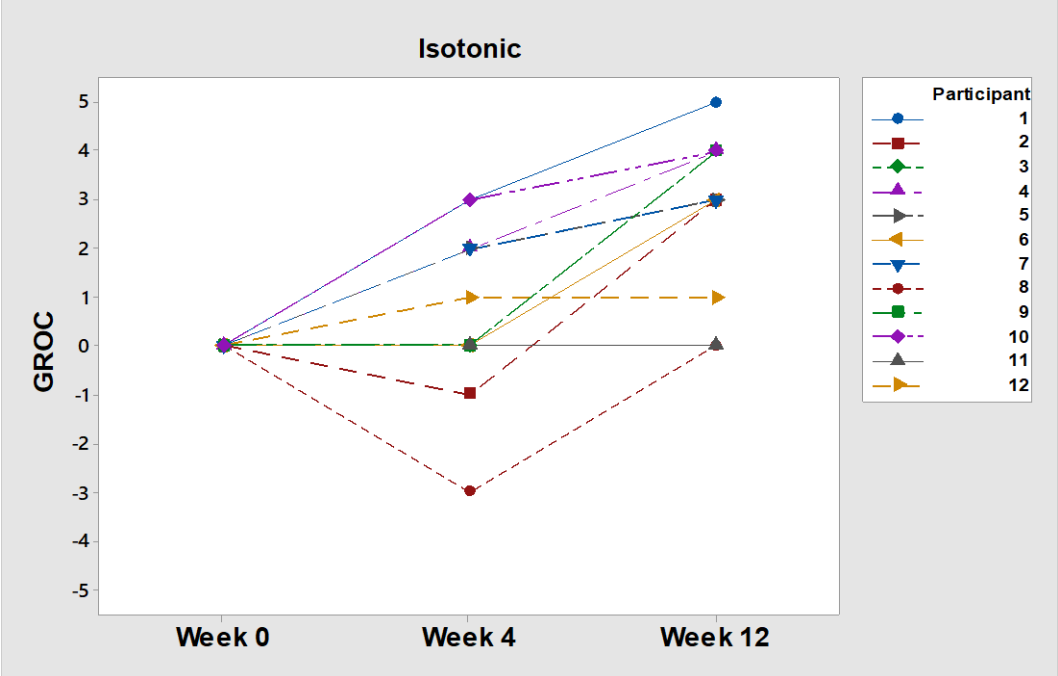

Figure 2-9. Global Rating of Change (GROC) scale for isotonic exercise. Note: due to the same scores reported for different participants, some lines overlap.

For the remaining secondary outcome measures, no significant difference between groups was observed at 4 and 12 weeks (Table 2-3). For the PCS, mean scores reduced by three points in the isometric exercise group and six points in the isotonic exercise at week 12. For the HOOS, the scores for all five domains improved in both groups by the end of the study with trends towards statistically significant findings in the isotonic group for both pain and quality of life. Index and health scores for the EQ-5D-5L in both groups were unchanged at both time points. Finally, for the IPAQ-SF, there was minimal change in physical activity levels over the course of the 12 weeks for both groups.

2.3.3 Exercise adherence

The exercise diary was completed by 22 out of 23 participants. Twenty-two participants completed at least 50% of the daily exercise sessions. 7/10 (70%) of the isometric group completed at least 80% of the sessions compared with 7/12 (58%) of the isotonic group. Twenty-two participants were able to progress the loading intensity of the exercises over the course of the 12-week programme by using resistance bands.

Table 2-3 Secondary outcome measures

	Group mean scores and (SD)							Difference within groups (95% CI)					Difference between groups (95%CI)	
	0 weeks		4 weeks		12 weeks			0 to 4 weeks		0 to 12 weeks			4 weeks	12 weeks
	Isometric	Isotonic	Isometric	Isotonic	Isometric	Isotonic		Isometric	Isotonic	Isometric	Isotonic			
Outcome	(n=11)	(n=12)	(n=11)	(n=12)	(n=11)	(n=12)		(n=11)	(n=12)	(n=11)	(n=12)			
PCS (0-52)	10.3 (10.7)	13.0 (13.6)	7.4 (7.2)	11.2 (10.4)	7.3 (9.8)	6.8 (8.6)		2.9 (-5.2 to 11)	1.8 (-8.4 to 12.1)	3.0 (-6.1 to 12.1)	6.3 (-3.4 to 15.9)		0.7 (-4.4 to 5.8)	-3.3 (-12.8 to 6.3)
								p 0.462	p 0.714	p 0.500	p 0.193		p 0.777	p 0.487
HOOS (0-100)														
Symptoms	60.9 (15.6)	65.0 (18.7)	67.3 (14.2)	64.2 (17.8)	72.7 (19.8)	76.7 (12.5)		6.4 (-6.9 to 19.6)	-0.8 (-16.3 to 14.6)	11.8 (-4.0 to 27.7)	11.7 (-1.8 to 25.3)		8.7 (-11.4 to 28.7)	0.2 (-19.3 to 19.6)
								p 0.329	p 0.912	p 0.136	p 0.086		p 0.378	p 0.987
Pain	53.6 (15.8)	53.8 (16.8)	61.1 (15.5)	59.8 (15.9)	65.7 (20.2)	70.7 (24.3)		7.5 (-6.4 to 21.4)	6.0 (-7.0 to 19.1)	12.0 (-3.6 to 27.6)	17.0 (0.7 to 33.3)		-0.3 (-17.1 to 16.4)	-3.4 (-27.0 to 20.2)
								p 0.274	p 0.351	p 0.125	**p 0.042**		p 0.966	p 0.768
Function/daily living	59.4 (18.4)	64.0 (17.4)	68.5 (18.3)	68.9 (17.8)	72.56 (19.7)	73.0 (26.8)		9.1 (-7.7 to 25.8)	4.9 (-9.1, 18.9)	13.2 (-3.7 to 30.1)	9.0 (-8.6 to 26.5)		0.7 (-18.9 to 20.3)	1.6 (-23.1 to 26.4)
								p 0.272	p 0.480	p 0.144	p 0.303		p 0.937	p 0.890
Sports	51.1 (26.4)	60.0 (20.8)	60.4 (23.6)	61.0 (17.7)	63.8 (23.2)	68.8 (28.9)		9.3 (-13.5 to 32.2)	1.0 (-15.5 to 17.5)	12.7 (-10.2 to 35.6)	8.7 (-12.3 to 29.8)		10.2 (-9.0 to 29.4)	7.2 (-14.8 to 29.1)
								p 0.402	p 0.899	p 0.260	p 0.398		p 0.280	p 0.502
QoL	44.3 (22.6)	50.0 (16.0)	51.7 (12.5)	50.0 (20.0)	56.8 (20.4)	67.2 (19.2)		7.6 (-7.6 to 22.8)	0.0 (-14.6 to 14.6)	12.5 (-6.3 to 31.3)	17.2 (3.2 to 31.2)		5.6 (-11.6 to 22.7)	-10.7 (-28.9 to 7.4)
								p 0.313	p 1.000	p 0.180	**p 0.018**			p 0.231
EQ-5D-5L														
Index (0-1)	0.64 (0.19)	0.63 (0.15)	0.69 (0.14)	0.62 (0.17)	0.70 (0.15)	0.69 (0.18)		0.05 (-0.104 to 0.194)	-0.01 (-0.147 to 0.128)	0.06 (-0.089 to 0.217)	0.07 (-0.076 to 0.201)		0.040 (-0.063 to 0.142)	-0.03 (-0.132 to 0.125)
								p 0.535	p 0.887	p 0.397	p 0.343		p 0.435	p 0.960
Health Score (0-100)	66.8 (13.8)	70 (19.3)	66.8 (15.4)	69.2 (16.5)	70.5 (15.7)	72.1 (20.5)		0.0 (-13.0 to 13.0)	-0.8 (-16.0 to 14.34)	3.6 (-9.5 to 16.8)	2.1 (-14.8 to 18.9)		0.8 (-13.7 to 15.4)	1.6 (-18.6 to 21.7)
								p 1.000	p 0.911	p 0.571	p 0.800		p 0.906	p 0.871
IPAQ														
Low	4	3	3	3	4	4								
Moderate	4	5	7	4	3	3								
High	3	4	1	4	3	4								
				(1 missing)	(1 missing)	(1 missing)								

2.4 Discussion

This was the first study to compare isometric and isotonic exercise for greater trochanteric pain syndrome. Similar improvements were observed for both groups over various clinical outcomes at 4 and 12 weeks. The mean VISA-G scores increased by 11 points in both groups at the end of the study. The MCID for the VISA-G is currently unknown so it is unclear whether these improvements were clinically significant. The percentage of participants who reported a pain reduction of at least two points (MCID) on the NPRS was identical between groups at 12 weeks. For GROC, almost 50% of participants in both groups reported a clinically significant improvement at 4 weeks. Further improvements were observed at 12 weeks but this was more evident in the isotonic exercise group with a higher percentage of participants reporting a clinically important change. Small improvements were observed in both groups for pain catastrophising. Improvements for both groups were identified across all five domains of the HOOS but no between-group differences were detected at 12 weeks. No meaningful differences were identified in either group for physical activity or health status as measured by the IPAQ-SF and EQ-5D-5L respectively. This is not unexpected given the relatively short intervention period.

A small number of studies have investigated isometric exercise in lower limb tendinopathy. The immediate effect of isometric exercise for pain has reported variable results (Holden et al. 2020, O' Neill et al. 2019, Pearson et al. 2020, Rio et al. 2015, Rio et al. 2017). However, isometric and isotonic exercise programmes appear to have similar short-term effects on lower limb tendinopathy. In the current study, no difference was identified between isometric and isotonic exercise at 4 or 12 weeks. These results are similar to the findings for patellar tendinopathy with similar improvements in pain and function after a four-week programme of isometric or isotonic exercise (van Ark et al. 2016). In both studies, the total amount of time the muscle-tendon unit was under load or time under tension (TUT) was identical between groups. Participants in the current study completed 30s isometric contractions compared with 45s for patellar tendinopathy. A similar immediate pain reduction occurred with long duration (40s) and short duration holds (10s) in patellar tendinopathy when TUT was equal (Pearson et al. 2020). Taken together, these findings suggest there is currently no optimal duration of isometric contraction, providing clinicians with flexibility when designing a rehabilitation programme which includes isometric exercise.

Four studies have investigated the effectiveness of exercise in GTPS (Cowan et al. 2022, Ganderton et al. 2018, Mellor et al. 2018, Rompe et al. 2009). In the LEAP trial the mean VISA-G score increased by 19 points in the exercise plus education group at 12 weeks (Mellor et al. 2018). This was higher than the mean score of 11 points for both groups in the current study. Mellor et al. (2018) excluded participants if low back pain or groin pain of > 2/10 on the NPRS was present. Co-existing low back and/or groin pain is common in GTPS with the prevalence of low back pain ranging from 21% - 62% (Rompe et al. 2009, Stephens et al. 2020, Woodley et al. 2008b). In the current study, 10/30 (33%) reported low back pain > 2/10 and 7/30 (23%) groin pain of > 2/10 at baseline. Individuals with co-existing low back pain and/or groin pain may not respond as favourably to a targeted hip abductor exercise programme which could explain the differences observed when comparing the results of the current study and Mellor et al. (2018). Further research is required to determine whether a management programme focusing on lateral hip pain in combination with low back and/or groin pain would lead to more favourable clinical outcomes for GTPS.

The GLoBE study compared 12 weeks of lower limb exercise to sham exercise in postmenopausal women with GTPS (Ganderton et al. 2018). After 12 weeks VISA-G scores had improved by 12 points for both groups which is similar to the current study. Both groups received education on activity modification and advice on minimising tendon compression. Similar information was provided to participants in the current study and also by Cowan et al. (2022) and Mellor et al. (2018). In the current study, > 90% of participants who reported a pain reduction of at least two points on the NPRS at week 12 had already achieved this by week 4. Similar improvements in pain intensity were reported after 4 weeks in the exercise plus education group with a mean reduction of more than two points (Mellor et al. 2018). This infers that a clinically significant reduction in pain can occur relatively quickly in GTPS after commencing a treatment programme. Muscle hypertrophy and tendon adaptation are unlikely to occur within four weeks in response to resistance exercise, although neuromuscular adaptations can occur quickly and could explain the initial improvement in pain (Aagaard et al. 2020). A further possibility is that the improvements observed across all four studies could be attributed to the education component of the management programme. Future studies which investigate an ‘education-only’ intervention will help to determine the importance of patient education in GTPS.

In the current study, 45% of participants reported a clinically significant change of at least two points on the GROC scale after 4 weeks. This increased to 64% in the isometric exercise group and 75% in the isotonic exercise group after 12 weeks. In the study by Rompe et al. (2009) only 7% of participants reported an improvement at 4 weeks increasing to 41% after 4 months on the GROC scale. The inclusion of daily ITB stretching exercises which encouraged sustained periods of hip adduction could explain the lack of initial improvement. Compression of the gluteal tendons and trochanteric bursa is believed to occur in this position and may contribute to the persistence of pain. In contrast, stretching exercises and compressive loading during activity were not advocated in the current study or by Cowan et al. (2022), Ganderton et al. (2018) and Mellor et al. (2018). The importance of minimising compressive loading in the management of tendinopathy was proposed by Cook and Purdam (2012). Although McMahon et al. (2013) highlighted that loading in a lengthened position is more effective than in a shortened position for tendon adaptation, this may not be possible in the initial stages of GTPS management due to pain. Instead, muscle-tendon loading in lengthened positions may be more appropriate in later stages of management when symptoms are less easily provoked.

As discussed in Chapter 1.9.2, the mechanism by which loading reduces pain in tendinopathy is still not fully understood (Kjaer et al. 2009). Pain relief in tendinopathy and GTPS may be related to the CNS and descending inhibition that is known to occur with exercise, at least in pain free individuals (Naugle et al. 2012). Therefore, the act of engaging in exercise is perhaps more important than the specific exercise type. This would be supported by the results of the current study where similar outcomes were observed from two different exercise programmes. Interestingly, this is a consistent finding across tendinopathy clinical trials when exercise programmes are directly compared. Cowan et al. (2022) and Ganderton et al. (2018) utilised identical lower limb and sham exercise programmes, combined with education, in post-menopausal females with GTPS. In both studies, there was no between-group difference. Habets et al. (2021) reported similar findings for Achilles tendinopathy when the Alfredson et al. (1998) eccentric loading programme was compared to the Silbernagel et al. (2007) concentric-eccentric programme. Clinical symptoms improved in both groups with no differences identified between programmes. Beyer et al. (2015) and Kongsgaard et. al (2009), compared heavy slow resistance (HSR) and eccentric exercise for Achilles tendinopathy and patellar tendinopathy respectively. Despite the variation in both the magnitude and frequency of loading between programmes, VISA scores were similar in both studies. For rotator cuff

tendinopathy no superior benefit was identified when high load exercise was compared to low load exercise for a period of three months (Ingwersen et al. 2017). Overall, different loading programmes, including the two programmes compared in this chapter, appear to result in similar outcomes, regardless of pain location, muscle contraction type, loading intensity or frequency.

Although the benefits of both isometric and isotonic exercise have been demonstrated in this study, over 35% of participants in both groups did not improve despite completing 12 weeks of exercise. VISA-G scores were worse or unchanged in 4/11 (36%) of the isometric group and 5/12 (42%) of the isotonic group. In the GLoBE study, approximately 50% of participants reported either increased pain or no change in pain at 52 weeks. Although the LEAP trial demonstrated high success rates, 20% of participants did not achieve a satisfactory outcome at long-term follow-up (Mellor et al. 2018). At present, it is unknown why 20-50% of individuals with GTPS fail to improve with exercise combined with load management advice. As discussed in Chapter 1.11, the presence of certain clinical characteristics may explain the poor response to exercise observed in GTPS. Psychological factors are believed to contribute to inferior clinical outcomes in musculoskeletal pain (Luque-Suarez et al. 2019, Martinez-Calderon et al. 2020, Stubbs et al. 2020). Such factors may also contribute to a suboptimal outcome in tendinopathy (Mallows et al. 2017). Kinesiophobia, depression, and anxiety and pain catastrophising have all been associated with GTPS (Plinsinga et al. 2018, Plinsinga et al. 2020). The prevalence of catastrophising in the current study however was low with only two participants scoring $\geq$ 30 at baseline. The prevalence of psychological factors in GTPS warrants further consideration and will be investigated in Chapter 4 of this thesis.

2.4.1 Strengths and limitations

A strength of the current study was the similarities between both exercise programmes. Two exercises were completed by each group with equal TUT, enabling a direct comparison between muscle contraction type to be made. Moreover, each programme consisted of one weight bearing exercise and one non-weight bearing exercise. Exercise adherence was also measured which is likely to be critical when measuring the effectiveness of exercise interventions in tendinopathy clinical trials.

The conclusions of this study are, however, limited by a number of factors including the small sample size and drop-out rate of at least 20% in each group. Nevertheless, 23

participants were included in the final analysis which is comparable to other tendinopathy studies that have compared isometric and isotonic exercise (Stasinopoulos and Stasinopoulos 2017, van Ark et al. 2016). In the absence of a no treatment 'control' group, it is possible that a number of the participants improved due to natural recovery, although it should be acknowledged that the mean duration of symptoms upon entering the study was almost two years. Due to available resources, the presence of gluteal tendinopathy could not be confirmed with MRI or USS and it is therefore possible that participants with other pathologies were included. However, this is reflective of NHS physiotherapy clinical practice where such imaging modalities are not readily accessible. Moreover, the pain provocation tests used for study inclusion have high diagnostic utility when compared with MRI (Grimaldi et al. 2017). Participant screening, clinical examination, outcome measure assessments and exercise sessions were all completed by the PhD student which introduces the potential for bias.

2.5 Conclusion

This was the first randomised controlled trial to compare isometric exercise and isotonic exercise over a period of 12 weeks for GTPS. Isometric and isotonic exercise programmes incorporating load management advice appear to be effective in reducing pain and improving function after 4 and 12 weeks but no difference was observed between groups. The specific muscle contraction type may not affect the clinical outcome for individuals with GTPS when loading intensity and TUT are equal. However, this hypothesis would require to be confirmed in a larger appropriately powered clinical trial. Given that isometric exercise does not appear to be superior to isotonic exercise in GTPS/gluteal tendinopathy, in the next chapter by critically appraising the literature I will investigate whether isometric exercise is superior to isotonic exercise in other tendinopathies.

Chapter 3

Effectiveness of isometric exercise in the management of tendinopathy: a systematic review and meta-analysis of randomised trials

Content of this chapter has been published in the following manuscript:

Clifford C, Challoumas D, Paul L, Syme G, Millar NL. Effectiveness of isometric exercise in the management of tendinopathy: a systematic review and meta-analysis of randomised trials. BMJ Open Sport Exerc Med. 2020 Aug 4;6(1):e000760.

3.1 Aims and introduction

This chapter presents the second study in the thesis, a systematic review of randomised controlled trials which assessed the effectiveness of isometric exercise in comparison with other treatment strategies, including isotonic exercise, or no treatment in tendinopathy. Although the studies in chapter 2, and chapter 4, are related to GTPS/gluteal tendinopathy, this current study will include all tendinopathies due to the small number of eligible studies for GTPS and lower limb tendinopathy.

Tendinopathy is the preferred term for persistent tendon pain and loss of function due to mechanical loading (Scott et al. 2020). The burden of disease associated with tendinopathy is significant, accounting for 30% of all musculoskeletal conditions seen in general practice (McCormick et al. 1995). It affects both sedentary and active individuals and is responsible for 30% - 50% of all sporting injuries (Rolf and Movin 1997, Scott and Ashe 2006). Both the upper and lower limbs are involved, with the rotator cuff, lateral elbow, gluteal, patellar and Achilles tendons commonly affected (Albers et al. 2016, Scott and Ashe 2006).

Exercise programmes are usually the first-line treatment for tendinopathy, and evidence of their effectiveness in reducing pain and improving function has been demonstrated (Cullinane et al. 2014, Desmeules et al. 2016, Everhart et al. 2017, Mellor et al. 2018, Wilson et al. 2018). Different types of exercise or 'loading' programmes have been investigated, with those focusing on eccentric exercises the most commonly researched (Beyer et al. 2015, Kongsgaard et al. 2009, Larsson et al. 2019, Ortega-Castillo and Medina-Porqueres 2016). However, eccentric loading has not been consistently found to be superior when compared with combined concentric-eccentric programmes (Beyer et al. 2015, Kongsgaard et al. 2009, Larsson et al. 2019, Ortega-Castillo and Medina-Porqueres 2016). Although the benefits of loading programmes are well recognised, 35% - 45% of individuals do not experience a significant reduction in symptoms from either eccentric or combined concentric-eccentric exercise (Bahr et al. 2006, Clifford et al. 2019, Sayana and Maffuli 2007). In contrast to isotonic exercise, in which the tension in the muscle remains constant despite a change in length, the muscle-tendon unit remains at a constant length during isometric exercise (Oranchuk et al. 2019). Importantly however, and as discussed in Chapter 1-7, tendon will lengthen or 'strain' in a similar manner when subjected to loading regardless of muscle contraction type (Couppé et al. 2015, Magnusson and Kjaer 2019).

There has been recent clinical and research interest in isometric exercise programmes in the management of tendinopathy since the clinical trial by Rio et al. (2015). Significantly greater pain relief was reported immediately post-intervention following a single session of isometric exercise when compared with isotonic exercise in patellar tendinopathy. Subsequently, it was proposed that isometric exercise be used at the start of a rehabilitation programme to achieve a reduction in pain (Malliaras et al. 2015). A number of research groups have since investigated the effect of isometric loading programmes for immediate pain relief in various tendinopathy populations and reported variable results (Holden et al. 2020, O'Neill et al. 2019, Pearson et al. 2020, Riel et al. 2018).

Previous systematic reviews have evaluated eccentric and combined concentric-eccentric programmes, but only one review to date has evaluated isometric exercise (Lim and Wong 2018). This review focused on patellar tendinopathy and concluded that isometric exercise programmes appeared to be effective for short-term pain relief in athletes during the competitive season. Despite their recent popularity, it is unclear if isometric exercise provides superior pain relief when directly compared with other interventions, including isometric exercise. Conclusions about the benefits of isometric exercise for tendinopathy can therefore not be made, and no previous systematic reviews have evaluated the effectiveness of isometric exercise in the management of all tendinopathies.

The aim of this systematic review of RCTs was to assess the effectiveness of isometric exercise in comparison with other treatment strategies or no treatment in tendinopathy. Pain was the primary outcome measure. Functional disability, range of movement (ROM), muscle strength, quality of life (QoL), satisfaction, structural integrity and cortical inhibition were secondary outcome measures.

3.2 Methods

This systematic review has been conducted and authored according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009). The review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) prior to identification of articles and data extraction (Appendix 17). Registration number CRD42019147179.

3.2.1 Eligibility criteria

Included studies had a randomised design (of any kind) and compared isometric exercise with any treatment modality (or no treatment) for any type of tendinopathy in terms of any of the following outcomes: 'pain', 'functional disability', 'range of movement', 'strength', 'satisfaction', 'quality of life', 'structural integrity' and 'cortical inhibition'. Non-randomised observational studies, case reports, case series, literature reviews and studies comparing different regimens of isometric exercise were excluded. Participants had to be 16 years of age and above with a clinical diagnosis of tendinopathy with or without radiological signs. No specific criteria were used for the diagnosis of tendinopathy; however, studies were excluded if they did not include appropriate diagnostic criteria. Studies of patients with full tendon tears or previous tendon surgery were excluded. Duration of symptoms/signs was not an exclusion criterion, neither was length of conservative treatment and follow-up. Studies were only included if published in English.

3.2.2 Search strategy

A thorough literature search was conducted by two of the authors (CC and DC) independently via Medline, EMBASE, Cochrane and CINAHL from inception to May 2020, with the following Boolean operators: "(tendinopathy OR tendinosis OR tendinitis OR rotator cuff OR shoulder OR lateral elbow OR tennis elbow OR epicondylitis OR gluteal OR greater trochanteric OR patella* OR Jumper's knee OR Achilles) AND (isometric OR static)". Medical Subject Headings (MeSH) terms were not used to minimise the risk of missing relevant articles. Review articles were used to identify eligible articles that were missed at the initial search. Additionally, reference list screening and citation tracking in Google Scholar were performed for each relevant article. A total of 264 articles were initially identified, including those from missed studies identified by review articles. After exclusion of duplicate and non-eligible articles from title and abstract screening, reference list screening and citation tracking, 10 studies were found to fulfil the eligibility criteria. For completeness, an updated search was performed in May 2022. The studies by Van Der Vlist et al. (2020) and Bradford et al. (2021) were published following the completion of the current systematic review and the findings of both studies will be included in the discussion section of this chapter. Figure 3-1 illustrates the article screening process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

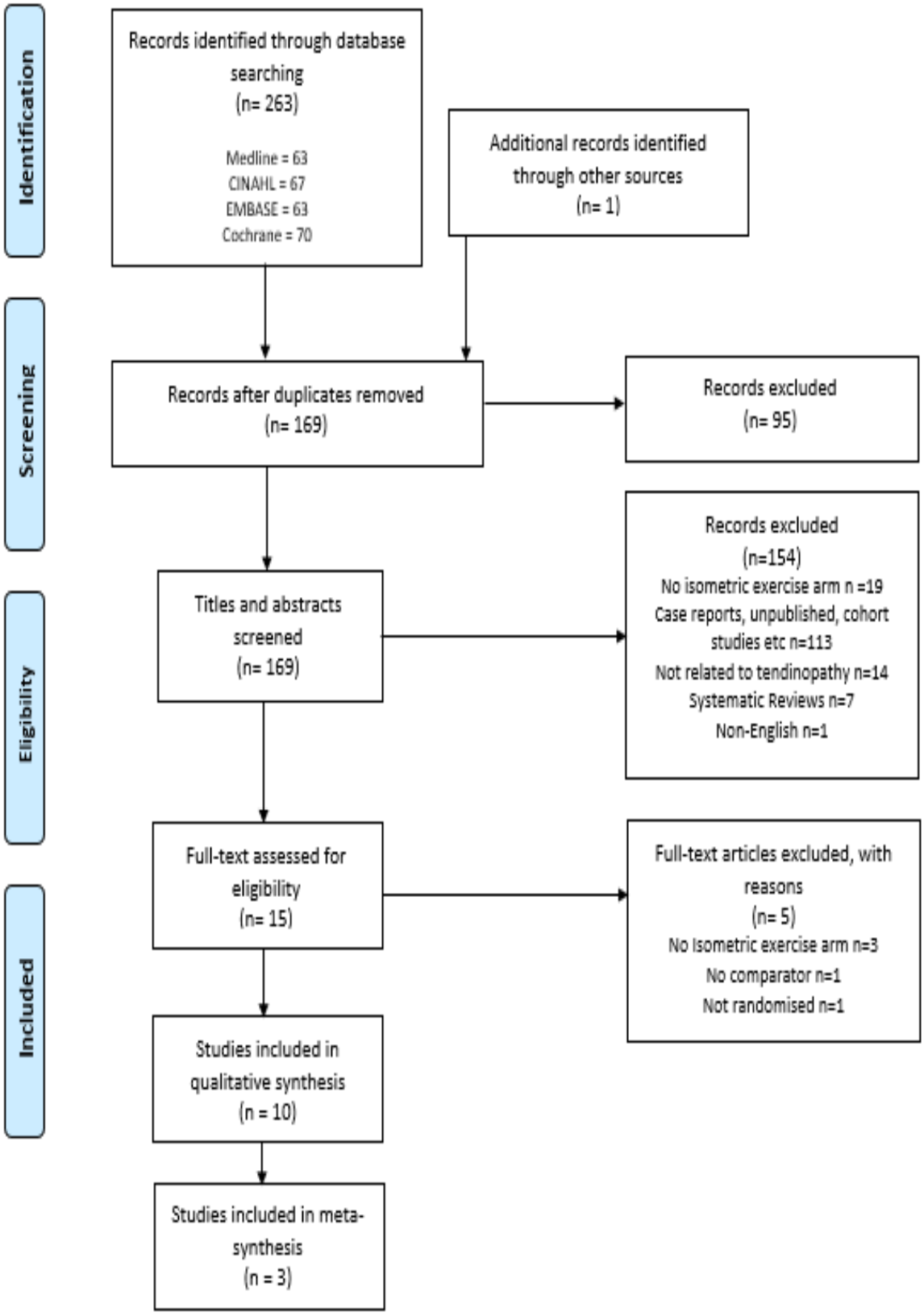

Figure 3-1. PRISMA flow diagram of included studies.

3.2.3 Quality assessment

For a thorough assessment of the studies, internal validity (freedom from bias), external validity (generalisability/applicability) and precision (reproducibility/freedom from random error) were all assessed separately by two of the authors (DC and CC) independently, and a third independent opinion (NLM) was sought where disagreements existed. For internal validity the 'Cochrane Collaboration's tool for assessing risk of bias in randomised trials' was used on a study level (not outcome measure level), which includes seven questions/criteria (making up six categories) assessing the risk of six specific and one non-specific ('other') types of bias (Higgins et al. 2011). As 'other' bias, our pre-set assessment criteria were (1) adequate and appropriate inclusion and exclusion criteria, (2) differences between treatment and control groups at baseline (confounding), (3) appropriateness of statistical tests deployed, (4) adherence of participants to assigned treatment, and (5) other methodological flaws not included in the specific categories of the tool. External validity was assessed based on the population, age range and clinical relevance of interventions and outcome measures. For the assessment of precision, performance of statistical power calculation (sample size adequate for at least 80% power) and p values that were used to define statistical significance were considered. In the Cochrane Collaboration's tool, each item is classified as of 'high', 'low' or 'unclear' risk of bias. No total scores are given. External validity and precision of each study were rated separately as of 'high', 'low' or 'unclear' risk. Overall, studies were characterised as of 'good', 'moderate' or 'poor' quality based on a combined assessment of their internal validity, external validity and precision, which was again conducted by two of the authors independently (CC and DC) and the opinion of a third and fourth author (LP and GS) was provided where the two judgements differed. The criteria used for overall quality assessment were as follows: 'Good' quality studies had 'high' risk of bias in less than two of the internal validity categories, external validity and precision. 'Moderate' quality studies had 'high' risk of bias in two of the internal validity categories, external validity and precision. 'Poor' quality studies had 'high' risk of bias in more than two of the internal validity categories, external validity and precision.

3.2.4 Data extraction: handling

Each of the eligible articles was read by the first and second authors and their key characteristics were extracted into tables to facilitate analysis and presentation. Two separate sets of tables were created by the two authors and these were subsequently compared and merged into one set to maximise accuracy of data extraction and analysis.

For the classification of strength of evidence for each outcome reported, the rating system formulated by van Tulder et al. (2003) was used, which consists of four levels of evidence. Strong evidence (level 1) is provided by generally consistent findings in multiple high-quality RCTs. Moderate evidence (level 2) is provided by generally consistent findings in one high-quality RCT and one or more low-quality RCTs, or by generally consistent findings in multiple low-quality RCTs. Limited or conflicting evidence (level 3) is provided by only one RCT (either high or low quality) or by inconsistent findings in multiple RCTs. No evidence (level 4) is defined by the absence of RCTs. As our overall quality assessment included a 'moderate' quality category, we extended level 2 to 'evidence provided by generally consistent findings in high-quality RCT and 1 or more low-quality or moderate-quality RCTs or multiple-moderate quality RCTs'. Two of the authors (DC and CC) jointly decided on the level of evidence for each outcome based on the aforementioned system without any disagreements. Results were considered to be significant when they were based on either strong or moderate evidence.

Where studies used tools and questionnaires with mixed outcome measures (e.g., Victorian Institute of Sport Assessment (VISA): 'pain' and 'function'), their results were tabulated under the generic outcome category 'functional disability'. Where results of their specific subcomponents were presented too, additional results were tabulated under the corresponding outcome category (e.g., pain subcomponent VISA-P score: 'pain').

Due to the significant heterogeneity of outcome measures used in studies, some of them were considered to represent one of our pre-set outcome measures as follows (according to their overall intended purpose), in order for grouping of results and hence conclusions to be possible: Global Rating of Change (GROC): 'satisfaction'; Patient-Rated Tennis Elbow Evaluation (PRTEE): 'functional disability'; pain-free grip strength: 'functional disability'; Disabilities of the Arm, Shoulder and Hand (DASH): 'functional disability'; Western Ontario Rotator Cuff Index (WORC): 'QoL'; and Victorian Institute of Sport Assessment (VISA): 'functional disability'.

3.2.5 Statistical analysis

Where two or more studies reported results on the same comparisons and at similar follow-up time frames, the data were meta-analysed only if study participants had the same type of tendinopathy, otherwise they were only included in the qualitative analysis. An inconsistency test was conducted first (χ^2 and I^2 statistic), and statistical tests and forest

plots were only produced if heterogeneity was no greater than 75%. The Review Manager V.5 (RevMan) software was used for statistical tests and forest plots. A random-effects meta-synthesis was employed as wide-range variability in studies' settings was expected. For the calculation of 95% CI, where not stated by the authors, the SD was used as per the following formula:

$CI=(mean1–mean2)\pm2\sqrt{[(SD1\ 2/n1) + (SD2\ 2/n2)]}$

When only IQR was reported, the SD was calculated as IQR/1.35. When only median was reported, mean was assumed the same as median as suggested by the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, Chapter 7.7.3.5 (Higgins et al. 2019). When CIs of means were reported, SDs were calculated by dividing the length of the CI by 3.92, and then multiplying by the square root of the sample size.(Higgins et al. 2019). Statistical significance was set at $p<0.05$, and all values are given at one decimal place. Publication bias was not formally assessed as the number of included studies was small.

3.2.7 Deviations to protocol

According to the published protocol, (Appendix 17), results of the review would be reported at short-term (< 6 weeks), mid-term (6 weeks – 6 months) and long-term (> 6 months) follow-up. We additionally included 'immediate post-intervention' results as reported by some studies as their aim was to assess for pain relief immediately after the intervention. Additionally, we extended our 'short-term' follow-up category to < 12 weeks, which was the maximum follow-up time point in our results and also that reported as the upper limit of 'short-term' by most other published reviews.

3.3 Results

Overall 10 eligible studies were identified with a total of n=294 participants. The following interventions were used: n=8 studies isolated isometric exercise, n=8 studies isolated isotonic exercise, n=2 studies combined isotonic/isometric exercise, n=2 studies ice therapy, n=1 study combined isometric exercise/ice therapy, and n=1 study no treatment ('wait and see'). In one study where the treatment groups had either isometric exercise or ice therapy for 2 weeks, both groups subsequently had isotonic exercise for 4 weeks (Dupuis et al. 2018). Otherwise there was no overlap of treatment modalities except for the aforementioned combined groups. The mean age was 39.2 years (range 16–86).

Affected tendons by anatomical area were rotator cuff (Dupuis et al. 2018, Parle et al. 2017) (n=2 studies, 63 participants), lateral elbow (Stasinopoulos and Stasinopoulos 2017, Vuvan et al. 2020) (n=2 studies, 74 participants), patellar (Holden et al. 2020, Rio et al. 2015, Rio et al. 2017, van Ark et al. 2016) (n=4 studies, 76 participants), Achilles (Gatz et al. 2020) (n=1 study, 44 participants) and gluteal (Clifford et al. 2019) (n=1 study, 30 participants). All 10 studies had a randomised design with a control group (isotonic exercise n=7 studies, ice therapy n=2 studies, no treatment n=1 study). Two studies had a cross-over design (Holden et al. 2020, Rio et al. 2015). Two studies included patients with acute tendinopathy (duration of symptoms ≤ 12 weeks) (Dupuis et al. 2018, Parle et al. 2017), seven with chronic tendinopathy (duration of symptoms >12 weeks) (Clifford et al. 2019, Gatz et al. 2020, Holden et al. 2020, Rio et al. 2017, Stasinopoulos and Stasinopoulos 2017, van Ark et al. 2016, Vuvan et al. 2020) and one with tendinopathy of unspecified chronicity (Rio et al. 2015). Treatment duration varied from a single session to 3 months and length of follow-up from 45 min to 3 months. Results were divided into (1) immediate post-treatment (three studies) and (2) short-term (≤ 12 weeks; seven studies). Publication years ranged from 2015 to 2020, with no RCTs published prior to 2015. Table 3-1 shows the methodological characteristics, and table 3-2 presents a summary of samples, interventions and outcome measures of the included studies.

Table 3-1. Methodological characteristics

Author	Study Type	Randomization Method	Blinding Method	Allocation Concealment	Statistical Power Calculation	Baseline Comparison	Inclusion Criteria	Exclusion Criteria	Follow-up Completion
Gatz *et al.* (2020)	RCT	Numbered envelopes	None	Sealed envelopes	Yes; sample size adequate for 82% power	No difference	≥ 18 years, insertional or midportion Achilles tendinopathy diagnosed with history and examination (provoked pain by palpation)	Pregnancy, BMI < 17 or > 35, previous Achilles tendon rupture or surgery, injections in last 6 months	71%
Clifford *et al.* (2019)	Pilot RCT	Random selection of sealed opaque envelopes from box	None	Sealed opaque envelopes	No	No difference	≥ 18 years, lateral hip pain > 3 months, pain over greater trochanter and at least one of the following 1) FADER 2) FADER and resisted IR 3) FABER 4) resisted hip abduction at end-range adduction 5) single leg stand 30-s	Physiotherapy in previous 6 months, corticosteroid injection in previous 3 months, hip or lumbar spine surgery in previous 12 months, moderate to severe hip osteoarthritis	77%
Holden *et al.* (2019)	RCT single-blind (cross-over)	Computer-generated allocation sequence	Researcher blinded to sequence allocation Participants blinded to study hypothesis	Sealed opaque envelopes, sequence randomised by independent researcher	Yes; sample size adequate for 90% power	No difference	18-40 years of age, patellar tendinopathy clinically and radiologically.	Concurrent knee pathologies, previous knee surgery, corticosteroid injection in last 6 months	95%
Vuvan *et al.* (2019)	RCT	Computer generated	Not stated	Sealed opaque envelopes	Yes; sample size adequate for 80% power	No difference	18-70 years, symptoms for > 6 weeks, NPRS ≥ 2/10, At least 2 of the following 1) gripping	Other sources of elbow pain, major neurological, inflammatory or systemic conditions; treatment by a healthcare practitioner	98%

Table 3-1 continued

							2) Palpation of lateral epicondyle 3) Stretching of forearm muscles 4) resisted wrist, 2nd or 3rd finger extension 5) reduced pain-free grip strength	within the previous 3 months; injections within the preceding 6 months; or major trauma, fracture or surgery in the last year.	
Dupuis *et al.* (2018)	RCT single-blind	Random number generator and block design	Blinded outcome assessment (participants asked not to discuss their treatment with assessor)	Sealed opaque envelopes	Yes; sample size adequate for 80% power	Cryotherapy group older	16-65years, symptoms <6weeks, Painful arc of movement, positive Neers or Kennedy-Hawkins and pain on resisted isometric external rotation, abduction, or positive Jobe's all present	Upper limb fracture, previous neck or shoulder surgery, cervical spine involvement, frozen shoulder, sign of full cuff tear, rheumatological, inflammatory or neurological disease	77%
Parle *et al.* (2017)	RCT single-blind pilot	Random number generator	Chief investigator and sonographer blinded to groups	Sealed opaque envelopes	No	Not done	Unilateral shoulder pain < 12 weeks, symptoms aggravated with active or resisted movement, unaccustomed increase in shoulder activity preceding symptoms, evidence of bursitis or tendinosis on ultrasound.	Dominant biceps pain, frozen shoulder, full thickness or large partial thickness tears and traumatic onset of pain.	100%
Rio *et al.* (2017)	RCT single-blind	Random number generator function of Microsoft Excel	Not stated	Unmarked, opaque envelopes	No	No difference	Elite and sub-elite volleyball and basketball athletes aged > 16 years, Diagnosis made clinically and radiologically	Other knee pathology, previous patellar tendon rupture or surgery, inflammatory disorders, metabolic bone diseases, Type II diabetes, use of fluoroquinolones or corticosteroids in the last 12 months	62%

Table 3-1 continued

Stasinopoulos & Stasinopoulos (2017)	RCT single-blind	"by drawing lots"	Outcome assessor blinded to groups	Not stated	No	No difference	Amateur tennis athletes. Clinical diagnosis of lateral elbow tendinopathy for at least 4 weeks.	Dysfunction in the shoulder, neck (radiculopathy), and/or thoracic region, local or generalized arthritis, neurologic deficit, radial nerve entrapment, limitations in arm functions, the affected elbow had been operated on, had received any conservative treatment in the 4 weeks before entering the study.	100%
Van Ark *et al.* (2016)	RCT single-blind	Random number generator function of Microsoft Excel	Not stated	Unmarked, opaque envelopes	No	No difference	Elite and sub-elite volleyball and basketball athletes over 16 years of age. Diagnosis made clinically and radiologically	Existence of other knee pathology, previous patellar tendon rupture or surgery, inflammatory disorders, metabolic bone diseases, Type II diabetes, use of fluoroquinolones or corticosteroids in the last 12 months, known familial hypercholesterolemia and fibromyalgia	62%
Rio *et al.* (2015)	RCT single-blind (cross-over)	Participants chose an envelope for order of intervention	Not stated	Unmarked, opaque envelopes	No	No difference	Volleyball players who were taking no medications. Diagnosis made clinically and radiologically	-	100%

Abbreviations; *BMI, body mass index; FABER, flexion abduction external rotation; FABER, flexion external rotation; IR, internal rotation, NPRS, Numerical Pain Rating Scale; RCT, randomised controlled trial.*

Table 3-2. Samples, characteristics of interventions and outcome measures of the included studies.

Author	Tendon Affected	Sample, mean/median age (range); %F	Symptom duration	Interventions	Treatment Duration (Follow-up)	Adherence to treatment	Outcome Measures
Clifford *et al.* (2019)	**Gluteal**	n=30; mean 59.3y (24y-86y); 90%	mean 23m	1. Isometric exercise (n=15) 2. Isotonic exercise (n=15)	12w (0, 4w, 12w)	70% of isometric group and 58% of isotonic group completed 80% of treatment sessions	(1) VISA-G (pain, function) (2) NPRS 0-10 for pain (3) EQ-5D-5L (QoL) (4) IPAQ-SF (5) Global Rating of Change (6) Pain Catastrophising Scale (7) HOOS
Holden *et al.* (2019)	**Patellar**	n=21; mean 26.5y (18y-40y); 41%	10-84m (mean 24m)	1. Isometric exercise (n=10) 2. Dynamic (isotonic) exercise (n=11)	Single session of each intervention (0 ,45 mins)	N/A	(1) Pain intensity during SLDS (0-10) (2) Pressure pain thresholds (tenderness) (3) Patellar tendon thickness (USS)
Vuvan *et al.* (2019)	**Wrist Extensors**	n=40; mean 48.5y (?y - ?y); 28%	2-8m (mean 4m)	1. Wait-and-see (n=19) 2. Isometric exercise (n=21)	8w (0, 8w)	87%	(1) Global rating of change (2) Tendon specific: Patient-rated tennis elbow evaluation (pain, function) (3) VAS 0-10 for pain (4) Pain-free grip strength (function) (5) Thermal and pressure pain threshold (nervous system sensitisation)
Dupuis *et al.* (2018)	**Rotator cuff**	n=43; mean 38.3y (18y-65y); 44%.	<6w	Weeks 0-2 1. Isometric exercise (n=20) 2. Ice therapy (n=23) Weeks 3-6 both groups same isotonic exercise programme	6 w (0, 2w, 6w)	Weeks 0-2 Exercise group 76% and Cryotherapy group 80%. Weeks 3-6 Exercise group 40%	(1) USS to measure acromiohumeral distance (2) Strength (3) ROM (4) DASH (function)

Table 3-2 continued

						and Cryotherapy group 70%.	(5) Tendon specific: Western Ontario Rotator Cuff Index (pain, strength, function, QoL, emotions)
Parle *et al.* (2017)	**Rotator Cuff**	n=20; mean 50y (20y-67y); 65%	<12w	1. Ice therapy (n=6) 2. Isometric exercise (n=7) 3. Ice therapy plus isometric exercise (n=7)	1w (0, 1w)	Unclear	(1) VAS 0-10 for pain (2) DASH (function) (3) Strength (arm forward flexion at 90deg) (4) Structural integrity (USS)
Rio *et al.* (2017)	**Patellar**	n=29; mean 23y (16y - 32y); 7%	1-120m (mean 35.8m)	1. Isometric exercise (n=13) 2. Isotonic exercise (n=16)	4w (0, daily pre- and post-exercise, 4w)	Unclear	(1) Pain during the SLDS (0–10) pre- and post-intervention (2) VISA-P (pain, function)
Stasinopoulos & Stasinopoulos (2017)	**Wrist Extensors**	n=34; mean 43y (?y - ?y); 56%	>4w (mean 6m)	1. Eccentric exercise (n=11) 2. Eccentric-Concentric exercise (n=12) 3. Eccentric-Concentric exercise + Isometric exercise (n=11)	4w (0, 4w, 8w)	Unclear	(1) VAS 0-10 for pain (2) pain-free grip strength (function) (3) VAS 0-10 for function
Van Ark *et al.* (2016)	**Patellar**	n=29; mean 23y (16y - 32y); 7%	1-120m (mean 35.8m)	1. Isometric exercise (n=13) 2. Isotonic exercise (n=16)	4w (0, 4w)	Unclear	(1) Pain during the SLDS (0–10) (2) VISA-P (pain, function)
Rio *et al.* (2015)	**Patellar**	n=6; median 27y (18y – 40y); 0%	Not stated	1. Isometric exercise (n=6) 2. Isotonic exercise (n=6) Same group performed both interventions	Single session of each intervention (0, 45min)	N/A	(1) Pain during the SLDS (0–10) (2) Strength (quadriceps maximal voluntary isometric contraction) (3) Measures of corticospinal excitability and inhibition

The clinical parameters assessed by each questionnaire in the outcome measures are stated in brackets. AOFAS: American Orthopaedic Foot and Ankle score; BPI: Brief Pain Inventory; DASH: Disabilities of the Arm, Shoulder and Hand; EQ-5D-5L: EuroQoL 5 Dimensions 5 Level index; F: females; GROC: Global Rating of Change; HOOS: Hip Disability and Osteoarthritis Outcome Score; IPAQ-SF: International Physical Activity Questionnaire – Short Form; M: months; MVIC: Maximum Voluntary Isometric Contraction; N/A: not applicable; NRS: Numeric Rating Scale; NPRS: Numeric Pain Rating Scale; PCS: Pain Catastrophising Scale; PRTEE: Patient-rated Tennis Elbow Evaluation; QoL: Quality of Life; ROM: Range of Movement; SLDS: Single Leg Decline Squat; USS: Ultrasound Scan; VAS: Visual Analogue Scale; VISA-A: Victorian Institute of Sport Assessment – Achilles tendon; VISA-G: Victorian Institute of Sport Assessment – Gluteal tendons; VISA-P: Victorian Institute of Sport Assessment – Patellar tendon; w: weeks; WORC: Western Ontario Rotator Cuff Index; y: years.

3.3.1 Quality assessment

Table 3-3 illustrates our assessment of internal validity, external validity, precision and overall quality of each study. Three studies were found to be of 'good' overall quality and seven of 'poor' quality.

3.3.1.1 Internal validity

Selection bias

All 10 studies were randomised and were thought to have 'low' risk of bias for 'random sequence generation' (see Table 3-1, 'randomisation method'). Risk of bias with regard to allocation concealment was considered 'low' in nine studies, where the authors specifically stated that sealed, opaque envelopes were used. The study by Stasinopoulos and Stasinopoulos (2017) was classified as 'unclear' risk as details were not provided.

3.3.1.2 Performance bias

None of the studies was double-blinded due to the inherent differences between the interventions making it impossible for patients to be blinded. However, where attempts were made to minimise the risk of performance bias introduced by patients not being blinded, those studies were labelled as 'low' risk. In the study by Holden et al. (2020) participants were blinded to the study hypothesis, and similarly in the study by Dupuis et al. (2018) participants were unaware of the treatment provided to other participants.

3.3.1.3 Detection bias

Blinding of outcome measures was thought to be sufficient ('low' risk) in studies where attempts were made to blind the assessors by (1) using independent assessors and (2) asking the participants not to disclose the nature of their treatment to assessors (Dupuis et al. 2018, Holden et al. 2020, Stasinopoulos and Stasinopoulos 2017, Vuvan et al. 2020). Where it was obvious that the outcome assessors were not blinded or where it was not mentioned, studies were labelled as 'high risk' (Clifford et al. 2019, Gatz et al. 2020, Parle et al. 2017, Rio et al. 2015, Rio et al. 2017, van Ark et al 2016).

Table 3-3. Quality assessment of included studies (internal validity, external validity, precision and overall quality)

Author	Internal Validity (Cochrane's Collaboration Tool for Assessing Risk of Bias)							External Validity	Precision	Overall Quality
	Selection Bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other			
	Random sequence generation	Allocation concealment	Blinding of participants and investigators	Blinding of outcome measures	Completeness of outcome data	Selective reporting				
Gatz *et al.* (2020)	Low	Low	High	High	Low	High	Low	Low	Low	Poor
Clifford *et al.* (2019)	Low	Low	High	High	Low	High	High	Low	High	Poor
Holden *et al.* (2019)	Low	Low	Low	High	Low	Low	Low	Low	Low	Good
Vuvan *et al.* (2020)	Low	Low	High	Low	Low	Low	Low	Low	Low	Good
Dupuis *et al.* (2018)	Low	Low	Low	Low	Low	Low	High	Low	Low	Good
Parle *et al.* (2017)	Low	Low	High	Low	Low	Low	High	Low	High	Poor
Rio *et al.* (2017)	Low	Low	High	High	High	Low	High	High	High	Poor
Stasinopoulos & Stasinopoulos (2017)	Low	Unclear	High	Low	Low	Low	Unclear	High	High	Poor
Van Ark *et al.* (2016)	Low	Low	High	High	High	Low	High	High	High	Poor
Rio *et al.* (2015)	Low	Low	High	Unclear	Low	Low	High	High	High	Poor

3.3.1.4 Attrition bias

Rate of follow-up completion was considered of ‘high ‘risk in the study by Rio et al. (2017) and van Ark et al. (2016) (62%). Reasons for dropouts/withdrawals of participants were adequately reported in all studies (‘low’ risk). The study by Gatz et al. (2020) was rated as ‘low’ risk of attrition bias despite the significant loss to follow-up (25% and 32% in the two groups) as the remaining participants were sufficient for the minimum sample sizes based on their power calculation.

3.3.1.5 Reporting bias

Eight studies were thought to be of ‘low’ risk of bias regarding reporting of results as they included clinically relevant outcome measures, adequate graphical illustration of their results and reporting of results of statistical tests. In the study by Clifford et al. (2019) no p values were reported for the primary outcome measure (‘high’ risk). In the study by Gatz et al. (2020) performance in two of the secondary outcome measures (Likert scale, Roles and Maudsley score) was not compared with statistical tests. Additionally, even though it constitutes part of the VISA-A questionnaire, no specific comparisons were carried out for pain, which is considered an important clinical symptom (‘high’ risk).

3.3.1.6 Other bias

Inclusion and exclusion criteria were thought to be adequate for all but two studies: Rio et al. (2015) did not use any exclusion criteria, and the exclusion criteria in Parle et al. (2017) were very limited. Comparison of baseline characteristics of the treatment groups was reported by all but one study (‘high’ risk; Parle et al. (2017)). Of the remaining eight studies, one found a significant difference in the mean age of the treatment groups (‘high’ risk; Dupuis et al. (2018)). Two studies included a mixture of participants with both acute and chronic tendinopathy (range of duration of symptoms 1–120 months), which may respond differently to treatment (‘high’ risk; Rio et al. (2017) and van Ark et al. (2016)). Even though cross-over trials can sometimes be susceptible to carry-over effects, the cross-over design of two of the studies (Holden et al. (2020) and Rio et al. (2015)) was considered unlikely to introduce bias as the participants only had one session of each intervention separated by an adequate time period. Adherence of participants to assigned treatment was low in the studies by Dupuis et al. (2018) and Clifford et al. (2019) (‘high’ risk; Table 3-2), while it was unclear in the studies by Parle et al. (2017), Stasinopoulos and Stasinopoulos (2017), Rio et al. (2017) and van Ark et al. (2016) (‘unclear risk’).

3.3.1.7 External validity

General, non-specific populations were used in all but studies but four which included athletes of specific sports (tennis, volleyball and basketball) and were therefore rated as 'high' risk as their findings cannot be generalised to the wider population (Rio et al. (2015), Rio et al. (2017), van Ark et al. (2016) and Stasinopoulos and Stasinopoulos (2017). In the remaining six studies, age ranges of participants were wide enough to allow for good generalisability. Clinically relevant assessment tools and outcome measures were used in all studies. The nature, frequency and intensity of treatments were considered appropriate in all studies.

3.3.2 Precision

Statistical power calculation prior to recruitment was performed in only four studies, where their sample size was adequate for at least 80% power (Gatz et al. (2020), Holden et al. (2020), Dupuis et al. (2018) and Vuvan et al. (2020)). All other studies were characterised as 'high' risk of precision bias. Levels of significance were set at p=0.05 in all studies.

Findings of included studies

Tables 3-4 and 3-5 summarise the findings along with levels of evidence for the overall results of each outcome measure for studies. Tables 3-6 and 3-7 display the treatment effect for pain of isometric exercise versus control.

Table 3-4. Findings of studies that assessed outcomes immediately after exercise (45 minutes post-intervention)

Treatment modes	Tendon affected	Author	Pain	Functional disability	ROM	Strength	QoL	Structural Integrity	Cortical inhibition
Isometric Exercise versus Isotonic Exercise	**Patellar**	Rio *et al.* (2015)	↓ (NRS)	-	-	↑	-	-	↑
		Rio *et al.* (2017)	↓ (NRS)	-	-	-	-	-	-
		Holden *et al.* (2019)	↔ (NRS)	-	-	-	-	↔	-
Overall Isometric versus Isotonic Exercise (Evidence Level)			**↔ (3)**	-	-	**↑ (3)**	-	**↔ (3)**	**↑ (3)**

Abbreviations*; NRS: numeric rating scale; QoL: quality of life, ROM: range of movement; ↓: lower at statistical significance*; ↑: higher at statistical significance*; ↔: no statistically significant difference. *with the first vs the second intervention*

Table 3-5. Findings of studies reporting short-term outcomes (up to 12 weeks of follow-up)

Acute/Chronic Tendinopathy	Treatment modes	Tendon affected	Author (year)	Pain	Functional disability	ROM	Strength	Satisfaction	Structural Integrity	QoL
Acute	**Combined Isometric Exercise/Ice Therapy Vs Ice Therapy**	**Rotator Cuff**	Parle et al. (2017)	↔ (VAS)	↔ (DASH)	-	↔	-	↔	-
	Isometric Exercise Vs Ice	**Rotator Cuff**	Parle et al. (2017)	↔ (VAS)	↔ (DASH)	-	↔	-	↔	-
			Dupuis et al. (2018)	↔ (BPI)	↔ (DASH)	↔	↔	-		↔ (WORC)
	Overall Isometric Exercise Vs Ice (Evidence Level)			**↔ (3)**	**↔ (3)**	**↔ (3)**	**↔ (3)**	**↔ (3)**	**↔ (3)**	**↔ (3)**
Chronic	**Isometric Vs Isotonic Exercise**	**Patellar**	Van Ark et al. (2016)	↔ (NRS)	↔ (VISA-P)	-	-	↔ (GROC)	-	-
		Greater Trochanteric Pain Syndrome	Clifford et al. (2019)	↔ (NRS)	↔ (VISA-G)	-	-	↔ (GROC)	-	↔ (EQ-5D-5L)
	Overall Isometric Vs Isotonic Exercise (Evidence Level)			**↔ (3)**	**↔ (3)**	-	-	**↔ (3)**	-	**↔ (3)**
Chronic	**Combined Isometric/Isotonic Exercise Vs Isotonic Exercise**	**Wrist extensors**	Stasinopoulos (2017)	↓ (VAS)	↓ (pain free grip strength)	-	-	-	-	-
		Achilles	Ganz et al. (2020)	-	↔ (VISA-A, AOFAS)	-	-	-	-	-
	Overall Combined Isometric/Isotonic Exercise Vs Isotonic Exercise (Evidence Level)			**↓ (3)**	**↔ (3)**	-	-	-	-	-
	Isometric Exercise vs No Treatment	**Wrist extensors**	Vuvan et al. (2020)	-	↔ (pain free grip strength) ↓ (PRTEE)	-	-	↔ (GROC)	-	-

Table 3-6. Mean values of pain scales and treatment effect for pain of isometric exercise vs control (isotonic exercise); studies assessing outcomes immediately after exercise (45 minutes post-intervention)

Acute/Chronic	Treatment modes	Tendon affected	Author (year)	Pain scale	Scale range	Isometric Group pain score		Control Group pain score		Mean treatment effect for pain [CI 95%]	P <0.05
						Baseline (1)	Post-intervention (2)	Baseline (3)	Post-intervention (4)		
Chronic	Isometric vs Isotonic Exercise	Patellar	Rio et al. (2015)	NRS (during SLDS)	0-10	7	0.2	6.3	3.8	-4.3 [-1.2, -7.4]	Yes
			Rio et al. (2017)	NRS (during SLDS)	0-10	5	3.2	5	4.1	-0.9 [-1.1, -0.7]	Yes
			Holden et al. (2019)	NRS (during SLDS)	0-10	5	4.2	4.3	3.2	+0.3 [1.3, -0.7]	No

Abbreviations; *NRS, Numeric Rating Scale; SLDS, single leg decline squat*

Table 3-7. Mean values of pain scales and treatment effect for pain of isometric exercise vs control (isotonic exercise, ice or no treatment); outcomes in the short-term (up to 12 weeks)

Acute/Chronic	Treatment modes	Tendon affected	Author (year)	Pain scale	Scale range	Isometric Group pain score		Control Group pain score		Mean treatment effect for pain (2–1) – (4–3)[CI 95%]	P < 0.05
						baseline (1)	longest follow-up (2)	baseline (3)	longest follow-up (4)		
Acute	**Combined isometric Exercise/Ice Therapy Vs Ice Therapy**	**Rotator Cuff**	Parle *et al.* (2017)	VAS	0-10	4.8	3.7	5.5	4.5	-0.1 [N/A]	No
	Isometric Exercise Vs Ice	**Rotator Cuff**	Parle *et al.* (2017)	VAS	0-10	6.3	4.5	5.5	4.5	-0.8 [N/A]	No
			Dupuis *et al.* (2018)	BPI	0-10	3.2	1.6	2.7	1.2	-0.1 [-1.2, 1]	No
Chronic	**Isometric Vs Isotonic Exercise**	**Patellar**	Van Ark *et al.* (2016)	NRS	0-10	6.3	4	5.5	2	+0.5* [-1.6, 2.6]	No
		Greater Trochanteric Pain Syndrome	Clifford *et al.* (2019)	NRS	0-10	5.9	3.9	5.9	3.2	+0.7 [-0.7, 1.7]	No
Chronic	**Combined Isometric/Isotonic Exercise Vs Isotonic Exercise**	**Wrist extensors**	Stasinopoulos & *Stasinopoulos* (2017)	VAS	0-10	6.9	1.6	6.9	2.9	-1.3 [-0.8, -1.9]	Yes

CIs have been calculated (see Statistical analysis section).
*Values at baseline and follow-up are median and not mean; therefore, the 0.5 value (also median) reported by the authors cannot be obtained from the calculation

Lateral elbow tendinopathy

Isometric exercise versus no treatment

Short-term outcomes

One good-quality study compared (unsupervised) isometric exercise with no treatment for lateral elbow tendinopathy for 8 weeks (Vuvan et al. 2020). The isometric exercise group had a lower PRTEE score at 8 weeks compared with the 'wait and see' group, suggesting less functional disability. However, pain-free grip strength test, which we also classified as a test for 'functional disability', was similar between the two groups at 8 weeks. Similarly, GROC was also similar in the two groups at follow-up, even though 86% of participants in the isometric group reported an overall improvement versus 63% in the no treatment group (difference non-statistically significant). Pressure pain thresholds, heat pain thresholds and cold pain thresholds were also similar between the two groups at 8 weeks. Overall, there is insufficient evidence for definitive conclusions on the short-term effectiveness of isometric exercise compared with no treatment in chronic lateral elbow tendinopathy. A single study of good overall quality (limited evidence; level 3) reported conflicting results with regard to functional disability and no difference in satisfaction.

Combined isometric/isotonic exercise versus isolated isotonic exercise

Short-term outcomes

One study of poor overall quality compared combined isometric plus eccentric-concentric exercise versus exercise for 4 weeks in amateur tennis players with chronic lateral elbow tendinopathy (Stasinopoulos and Stasinopoulos 2017). Within all three treatment groups, both pain (Visual Analogue Scale (VAS)) and functional disability (pain-free grip strength) improved significantly at 4 weeks and 8 weeks. The improvement in the combined isometric/eccentric-concentric group was greater than the other two groups at both follow-up time points.

Achilles tendinopathy

Combined isometric/isotonic exercise versus isolated isotonic exercise

Short-term outcomes

One study of poor overall quality compared combined isometric and isotonic (eccentric) exercise versus isolated isotonic (eccentric) exercise for 3 months in patients with chronic Achilles tendinopathy (Gatz et al. 2020). However, the VISA-A improved significantly at 3 months compared with baseline in both groups and the American Orthopaedic Foot and Ankle Score (AOFAS) score in the isotonic-only group. No differences were found between the two groups at follow-up (1 and 3 months) in functional disability (VISA-A)

and (AOFAS); however, the VISA-A improved significantly at 3 months compared with baseline in both groups and the AOFAS score in the isotonic-only group.

Rotator cuff tendinopathy

Isometric exercise versus ice therapy

Short-term outcomes ≤ 12 weeks

One good-quality and one poor-quality study compared isometric exercise with ice therapy (cryotherapy) in patients with acute rotator cuff tendinopathy. Parle et al (2017) randomised participants to isometric exercise, ice therapy or a combination of both interventions for 1 week. No between-group differences were identified at 1-week follow-up with regard to pain (VAS), functional disability (DASH questionnaire), muscle strength or structural integrity (ultrasound scanning (USS)). All three groups demonstrated statistically significant improvements in all outcome measures at 1 week compared with baseline. In the study by Dupuis et al. (2018) participants were treated with either ice therapy or isometric exercise for 2 weeks. Both groups then completed isotonic exercise for a further 4 weeks. Both groups had statistically significant improvements in pain (Brief Pain Inventory), strength, ROM, functional disability (DASH) and QoL (WORC) at 2-weeks and 6-weeks follow-up compared with baseline, but there were no significant differences between groups at either time point.

Patellar tendinopathy

Isometric exercise versus isotonic exercise

Immediate post-intervention outcomes

One good-quality and two poor-quality studies compared the immediate, post-intervention effects of isometric and isotonic exercise in patellar tendinopathy following a single session of loading. Rio et al. (2015) performed a cross-over study of six jumping athletes with patellar tendinopathy (duration of symptoms not reported) comparing the two modes of exercise. All outcome measures (pain, strength and cortical inhibition) were recorded at baseline and immediately post-intervention, with pain and strength also recorded 45-min post-intervention. Pain (Numeric Rating Scale (NRS)) during a single leg decline squat (immediately post-intervention) decreased significantly from baseline for both isometric exercise and isotonic exercise however, the reduction was statistically greater in the isometric exercise group. This reduction was sustained at 45 min in the isometric exercise group, but not in the isotonic exercise group. Similarly, isometric exercise was associated with a statistically significant increase in strength (maximum voluntary isometric contraction torque) both immediately post-intervention and at 45 min compared with

baseline, which was not observed in the isotonic group. Finally, short-interval intracortical inhibition was found to be significantly higher (more favourable) post isometric exercise versus post isotonic exercise compared with baseline at statistical significance. Rio et al. (2017) compared the numerical pain rating score (NPRS) during a single leg decline squat immediately after intervention in a group treated with isometric exercise and a group treated with isotonic exercise over a 4-week period. The mean reduction in pain immediately post-intervention versus preintervention was significantly greater in the isometric group. In a cross-over study by Holden et al. (2020) participants performed a single session of either isometric or isotonic exercise and outcome measures were recorded immediately post-intervention and at 45 min. There were no differences in pain (NPRS) during a single leg decline squat immediately post-intervention or at 45 min compared with baseline with either isometric or exercise. There were no between-group differences at the two time points. Similarly, pressure point thresholds of the patellar tendon were similar at baseline, immediately post-intervention and at 45 min without intergroup differences. Finally, there were no changes in patellar tendon thickness on USS before and after intervention with isometric and isotonic exercise

Patellar tendinopathy

Isometric exercise versus isotonic exercise

Short-term outcomes (≤ 12 weeks)

One poor-quality study compared short-term effects of isometric and isotonic exercise in chronic patellar tendinopathy. Van Ark et al. (2016) conducted a study in jumping athletes with patellar tendinopathy where participants received either an unsupervised isometric or isotonic exercise programme for 4 weeks. Although both groups improved at 4 weeks compared with baseline in terms of all pain (NPRS), functional disability (VISA-P questionnaire) and satisfaction (GROC), no significant between-group differences were observed. Range of duration of symptoms was reported as 1–120 months (mean 35.8 months).

Gluteal tendinopathy

Isometric exercise versus isotonic exercise

Short-term outcomes (≤12 weeks)

One poor-quality study assessed the short-term benefits of isometric versus isotonic exercise in gluteal tendinopathy. Clifford et al. (2019) randomised patients with greater trochanteric pain syndrome (GTPS) to either isometric or isotonic exercise (both

unsupervised) for 12 weeks. In this pilot RCT, descriptive statistics suggested there were no observed differences between the two groups at either 4-week or 12-week follow-up even though p values were not used. Both groups had similar improvements in functional disability (VISA-G), pain (NPRS) and satisfaction (GROC) at both follow-up time points compared with baseline. The remainder of outcome measures (Pain Catastrophising Scale, Hip Disability and Osteoarthritis Outcome Score (HOOS), EuroQoL 5 Dimensions 5 Level Index, and International Physical Activity Questionnaire-Short Form) were also similar between groups at both time points with minimal changes between baseline and 12 weeks. The only statistically significant benefits were observed between baseline and 12 weeks in the pain and QoL subcomponents of the HOOS questionnaire in the isotonic exercise group.

Pooled results

Where two or more studies compared the same interventions at similar follow-up time points, their results were combined qualitatively based on direction of effect to make conclusions on the effectiveness of interventions.

Isometric exercise versus ice therapy

Overall, based on limited evidence (level 3), isometric exercise is not associated with short-term benefits in pain, functional disability, ROM, strength, QoL and structural integrity compared with ice therapy in acute rotator cuff tendinopathy.

Isometric exercise versus isotonic exercise

Based on limited evidence (level 3), immediate post-intervention pain, pressure point thresholds and tendon structural integrity appear to be similar with isometric and isotonic exercise in patellar tendinopathy. Based on a single study of good quality, there may be no immediate post-intervention benefits in pain with either isometric or isotonic exercise. Compared with isotonic exercise, isometric exercise may be associated with increased strength and cortical inhibition immediately after exercise; however, this is based on a single study of poor quality (Rio et al. 2015). Importantly, the results of all three studies are based on assessment before and immediately following exercise sessions. Figure 3-2 illustrates a forest plot for the comparison between isometric and isotonic exercise with regard to the immediate post-intervention improvement in reported pain for patellar tendinopathy. Statistical analysis showed no significant difference between the two interventions (p=0.19), which reinforces the aforementioned qualitative conclusion.

Study	Isometric exercise Mean	SD	Total	Isotonic exercise Mean	SD	Total	Weight	Mean Difference IV, Random, 95%CI
Holden et al. (2020)	-0.8	2.5	21	-1.1	2.5	21	34.1%	0.3 [-1.21, 1.81]
Rio et al. (2015)	-6.8	1.2	6	-2.5	3.8	6	16.0%	- 4.3 [-7.49, - 1.11]
Rio et al. (2017)	-1.8	0.4	10	-0.9	0.3	10	49.9%	-0.9 [-1.21, - 0.59]
Total (95% CI)			**37**			**37**	**100%**	-1.03 [-2.57, 0.50]

Heterogeneity: $Tau^2 = 1.21$; $Chi^2 = 6.77$, df =2 (p =0.03); $I^2 = 70\%$

Test for overall effect: Z = 1.32 (P = 0.19)

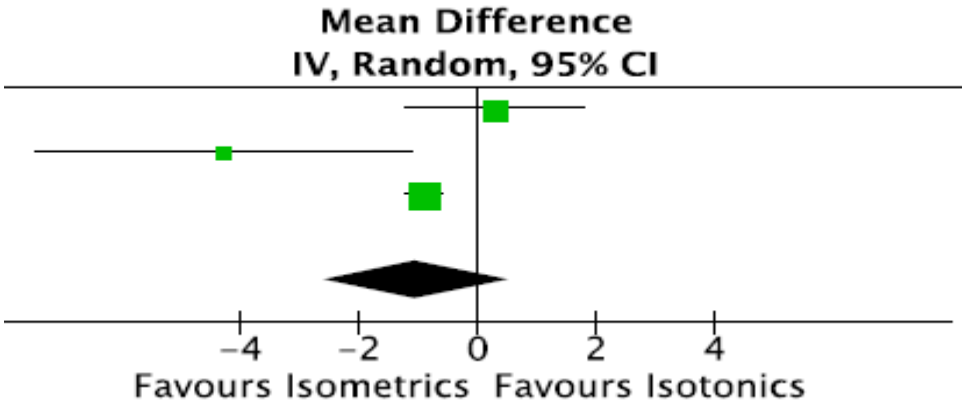

Figure 3-2. Forest plot for the comparison between isometric and isotonic exercise in patellar tendinopathy

With regard to short-term follow-up, based on limited evidence (level 3), isometric and isotonic exercises appear to be similar in terms of their benefits in pain, functional disability, satisfaction and QoL in chronic tendinopathy.

Combined isometric/isotonic exercise versus isolated isotonic exercise

Based on two studies of poor quality (limited evidence; level 3), combined isometric plus isotonic exercise may be superior to isolated isotonic exercise in the short term for pain but not for functional disability (conflicting evidence). This conclusion, however, may be biased due to the different types of isotonic exercise used (eccentric only versus concentric-eccentric) as control in the two studies. Furthermore, the heterogeneity in the last two grouped comparisons in terms of tendinopathy location (patellar versus gluteal and lateral elbow versus Achilles) in study participants is an important limitation and these findings should be interpreted with caution.

3.4 Discussion

This systematic review found that isometric exercise was not superior to isotonic exercise in terms of pain in chronic tendinopathy either immediately after a single session or in the short term (follow-up ≤ 12 weeks). These findings are based on limited evidence (level 3) and they arise from patients with tendinopathies of different sites, except for the conclusion from immediate post-intervention outcomes, which are specific to patellar tendinopathy. Analysis of secondary outcomes also failed to demonstrate any significant differences either immediately or short term. Additionally, we found no significant short-term benefits of isometric exercise compared with ice therapy for acute rotator cuff tendinopathy with regard to any of our primary or secondary outcome measures (limited evidence; level 3).

Three studies have investigated the immediate effect of both isometric exercise and isotonic exercise for pain in patellar tendinopathy with variable results (Holden et al. 2020, Rio et al. 2015, Rio et al. 2017). Rio et al. (2015) reported a significant reduction in pain following isometric exercise (mean=6.8 points), with a smaller reduction observed following isotonic exercise (mean=2.5 points) during a single leg decline squat. Both groups demonstrated improvement greater than the clinically important difference of 2 points (Farrar et al. 2001). A subsequent study by Rio et al. (2017) in jumping athletes found that isometric exercise was more effective than isotonic exercise at reducing pain (mean=1.8 versus 0.9 points). Holden et al. (2020) reported a pain reduction following isometric exercise (mean=0.8 points) and isotonic exercise (mean=1.1 points) in a study in which the methodology was almost identical to Rio et al. (2015), but with a larger population. Pearson et al. (2020) compared two different isometric loading protocols for patellar tendinopathy (10-s and 40-s holds) and an immediate reduction in pain (mean=1.7 points) was reported for both groups. Two observational studies for plantar fasciopathy Riel et al. (2018) and Achilles tendinopathy (O'Neill et al. 2018), both used a similar isometric loading protocol to Rio et al. (2015). However, the immediate pain response was variable in both studies. Isometric exercise was not superior to either isotonic exercise or walking in plantar fasciopathy, with only 15% of participants reporting a clinically meaningful pain reduction following isometric loading (Riel et al. 2018). For Achilles tendinopathy, 45-s isometric holds of the ankle plantar flexors resulted in a 1-point reduction in pain in some participants, with others reporting an immediate increase in pain (O'Neill et al. 2018). Since the publication of this review, two further studies for Achilles tendinopathy haven been completed (Bradford et al. 2021, Van der Vlist et al. 2020). No

significant reduction in pain was reported during hopping following either isometric or isotonic exercise and no between-group difference was identified (Van der Vlist et al. 2020). Similarly, in a cross-over pilot study with 11 participants, Bradford et al. (2021) reported that isometric plantarflexion exercises with the knee either fully extended or flexed to 80 degrees resulted in no significant difference in pain reduction between positions. Moreover, only 4 participants reported a clinically significant reduction in pain. Taken together, there is conflicting evidence that isometric exercise provides significant, immediate pain relief in chronic tendinopathy. The large pain reductions observed in a single study of six male volleyball players with patellar tendinopathy have not been replicated and therefore may not be generalisable to other tendinopathy populations.

We examined the short-term effects (≤ 12 weeks) of isometric exercise in comparison to any another treatment or no treatment in tendinopathy. Overall, isometric exercise was found to be effective in providing pain relief and improving functional disability, but there was no evidence to demonstrate that it is superior to isotonic exercise. Clifford et al. (2019) compared isometric exercise with isotonic exercise for GTPS and found no difference between groups at either 4 or 12 weeks. van Ark et al. (2016) also reported no difference between isometric and isotonic exercise after 4 weeks in patellar tendinopathy. In both studies, the volume of loading or time under tension (TUT) was identical in each group for the duration of the intervention. Given that no difference in pain or function was observed between isometric and isotonic loading after 4 or 12 weeks, the specific muscle contraction type may be less important when TUT is equal. This appears logical, and as discussed in Chapter 1-7, tendon will lengthen or ‘strain’ in a similar manner when subjected to loading regardless of the muscle contraction type (Bohm et al. 2015, Magnusson and Kjaer 2019). The findings of this chapter also imply that isometric exercise can be used for progressive tendon loading in specific patient populations and not only for immediate pain relief. For example, individuals with GTPS and co-existing moderate-to-severe hip osteoarthritis typically exhibit reduced hip joint range of motion and are unable to complete isotonic exercises which require repetitive large hip abduction movements. The isotonic exercise programme presented in Chapter 2 could be utilised for such individuals.

In lateral elbow tendinopathy a combined programme (isometric plus eccentric-concentric exercise) was more effective after 4 weeks than either an eccentric programme or an eccentric-concentric programme (Stasinopoulos and Stasinopoulos 2017). The combined programme consisted of 56 minutes of loading per session compared with 22 minutes for the other two programmes. Gatz et al. (2020) compared eccentric exercise with eccentric

exercise combined with isometric exercise for Achilles tendinopathy. No additional benefit was observed with the addition of isometric exercise at 1 or 3 months which is surprising as TUT was longer in the combined group. A possible explanation for the differences between both studies is related to the loading intensity. For the lateral elbow, progressive loading was achieved by adding weights. However, for the Achilles no external weight was used, and load was progressed in both groups from bilateral to unilateral loading using only bodyweight. Progressive tendon loading appears to be critical in the management of tendinopathy, and while this may be achieved by increasing TUT, it should be considered in conjunction with load intensity.

The mechanisms by which loading provides pain relief in tendinopathy are not fully understood, reflecting the complex multifactorial nature of tendon disease. Exercise-induced hypoalgesia (EIH) occurs in response to exercise, including isometric exercise, in healthy populations and is believed to occur via a number of pathways including descending pain inhibition (Hoffman et al. 2004, Naugle et al. 2014). In contrast, isometric exercise does not consistently induce EIH and is absent in some individuals with chronic musculoskeletal pain (Bonello et al. 2021, Naugle et al. 2012, Rice et al. 2019, Wewege et al. 2021). Thus far, no studies have measured EIH in tendinopathy but isometric exercise can increase pain in chronic widespread pain, secondary to a deficiency of central inhibition (Hoeger Bement et al. 2011, Naugle et al. 2012, Staud et al. 2005). Approximately 30% of individuals with tendinopathy fail to make significant improvements with loading programmes (Millar et al. 2021). Impaired or complete absence of EIH may partly explain the variable response to loading often observed within and across different tendinopathy populations. Central sensitisation (a physiological phenomenon characterised by widespread hypersensitivity resulting from an augmented response of central neurons to receptor activity) can also be a feature of tendinopathy (Eckenrode et al. 2019, Plinsinga et al. 2015). The presence of central sensitisation provides a further explanation as to why some individuals experience an increase in pain following isometric and isotonic exercise. This hypothesis would possibly be supported by the findings of Coombes et al. (2016) in lateral elbow tendinopathy where the response to isometric exercise was variable with an immediate increase in pain intensity reported following isometric exercise above an individual's pain free threshold.

Patient characteristics relating to general health are not routinely measured in tendinopathy studies but may also be associated with a poorer response to loading programmes and treatment outcome (Rio et al. 2020). Older and more sedentary individuals with chronic

tendinopathy frequently have associated health co-morbidities (Tilley et al. 2015). Metabolic factors such as diabetes, hyperlipidaemia and high BMI have been associated with tendinopathy (Gaida et al. 2009, Ranger et al. 2016, Yang and Qu 2018). Further research identifying which characteristics are more likely to affect the response to loading programmes and treatment outcome in both GTPS and tendinopathy are required.

3.4.1 Strengths and limitations

Despite the small number of studies included in this review, it was possible to perform a meta-analysis for the immediate effect of isometric exercise for pain in patellar tendinopathy. Clinicians should also be able to apply the findings of this review to clinical practice and feel confident that isometric exercise can be used, not only for acute pain relief, but also for progressive tendon loading.

Despite the inclusion of all relevant studies in the literature and the detailed quality assessment performed, we recognise the limitations of our systematic review. First, the majority of studies did not include a control group that received no treatment; therefore, the effect of time (natural healing/recovery) and its contribution to the improvement in outcome measures observed with the different exercise regimens could not be assessed. Additionally, due to the small number of eligible studies, our results were only based on limited evidence and were generalised to all types of tendinopathy with the assumption that they all share the same underlying pathophysiology and respond similarly to the same types of loading. Finally, the lack of homogeneity in loading programmes, follow-up time points and outcome measures precluded the conduct of quantitative analyses for the majority of comparisons.

3.5 Conclusion

This is the first systematic review to assess the effectiveness of isometric exercise in the management of tendinopathy. No strong evidence was found that isometric exercise is superior for immediate or short-term pain relief when compared with isotonic exercise, other treatments or no treatment. However, further well-designed RCTs with larger sample sizes and long-term follow-up are needed. The response to isometric exercise appears to be variable both within and across tendinopathy populations. The reasons for this variability following loading are unclear, but could be related to the presence or absence of certain

clinical characteristics, including health co-morbidities. In the next chapter the prevalence of such characteristics will be investigated for individuals with GTPS.

Chapter 4

Clinical characteristics associated with greater trochanteric pain syndrome: a cross-sectional survey

4.1 Aims and introduction

This chapter presents the final study in the thesis, an on-line survey completed by 261 individuals with GTPS. Results of the pilot study (Chapter 2) demonstrated that over 35% of patients with GTPS failed to improve following 12 weeks of either isometric or isotonic exercise. The reasons for this remain unclear, however, the presence of certain clinical characteristics may have affected the treatment outcome. In this chapter, clinical data relating to health co-morbidities, physical activity level, co-existing physical symptoms (pain sites, sleep disturbance, pain intensity during activity), disability and psychological factors (kinesiophobia, anxiety and depression) were gathered and analysed. Although this study was unable to determine which factors may contribute to a poor treatment outcome in GTPS, the prevalence of clinical characteristics was established. Respondents were also divided into subgroups based on age group and physical activity level for further evaluation.

The prevalence of tendinopathy increases with age, with older individuals ($\geq$ 45 years) more frequently affected than younger individuals (< 45 years) (Albers et al. 2016, Riel et al. 2019). Greater trochanteric pain syndrome (GTPS) affects 24% of women and 8% of men aged 50-79 years (Segal et al. 2007). Participants included in clinical trials with GTPS are typically female and older than 40 years. Rompe et al. (2009) did not report the age range of study participants, however the mean age was 46 years. Post-menopausal females, a population which is almost exclusively middle-aged and older, were included in the studies by Cowan et al. (2022) and Ganderton et al. (2018). In the LEAP trial, over 200 participants aged 35-70 years were recruited (Mellor et al. 2018). In the pilot study (Chapter 2), only 10% of participants were younger than 40 years (Clifford et al. 2019). Anderson et al. (2001) highlighted that younger females, especially running athletes, also develop this condition and the clinical experience of the PhD student (CC) would support this view. To summarise, the prevalence of GTPS in younger individuals is unknown and there is currently minimal clinical data describing the clinical presentation of this age group.

Active individuals typically develop tendinopathy secondary to overuse (Millar et al. 2021). However, lifestyle and metabolic factors are believed to contribute to the development of symptoms in people with a sedentary lifestyle (Tilley et al. 2015). Previous studies have reported that active and sedentary populations develop GTPS (Blank et al. 2012, Plinsinga et al. 2018, Plinsinga et al. 2020, Rompe et al. 2009). Up to one third of

individuals with Achilles tendinopathy were also found to be inactive (Corrigan et al. 2018, Rolf and Movin 1997). The World Health Organisation (WHO) currently recommends adults undertake at least 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity physical activity per week (Bull et al. 2020). A direct comparison between the clinical characteristics of sedentary and active individuals with GTPS has not been completed and represents a gap in the current literature.

Psychological factors including kinesiophobia, anxiety and depression have been associated with tendinopathy (Mallows et al. 2017). In Achilles tendinopathy, kinesiophobia has a prevalence of 38 - 76% (Chimenti et al. 2021, Corrigan et al. 2018). In a study of 40 people with gluteal tendinopathy, more than 50% had kinesiophobia, 25% were classified as having anxiety and 5% with depression (Plinsinga et al. 2020). Although psychological factors are believed to increase the risk of chronicity in musculoskeletal pain, strong evidence of such a relationship has yet to be established in tendinopathy (Martinez-Calderon et al. 2020, Stubbs et al. 2020). Determining the prevalence of kinesiophobia, anxiety and depression in a large population will provide further insight as to their potential importance in GTPS. The prevalence of these psychological factors in younger and older individuals and sedentary and active individuals will also be investigated.

The importance of measuring the clinical characteristics of participants in tendinopathy research has been recognised (Rio et al. 2020). As well as psychological factors, additional musculoskeletal pain sites are also poorly reported (McAuliffe et al. 2021). Over 80% of individuals with a musculoskeletal condition have additional sites of pain (Kamaleri et al. 2008). Localised pain at the site of the involved tendon is often a prerequisite for inclusion in tendinopathy research. However, the prevalence of additional musculoskeletal pain sites has not been investigated. In fact, participants with widespread pain or additional musculoskeletal conditions are frequently excluded from tendinopathy studies (McAuliffe et al. 2021). As a higher number of pain sites has been associated with poorer outcome in other musculoskeletal conditions (Hott et al. 2019, Kamaleri et al. 2008, Mallen et al. 2007), establishing their prevalence in GTPS will be of value.

Social media use has increased considerably in recent years with 71% of the UK population now regular users (Reuter 2020). As a consequence, it is a frequently utilised and effective method for identifying and recruiting participants in clinical research (Arigo

et al. 2018, Reuter 2020). Surveys are a cost-efficient method of conducting research, enabling a large amount of information to be collected over a short time period. This can be appealing to researchers as recruitment into clinical trials is often slow. Facebook, Twitter and Instagram are amongst the most popular social media platforms (Arigo et al. 2018). Facebook is an effective recruitment tool for research studies seeking to target middle-aged and older individuals (Arigo et al. 2018). Almost 80% of this age group use Facebook which is significantly higher than other platforms (Singh et al. 2019). Guthrie et al. (2019) successfully recruited post-menopausal women via Facebook, a demographic commonly affected by GTPS. Twitter enables widespread conversation and the sharing of ideas and only 10% of Twitter accounts are private (Wasilewski et al. 2019). This assists recruitment by providing less restricted access to potential participants and by facilitating 'snowball' sampling through the "retweet" function. A retweet involves sharing another person's message or 'tweet'. Messages that are retweeted will reach a wider audience, thus enabling a greater number of people to view the original tweet (Arigo et al. 2018). Hashtags (#) can also be used to precede a word and collate information about a specific topic. Users who search for a specific word or 'click' on the hashtag will be able to view all relevant tweets that include this specific hashtag. Instagram is one of the fastest growing social media channels, with an estimated one billion users worldwide (Kühne and Zindel 2020). Similar to Facebook, Instagram allows 'targeting' by user characteristics, which can increase the likelihood of a study advert being viewed by the target audience (Arigo et al. 2018). Younger adults make up a large proportion of the active users for Twitter and Instagram and have been successfully recruited through both platforms (Arigo et al. 2019, Wisk et al. 2019). For the current study, targeting and recruiting adults of all relevant age groups with GTPS should be feasible through these three social media platforms.

The first aim of this study was to compare the clinical characteristics, including health co-morbidities, co-existing physical symptoms (number of pain sites, sleep disturbance, pain intensity during activity), disability and psychological factors (kinesiophobia, anxiety and depression) between i) younger individuals (< 40 years) and older individuals (≥ 40 years) and ii) sedentary and active individuals with GTPS. The second aim was to identify if any clinical characteristics are associated with, and able to predict, disability, kinesiophobia, anxiety or depression in GTPS.

The first hypothesis was that younger individuals (< 40 years) will have fewer health co-morbidities, number of pain sites, lower disability, kinesiophobia, depression, anxiety and lower pain intensity during activity compared to older individuals (≥ 40 years). The second

hypothesis was that sedentary individuals will have a greater number of health co-morbidities, pain sites, higher disability, kinesiophobia, depression, anxiety and higher pain intensity during activity compared to active individuals. For the purpose of this study, sedentary individuals were classified as those who perform < 150 minutes of physical activity per week and active individuals ≥ 150 minutes of physical activity per week.

4.2 Methods

4.2.1 Study design

Due to the COVID-19 pandemic, clinical trial recruitment involving face-to-face interviews with participants was not permitted within NHS Greater Glasgow and Clyde. Therefore, a cross-sectional survey was designed, which was hosted by Online Surveys, (www.onlinesurveys.ac.uk), a platform advised for use by the University of Glasgow (UoG). An advert for the study was shared electronically on Facebook, Twitter and Instagram (Appendix 18). By clicking on a uniform resource locator (URL) link, participants were directed to the survey (Appendix 19). Participation in the survey was voluntary. Informed consent was required to start the survey and was given by selecting 'yes' on the first page of the survey. If 'no' was selected, participants were directed away from the survey and would not be able to answer the questions. This was a 'one-off' on-line survey taking approximately 10-15 minutes to complete. Individuals were not specifically targeted during recruitment; no personal or identifiable participant information was collected and all responses were anonymous. Participants were required to answer all questions. Prompts were given for unanswered questions, so if a question was missed they would be unable to move onto the next page. Participants were able to move backwards and forwards through the survey and change their answers if required. If they exited the survey before completion, they were advised that they could return and complete at a later date. An on-screen message displayed the expiry date for the survey, after which time the participant would not be able to return and complete. If participants started but did not complete the survey, responses were not included in the final analysis. The survey was open from 2nd March 2021 to 30th March 2021.

4.2.2 Ethics

The study was approved by the University of Glasgow Ethics Committee, Project No: 200200037 (Appendix 20).

4.2.3 Eligibility Criteria

Males and females aged 18 years or older and currently experiencing lateral hip pain were eligible to participate. The study advert asked four main questions:

- Is the side of your hip painful to touch?
- Is it painful when you lie on your side?
- Have you been diagnosed with Trochanteric bursitis, Gluteal tendinopathy or Greater Trochanteric Pain Syndrome (GTPS)?
- Does the pain at the side of your hip affect your daily activities and quality of life?

If participants were able to answer 'yes' to any of these four questions, they were eligible to participate. These questions were selected to increase the probability of participants having pain due to GTPS rather than another condition. Pain on direct palpation and pain with side-lying are both common in individuals affected by GTPS (Fearon et al. 2013).

4.2.4 Recruitment

Participants were recruited through social media platforms (Facebook, Twitter, and Instagram). Using multiple platforms is recommended and has been shown to increase recruitment reach (Wisk et al. 2019). The existing personal Twitter account of the PhD student (CC) was used to advertise the survey. Facebook and Instagram accounts were created specifically for this study.

Twitter

A message was posted from the PhD student's personal account. The study advert and URL link which would direct participants to the survey were included in the post. The message was as follows:

'Do you have pain at the side of the hip?' We are looking for people to participate in an on-line survey #lateralhippainsurvey @UoGlasgow. It is anonymous and takes 10-15 minutes to complete. Please retweet.
https://glasgowresearch.onlinesurveys.ac.uk/lateral-hip-pain-survey

The following hashtags were also used, #glutealtendinopathy, #lateralhippain, #trochantericbursitis, #greatertrochantericpainsyndrome, #hippain. Twitter accounts of selected healthcare professionals and organisations, some with large follower bases, e.g. Versus Arthritis (36,400 followers), were also 'tagged' in the post to optimise sample

diversity. More than 70% of people use the internet in the evening and posting messages at this time can improve engagement (Singh et al. 2019, Wasilewski et al. 2019). Messages were therefore posted in the evening to maximise the impact of the tweet and positively affect recruitment. After 10 days a further message was posted which served as a 'reminder'.

Facebook

A Facebook page was created specifically for the study. A personal account was opened by the PhD student and the page was linked to the study advert and URL link. Specific groups were found by typing keywords into the main search box. For example, by using the term 'hip pain' groups named 'Trochanteric Bursitis (hip)' (6400 members) and 'Hip Bursitis Support Group: Trochanteric Bursitis' (2,700 members) were identified. The moderators for both of these groups were contacted privately to request permission to advertise the study to group members. Athletics clubs were also specifically targeted as running athletes can develop GTPS. Through the Scottish Athletics webpage (www.scottishathletics.org.uk), 152 Athletics clubs throughout Scotland were identified. Athletics clubs in England, Wales and Northern Ireland were also contacted via Facebook. For all clubs that had a dedicated Facebook page, the group moderator was contacted by the PhD student with the request to post a message advertising the study. Athletics clubs that were exclusively for children, younger than 18 years, were not targeted.

Instagram

A personal Instagram account was created specifically for the study titled lateral_hip_pain_survey. The study advert was posted with the attached URL link. Identical keywords and hashtags were used for Instagram and Twitter. Given the eligibility criteria, an age restriction was placed on the post so that it could not be viewed by children.

4.2.5 Survey development

The full survey can be viewed in Appendix 19. The questionnaire consisted of six sections:

1. **Personal details:** Gender, age, country of residence and employment status.
2. **General health and physical activity:** Health co-morbidities (Poitras et al. 2012), whether respondents considered themselves overweight, current menopausal status, participation in sport and activity.
3. **Symptoms:** Number of pain sites, previous history of lateral hip pain, duration

of symptoms, pain intensity during activity and frequency of sleep disturbance due to lateral hip pain.

4. **Function and Activity:** Eight questions from the Victoria Institute of Sports Assessment-GTPS (VISA-G) questionnaire (Fearon et al. 2015).
5. **Thoughts and beliefs about activity and exercise:** Seventeen questions from the Tampa Scale for Kinesiophobia (TSK) (Miller et al. 1991).
6. **Emotional wellbeing:** Fourteen questions from the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al. 1983).

The majority of the questions were closed questions to allow ease of completion. However, three questions required the participant to input an answer in free text. Free text entries were question 4; country of residence, question 5; employment status, if 'other' was selected and question 9; type of sports and activity. Depending on the number of responses given, respondents were asked a maximum of 60 questions.

For question 11, participants were asked to select all sites of pain on the body chart. The total number of pain sections in body charts can vary, with 10 and 13 sites being used previously (Carnes et al. 2007, Kamaleri et al. 2008). For the current survey, the total number of sections was 30 (Figure 4-1). This enabled anterior hip pain and lateral hip pain to be considered as two separate sites of pain as hip osteoarthritis and GTPS frequently co-exist (Bicket et al. 2021). If using a version of the body chart with only 10 or 13 body sites, both of these conditions would be classified as one pain site under the umbrella term 'hip', increasing the likelihood of underestimating the presence of an additional musculoskeletal condition. Any respondent who did not select either number 29 or 30 were excluded as they were deemed not to be experiencing lateral hip pain. This increased the diagnostic probability of only including individuals with GTPS in the analysis.

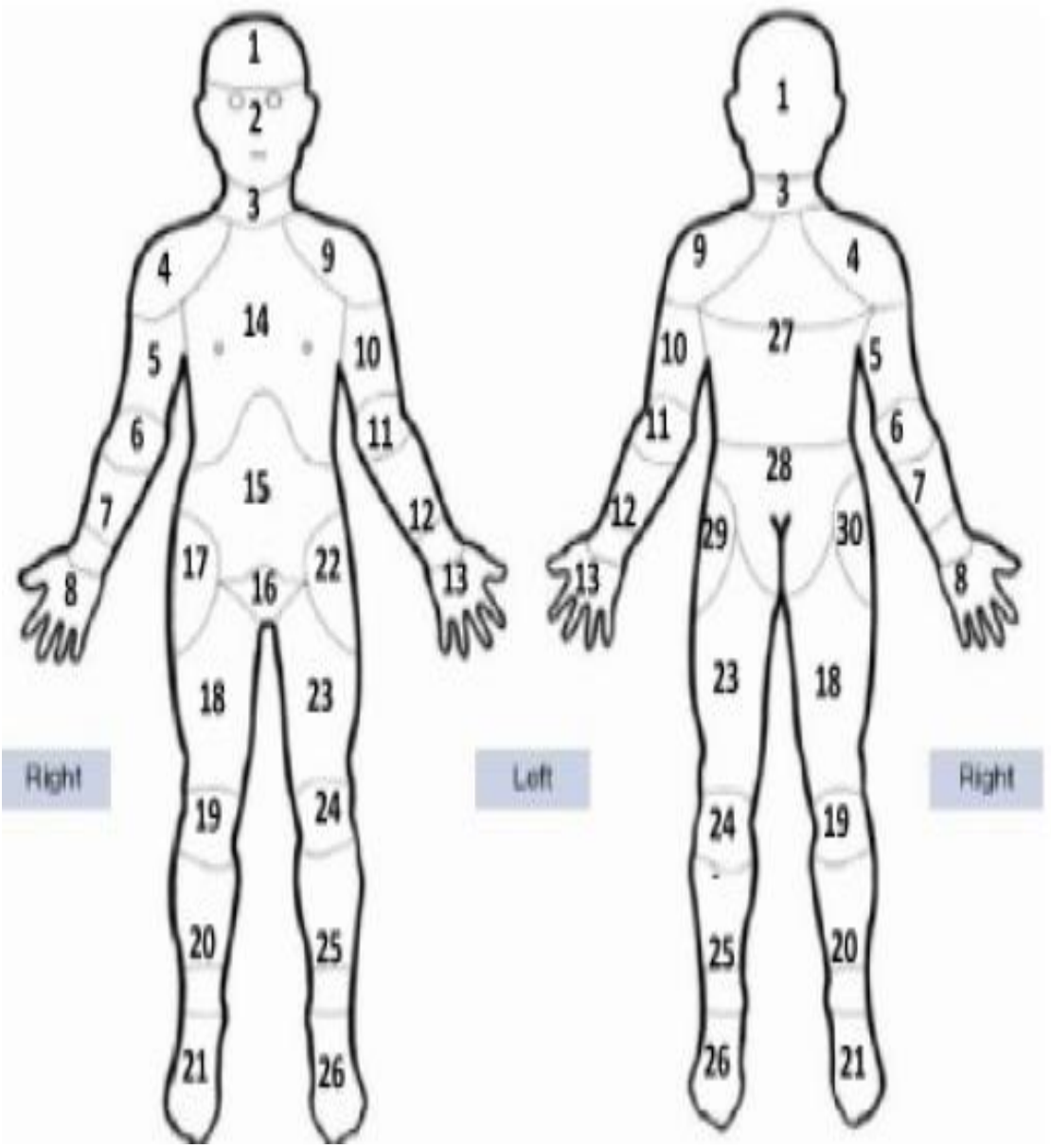

Figure 4-1. Adapted from von Baeyer et al. (2011), with permission

Tendinopathy is a load related musculoskeletal condition and measuring pain intensity during activity has been recommended for inclusion in research studies (Vicenzino et al. 2020). In question 14, participants were asked to rate their pain on an 11-point scale between 0 (no pain) and 10 (maximum pain) when performing gluteal tendon loading activities (lying on painful hip, sitting with legs crossed, walking, going up stairs and running).

Patient reported outcome measures are commonly used in clinical research to measure the impact of a condition on the individual. The VISA-G questionnaire measures the severity of disability in GTPS and has been used in previous clinical trials, including the pilot study (Chapter 2.2.5.1). The TSK-17 is a 17-item questionnaire used to assess fear of movement

and reinjury (Miller et al. 1991). Four-point Likert scales are used. Total scores range from 17 to 68 with a score greater than 37 indicating kinesiophobia. Although not validated for use in tendinopathy populations, the TSK demonstrates good test-retest reliability (Cronbach's alpha = 0.84) and validity in people with chronic musculoskeletal pain (French et al. 2007). Anxiety and depression were measured by the HADS questionnaire. Total scores ranged from 0 to 21 with higher scores indicating higher levels of anxiety and depression. A score of greater than 7 is indicative of anxiety and depression. The HADS has good validity and reliability for anxiety (Cronbach's alpha 0.78 - 0.93) and depression (Cronbach's alpha 0.82 - 0.90) (Bjelland et al. 2002, Smarr and Keefer 2011).

4.2.6 Statistical analysis

All data were analysed using SPSS Statistics version 28.0. For descriptive statistics continuous data were presented as median (interquartile range (IQR)) and categorical data as numbers and percentages. The four dependent variables were either continuous (VISA-G) or categorical (TSK, anxiety and depression). The 18 independent variables were either continuous (number of health co-morbidities, number of days of physical activity in the past week, number of pain sites and pain intensity while lying on side, sitting with legs crossed, walking, going upstairs and running) or categorical (age group, gender, weight, hormonal status, physical activity participation at least once a week, physical activity of 150 minutes or less, first episode of lateral hip pain, number of previous episodes of lateral hip pain, duration of symptoms and sleep disturbance secondary to lateral hip pain). Continuous variables were checked for normality and did not fit a normal distribution, Shapiro-Wilk $p < 0.05$. Non-parametric tests were therefore utilised. The Kruskal-Wallis test was used to determine associations between continuous and categorical variables. The chi-squared (Chi^2) test measured the association between pairs of categorical variables. Despite not fitting a normal distribution, Pearson's correlation co-efficient was performed between two continuous variables and interpreted as a strong correlation ($r \geq 0.7$), a moderate correlation ($r \geq 0.3$ and < 0.7) and a weak correlation ($r < 0.3$) (Ratner 2009). Pearson's correlation was used instead of Spearman's co-efficient due to the central limit theory (Kwak et al. 2017). Scatterplots were used to detect outliers in both the dependant and independent variables. Multicollinearity reflected by a variance inflation factor (VIF) < 2 was considered acceptable. Confidence intervals were 95% and significance values were set at $p < 0.05$ unless otherwise described.

For the VISA-G, total scores (0-100) were calculated. TSK, anxiety and depression scores were totalled and then dichotomised based on whether each respondent had the condition or not. For inferential statistics, hormonal status was dichotomised into either 1) pre-menopause or 2) menopausal and post-menopausal. Group comparisons were made between i) younger individuals (< 40 years) and older individuals (≥ 40 years) and ii) sedentary (< 150 minutes of physical activity per week) and active individuals (≥ 150 minutes of physical activity per week).

Regression analysis enables the identification and characterisation of relationships between dependent and independent variables (Schneider et al. 2010). Furthermore, regression explores the predictive ability of the independent variables on the dependent variable. For every independent variable, there should be no fewer than 10 outcomes (Stoltzfus 2011). Given that there were 18 independent variables in this study, at least 180 survey responses were required. Simple linear regression can model the response between a single dependent and a single independent variable when both are continuous. However, if the dependent variable is likely to be associated with more than one independent variable, simple linear regression is inappropriate (Schneider et al. 2010). In this instance, multivariate analysis was used to simultaneously determine the influence of multiple independent variables on the outcome variable.

Logistic regression can be used to analyse the effect of a combination of independent variables on a binary outcome by quantifying each independent variable's unique contribution (Stoltzfus 2011). It is able to model the probability of an event occurring or an individual having a condition. Binary logistic regression was performed for the TSK, anxiety and depression scores as each respondent was classified as either having the condition or not having the condition.

4.2.7 Building the regression models

Multivariate regression models were created that included all independent variables found to have a statistically significant association with the VISA-G. Thereafter, a process of deleting non-significant variables ($p > 0.05$) from the model was performed one at a time. Linear regression analysis (using 'enter' method) was performed to determine the best model to account for VISA-G score variability. Logistic regression (using 'enter' method) was also performed to determine the best model for the logistic regression. Findings from the logistic regression analysis were reported as odds ratios (OR) with 95% confidence

intervals (CIs) and accompanying p-values. A reference category was displayed if there were two or more categories for the categorical variable.

4.2.8 Data management

During data analysis and for the duration of the project all files were stored on OneDrive for Business. Data were backed up weekly to an encrypted, password protected USB drive which was only accessible to the student. Data were only accessible to the research team.

4.3 Results

When the survey expired there were 314 completed questionnaires. Fifty-three were excluded as respondents did not identify right-sided or left-sided lateral hip pain. Therefore, 261 responses were deemed eligible and included in the final analysis. Table 4-1 details the demographics of respondents. Respondents were predominantly female (83%). Seventy-seven individuals (30%) were younger than 40 years and 184 (70%) were 40 years or older. The majority of respondents (77%) lived in the UK. Seventy-four percent were currently employed with 3% off work due to lateral hip pain.

Table 4-1. Respondent demographics

Gender	**n(%)**
Male	42(16.1)
Female	218(83.5)
Prefer not to say	1(0.4)
Age group (years)	
18-29	22(8.4)
30-39	55(21.1)
40-49	77(29.5)
50-59	72(27.6)
60-69	28(10.7)
70 or older	7(2.7)
Country of residence	
United Kingdom	202(77.4)
United States of America	26(10.0)
Australia	10(3.8)
Canada	9(3.4)
Ireland	2(0.8)
South Africa	2(0.8)
Sweden	2(0.8)
Denmark	1(0.4)
France	1(0.4)
Germany	1(0.4)
Italy	1(0.4)
Malta	1(0.4)
Netherlands	1(0.4)
Norway	1(0.4)
Portugal	1(0.4)
Employment status	
Employed	170(65.1)
Retired	31(11.9)
Self-employed	23(8.8)
Homemaker	13(5.0)
Off work due to lateral hip pain	8(3.1)
Unemployed (other health reasons)	7(2.7)
Student	5(1.9)
Unemployed (other reasons)	3(1.1)
Non-paid work	1(0.4)

Table 4-2 details the health status of respondents. The most common health co-morbidities reported were anxiety or depression. Nearly one in five had co-existing osteoarthritis. Over 40% had two or more co-morbidities and 28% no co-morbidities. Due to the study design, it was not possible to measure BMI, however over one-third of respondents considered themselves overweight. From the 218 female respondents, 47.2% were pre-menopausal and 42.2% were either menopausal or post-menopausal. Nearly three-quarters of respondents (71.3%) participated in sport or activity at least once per week. Running (65%), walking (22.6%), cycling (18.3%) and circuit training (12.9%) were the most common activities. Eighty-seven respondents (33%) engaged in physical activity every day and 116 (45%) were physically active four times per week or less. Fifty-two respondents (20%) participated in physical activity for less than 150 minutes per week.

Table 4-2. Health status and physical activity level of respondents

Health co-morbidity	**n(%)**
Anxiety or Depression (diagnosed)	52(19.9)
Osteoarthritis	45(17.2)
Reflux	39(14.9)
Asthma	35(13.4)
Intestinal problem	30(11.5)
Tendonitis	22(8.4)
Hypertension	21(8.0)
Thyroid disorder	17(6.5)
High cholesterol	12(4.6)
Rheumatoid arthritis	11(4.2)
Osteoporosis	11(4.2)
Diabetes	9(3.4)
Hearing problem	7(2.7)
Circulatory problem	5(1.9)
Visual problem	5(1.9)
Cancer in past five years	4(1.5)
Cardiac illness	3(1.1)
Chronic bronchitis/Emphysema	2(0.8)
Previous stroke	1(0.4)
Heart failure	1(0.4)
None of the above	73(28)
Do you consider yourself overweight?	
Yes	96(36.8)
No	165(63.2)
Hormonal Status	
Pre-menopause	103(39.5)
Post menopause	52(19.9)
Menopausal	40(15.3)
Unknown	20(7.7)
Non-applicable	46(17.6)
Physical activity participation (≥ once per week)	
Yes	186(71.3)
No	75(28.7)

Table 4-3 details the clinical characteristics of respondents. Thirty-five (13%) reported lateral hip pain that had been present for less than three months. Over two-thirds reported symptoms for 12 months or longer. Over 70% described at least one previous episode of lateral hip pain. Sleep disturbance at least once per night due to lateral hip pain was reported by 99 (38%) respondents. The median (IQR) pain intensity (0-10) was highest during running, 5 (2-8) and lying on the affected side, 5 (3-7).

Table 4-3. Clinical characteristics of respondents

Duration of symptoms	**n(%)**	**Median (IQR)**
< 3 months	35(13.4)	
3 - 6 months	27(10.3)	
> 6 months but < 12 months	18(6.9)	
≥ 12 months	181(69.3)	
First episode of lateral hip pain		
Yes	76(29.1)	
No	185(70.9)	
Number of previous episodes		
1	16(8.6)	
2	16(8.6)	
3	12(6.5)	
4	7(3.8)	
5 or greater	134(72.4)	
Sleep disturbance		
Never	37(14.2)	
Once a week or less	67(25.7)	
Every 2 to 3 nights	58(22.2)	
Once a night	28(10.7)	
More than once a night	71(27.2)	
Pain during activity		
Lying on side		5(3-7)
Sitting with legs crossed		4(1-6)
Walking		3(1-6)
Stairs		3(1-6)
Running		5(2-8)

Figure 4-2 displays the percentage of respondents who reported pain at each of the 30 sites. Right-sided lateral hip pain (67%) was more common than left-sided lateral hip pain (62.8%). Bilateral lateral hip pain was present in 30% of individuals but only seven respondents (less than 3%) reported bilateral hip pain with no additional pain elsewhere. The prevalence of low back pain was 44% and almost one-third reported anterior hip pain. Co-existing lower limb pain was more prevalent than upper limb pain. Single-site pain was uncommon with 14% of respondents reporting unilateral lateral hip pain. The median (IQR) number of pain sites for all respondents was 4 (2-5). For individuals younger than 40 years and 40 years or older, the median (IQR) was 4 (2-6) and 3 (2-5) respectively. In sedentary individuals the median (IQR) was 5 (3-7) and for active individuals 3 (2-5).

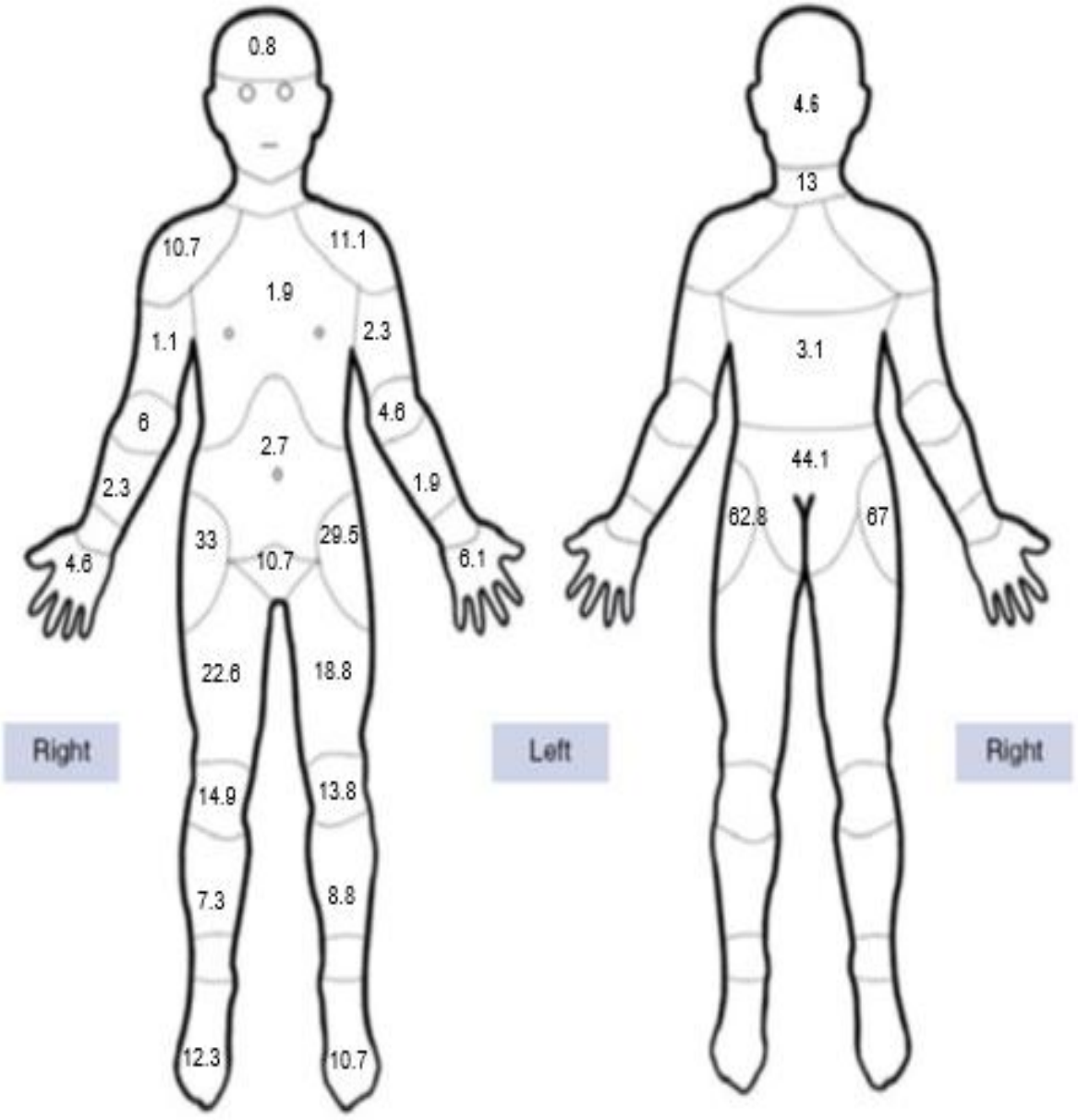

Figure 4-2. Percentage (%) of respondents who reported pain at each site

4.3.1 Association between dependent and independent variables

VISA-G

The median (IQR) score for the VISA–G was 62 (43-76). A strong and statistically significant correlation was observed between the VISA-G and pain intensity during walking ($r = 0.77$, $p < 0.01$), moderate correlations for pain intensity sitting with legs crossed ($r = 0.559$, $p < 0.01$), lying on the affected side ($r = 0.544$, $p < 0.01$), number of pain sites ($r = 0.499$, $p < 0.01$), number of health co-morbidities ($r = 0.480$, $p <0.01$) and number of days of physical activity in past week ($r = 0.374$, $p <0.01$) (Table 4-4). A positive correlation was observed for number of days of physical activity of more than 30 minutes in the past week. The negative correlations indicate that a reduction in the VISA-G score, i.e. worsening disability, occurs as the number of health co-morbidities, pain sites and pain intensity sitting with legs crossed or during side-lying increases. Gender, being overweight, physical activity less than or more than 150 minutes in the past week and duration of symptoms all showed an association with the VISA-G ($p < 0.001$). VISA-G scores were not significantly different between age groups (Figure 4-3). Lower VISA-G scores were observed in sedentary populations (< 150 minutes physical activity per week) (Figure 4-3). Worsening sleep disturbance due to lateral hip pain was associated with higher disability (Figure 4-4). No significant difference in disability was observed between pre-menopausal and menopausal or post-menopausal females, with VISA-G scores of 60 and 57 respectively (Figure 4-4). Three respondents selected ‘non-applicable’ for pain intensity going upstairs and sixty respondents selected ‘non-applicable’ for pain intensity while running.

Table 4-4. Association between dependant and independent variables

Variable	VISA-G		TSK			Anxiety			Depression		
	Pearson's	Kruskal-Wallis	Chi^2		Kruskal-Wallis	Chi^2		Kruskal-Wallis	Chi^2		Kruskal-Wallis
	(r)	p-value	value	p-value	p-value	value	p-value	p-value	value	p-value	p-value
No. of health co-morbidities	**-0.480**				**0.001**			**<0.001**			**<0.001**
No. of days of physical activity in past week	**0.374**				**<0.001**			0.454			**0.012**
No. of pain sites	**-0.499**				**<0.001**			**<0.001**			**<0.001**
Pain during activity											
Lying on side	**-0.544**				**<0.001**			**0.049**			**0.002**
Sitting with legs crossed	**-0.559**				**<0.001**			**<0.001**			**<0.001**
Walking	**-0.770**				**<0.001**			**<0.001**			**<0.001**
Stairs	0.047				**0.03**			0.33			0.929
Running	0.04				0.147			0.321			0.669
Gender		**<0.001**	1.007	0.316		1.586	0.208		3.185	0.074	
Overweight		**<0.001**	12.95	**<0.001**		7.648	**0.006**		13.089	**<0.001**	
Hormonal status		0.24	0.003	0.959		3.937	**0.047**		0.227	0.634	
Physical activity participation (≥ once per week)		**<0.001**	16.014	**<0.001**		15.433	**<0.001**		11.217	**<0.001**	
Physical activity (< or ≥ than 150 minutes)		**<0.001**	0.071	0.79		0.035	0.852		7.882	**0.005**	
Duration of symptoms		**<0.001**	6.431	0.092		8.713	**0.033**		6.608	0.085	
First episode of lateral hip pain		0.061	0.055	0.814		12.943	**<0.001**		3.696	0.055	
No. of previous episodes of lateral hip pain		**0.007**	21.84	**<0.01**		5.704	0.222		6.765	0.149	
Sleep disturbance		**0.001**	26.475	**<0.001**		14.67	**0.005**		21.599	**<0.001**	

Bold = statistically significant $p < 0.05$

Abbreviations: VISA-G (Victorian Institute of Sports Assessment-Gluteal questionnaire), TSK (Tampa Scale of Kinesiophobia), Chi^2 (Chi-squared test)

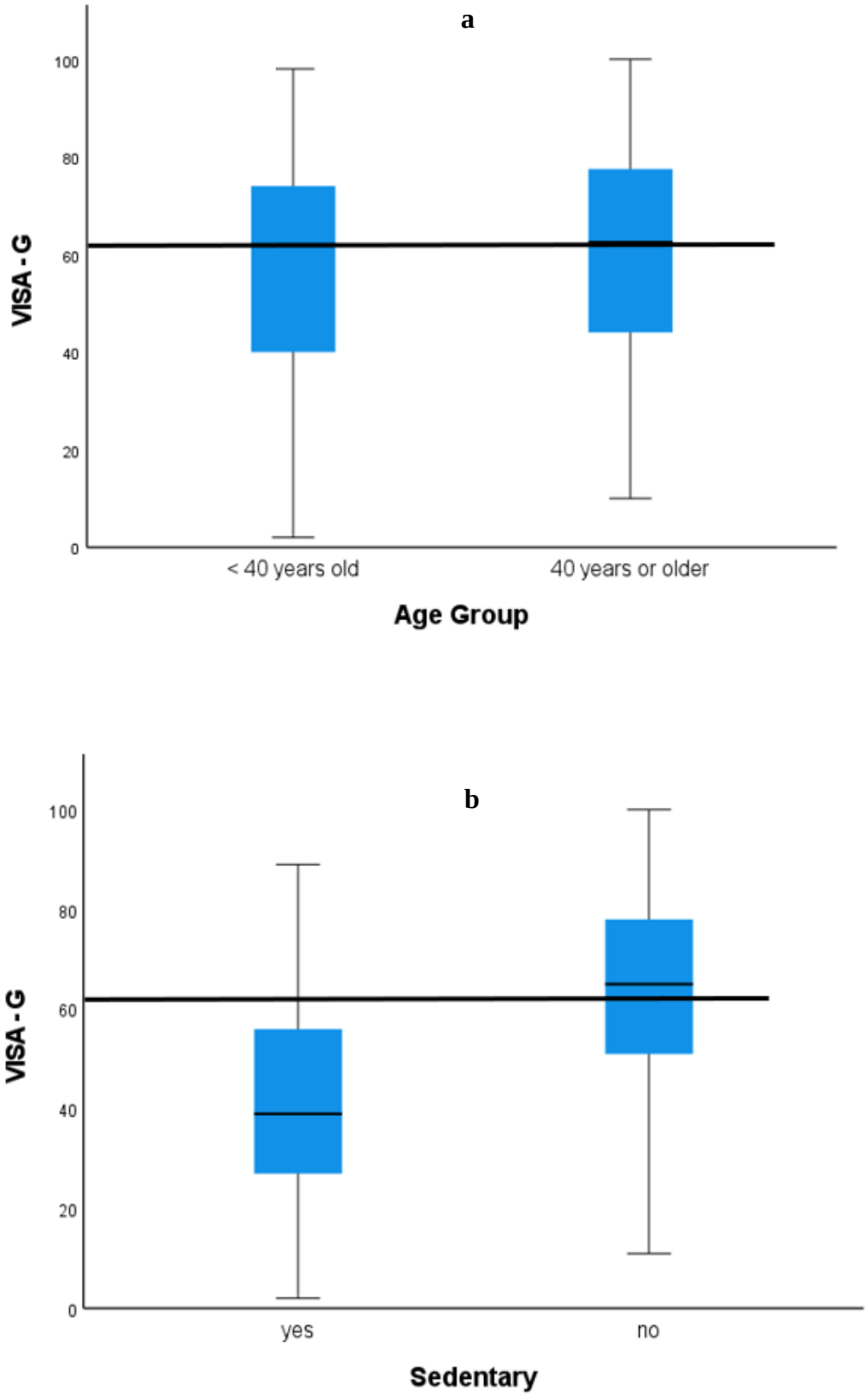

Figure 4-3. Relationship between VISA-G and (a) age group and (b) physical activity level. Horizontal solid line indicates group median.

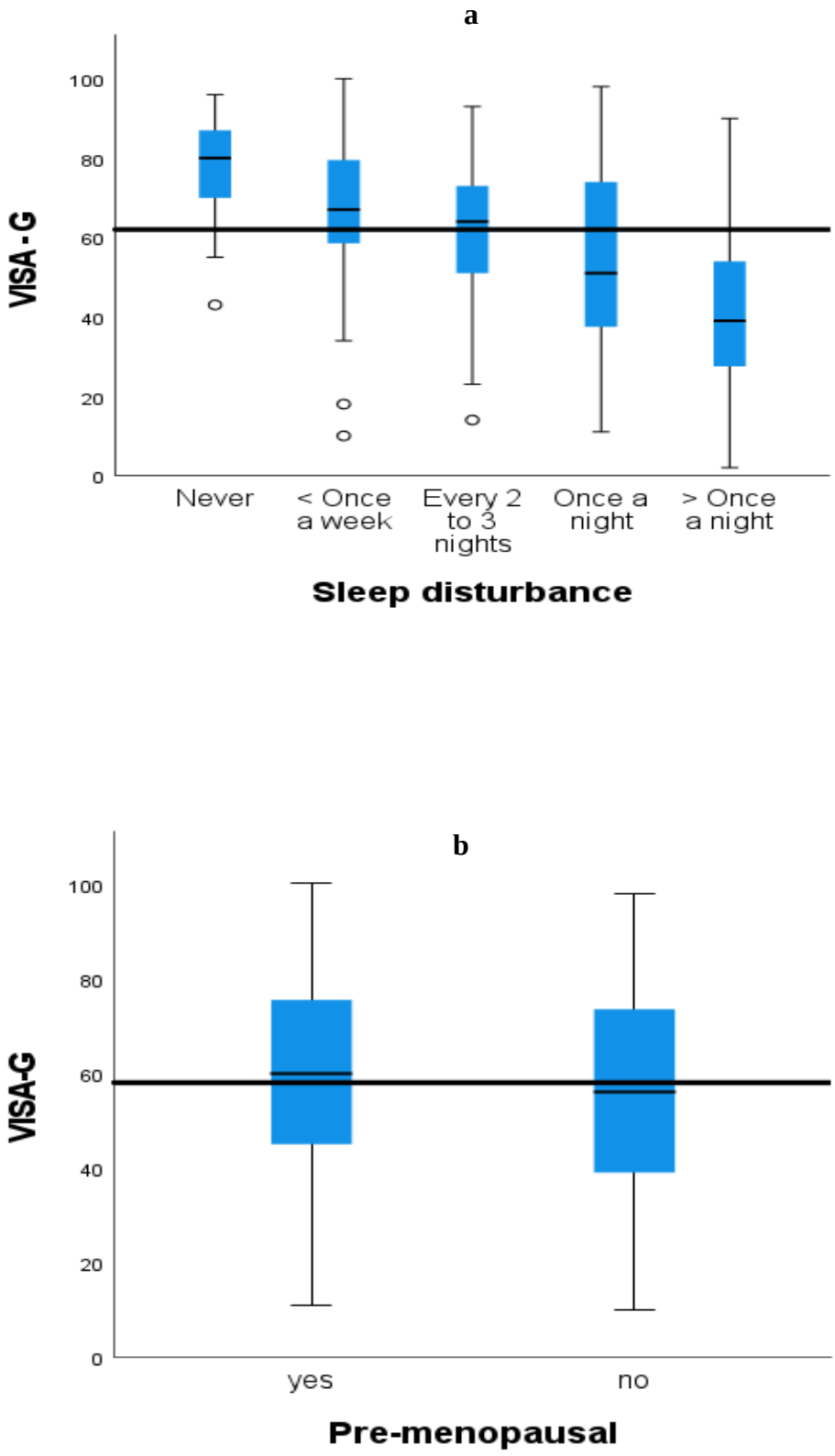

Figure 4-4. Relationship between VISA-G and (a) sleep disturbance and (b) hormonal status. Horizontal solid line indicates group median.

4.3.2 Psychological factors

Kinesiophobia

Kinesiophobia was identified in 181 respondents (69.3%). Sixty-six percent of younger individuals (<40 years) and 71% of older individuals (≥ 40 years) exhibited kinesiophobia. Seventy-nine percent of sedentary individuals and 67% of active individuals had kinesiophobia. There was evidence of an association between kinesiophobia and respondents who reported being overweight, physical activity participation more than once per week, number of previous episodes of lateral hip pain and sleep disturbance ($p < 0.01$) (Table 4-4). Associations were identified between kinesiophobia and number of days of physical activity in the past week, number of pain sites, pain intensity lying on side, sitting with legs crossed and walking ($p < 0.001$), number of health co-morbidities ($p = 0.001$) and pain intensity going upstairs ($p = 0.03$). No associations were found between kinesiophobia and gender, hormonal status or duration of symptoms.

Anxiety

Anxiety was present in 119 respondents (45.6%). An association was observed between anxiety and physical activity participation more than once per week and anxiety and first episode of lateral hip pain ($p < 0.001$), being overweight ($p = 0.006$), hormonal status ($p = 0.047$), duration of symptoms ($p = 0.033$), and sleep disturbance ($p = 0.005$) (Table 4-4). Further associations were identified between anxiety and number of health co-morbidities, number of pain sites, pain intensity while walking and sitting with legs crossed, Kruskal-Wallis ($p < 0.001$) and pain intensity while lying on side ($p = 0.049$).

Depression

Ninety respondents (34.5%) had depression. There was evidence of an association between depression and being overweight and also depression and sleep disturbance ($p < 0.001$). Further associations were identified for physical activity participation more than once per week, ($p < 0.001$) and physical activity less than or more than 150 minutes in the past week ($p = 0.005$) (Table 4-4). Associations were also observed between depression and number of health co-morbidities, number of pain sites and pain intensity while walking and sitting with legs crossed ($p < 0.001$), number of days of physical activity in the past week, ($p = 0.012$) and pain intensity while lying on side ($p = 0.002$).

4.3.3 Subgroups

Table 4-5 details associations between variables and i) younger (< 40 years) and older individuals (≥ 40 years) and ii) sedentary (< 150 minutes of physical activity) and active individuals (≥ 150 minutes of physical activity).

Age group

There was evidence of an association between age group and the prevalence of anxiety, 55.8% and 41.3% (younger vs. older) ($p = 0.044$). Pain intensity going upstairs ($p < 0.002$) and running ($p = 0.009$) were significantly higher in the older age group. No evidence of a relationship was identified between age group and VISA-G, kinesiophobia or depression.

Physical activity level

Evidence of an association was found between physical activity level and depression ($p = 0.002$), being overweight ($p = 0.007$) and sleep disturbance ($p = 0.004$). Depression was identified in 53.8% of sedentary individuals and 29.7% of active individuals. In respondents who reported being overweight, 53.8.% were classified as sedentary compared to 32.5% who were active. Further statistically significant associations were identified for the VISA-G ($p < 0.001$) with median (IQR) scores of 39 (26-56) in the sedentary group and 65 (51-79) in the active group. Finally, associations were found for number of pain sites and pain intensity during walking ($p < 0.001$), pain intensity while lying on side ($p = 0.005$), number of health co-morbidities and pain intensity when sitting with legs crossed ($p = 0.008$). No evidence of a relationship was identified between physical activity level and kinesiophobia or anxiety.

Table 4-5. Association between variables for age groups and physical activity level subgroups

Variable	< 40 years and ≥ 40 years			Physical activity (< or ≥ 150 minutes)		
	Chi²		Kruskal-Wallis	Chi²		Kruskal-Wallis
	value	p-value		value	p-value	
VISA-G			0.428			**<0.001**
TSK	0.312	0.576		2.226	0.136	
Anxiety	4.059	**0.044**		0.061	0.806	
Depression	1.997	0.158		9.733	**0.002**	
No. of health co-morbidities			0.644			**0.008**
No. of days of physical activity in past week			0.227			**<0.001**
No. of pain sites			0.249			**<0.001**
Pain during activity						
Lying on side			0.855			**0.005**
Sitting with legs crossed			0.493			**0.008**
Walking			0.646			**<0.001**
Stairs			**0.002**			0.827
Running			**0.009**			0.637
Age group (< 40 years old and ≥ 40 years old)				2.506	0.158	
Gender	2.034	0.362		2.307	0.315	
Overweight	0.263	0.608		7.242	**0.007**	
Hormonal status	54.434	**< 0.001**		0.421	0.516	
Physical activity participation (≥ once per week)	1.024	0.312		21.555	**<0.001**	
Physical activity (< or ≥ than 150 mins)	2.506	0.158				
Duration of symptoms	1.611	0.657		5.441	0.142	
First episode of lateral hip pain	0.762	0.383		0.314	0.575	
No. of previous episodes of lateral hip pain	3.99	0.407		7.051	0.133	
Sleep disturbance	2.873	0.579		15.153	**0.004**	

Bold = statistically significant $p < 0.05$

Abbreviations: VISA-G (Victorian Institute of Sports Assessment-Gluteal questionnaire), TSK (Tampa Scale of Kinesiophobia), Chi² (Chi-squared test)

4.3.4 Regression analysis

Multivariate linear regression

Table 4-6 shows results from the multivariate linear regression analysis for the VISA-G. Thirteen independent variables identified as being statistically significant were included in the initial model. Eight variables were included in the final model and accounted for 76.1% of the variance in the VISA-G score. Within the model, pain intensity during walking was the strongest predictor of disability (40%), followed by sitting with legs crossed (13.6%), sleep affected more than once a night (13.4%), physical activity participation at least once a week (12.5%), sleep affected once a night (10.7%), sedentary (10.8%), overweight (6.9%) and number of pain sites (6.7%). In relation to pain intensity during walking, every one-point increase on a pain scale (0-10) leads to a four-point reduction in the VISA-G score. Sleep disturbance at least once per night reduced the VISA-G by eight points. Participation in physical activity at least once a week increased the VISA-G by eight points.

Multivariate logistic regression

Table 4-7 shows results of the multiple logistic regression models for the TSK, anxiety and depression.

Kinesiophobia

Eleven independent variables identified as being statistically significant were included in the initial model. Diagnostic tests of the final model indicated good fit (Hosmer and Lemeshow test, $p = 0.524$). The model was statistically significant, $Chi^2 = 70.015$, $p < 0.001$, and correctly predicted 78.5% of cases. For the final model, logistic regression ascertained that six variables were statistically significant, number of health co-morbidities, OR 1.416 CI (1.068-1.876) $p = 0.016$, number of days of physical activity in the past week, OR 0.818 CI (0.694-0.963) $p = 0.016$, pain intensity during walking, OR 1.185 CI (1.040-1.349) $p = 0.011$, two previous episodes of lateral hip pain, OR 0.086 CI (0.21-0.351) $p < 0.001$, sleep disturbance less than once a week, OR 0.295 CI (0.144-0.607) $p < 0.001$ and sleep disturbance every 2-3 nights, OR 0.296 CI (0.136-0.646) $p = 0.002$.

Table 4-6. Multivariate linear regression for the VISA-G

Variable	**Initial model**		**Final model**	
	p-value		p-value	
No. of health co-morbidities	0.726			
No. of days of physical activity in past week	0.113			
No. of pain sites	0.099		**0.031**	
Pain during activity				
Lying on side	0.097			
Sitting cross-legged	**<0.001**		**<0.001**	
Walking	**<0.001**		**<0.001**	
Gender				
Male	Ref			
Female	0.984			
Overweight				
No	Ref			
Yes	0.054		**0.027**	
Physical activity participation (≥ once per week)				
Yes	Ref			
No	**0.001**		**< 0.001**	
Physical activity (< or ≥ than 150 minutes)				
Active	Ref			
Sedentary	0.098		**< 0.001**	
Duration of symptoms				
< 3 months	Ref			
3-6 months	0.996			
6-12 months	0.703			
≥ 12 months	0.606			
No. of previous episodes of lateral hip pain				
0	Ref			
1	0.794			
2	0.646			
3	0.372			
4	0.5			
5 or greater	0.862			
Sleep disturbance				
Never	Ref			
≤ once a week	0.43			
Every 2-3 nights	0.764			
Once a night	**0.009**		**<0.001**	
> once a night	**0.02**		**<0.001**	

Bold = statistically significant $p < 0.05$, Ref = reference category

Anxiety

Eleven independent variables identified as being statistically significant were entered into the initial model. Diagnostic tests of the final model indicated good fit (Hosmer and Lemeshow test, $p = 0.406$). The final model was statistically significant, $Chi^2 = 41.233$, $p < 0.001$, and correctly predicted 65.4% of cases. Three variables were included in the final model and found to be statistically significant; number of pain sites, OR 1.172 CI (1.059-1.296), $p = 0.002$, sitting with legs crossed, OR 1.124 CI (1.026-1.230), $p = 0.012$ and first episode of lateral hip pain, OR 2.773 CI (1.507-5.103), $p < 0.001$. An association between anxiety and hormonal status was identified. However, hormonal status was not entered into the model as this association was based on female respondents who were either pre-menopausal or menopausal/post-menopausal meaning that all-male respondents would be excluded.

Depression

Ten independent variables identified as being statistically significant were entered into the initial model. Diagnostic tests of the final model indicated good fit (Hosmer and Lemeshow test, $p = 0.305$). The final model was statistically significant, $Chi^2 = 49.889$, $p < 0.001$, and correctly predicted 71.9% of the cases. Three variables were included in the final model and found to be statistically significant; number of pain sites OR 0.824 CI (0.744-0.914), $p < 0.001$, sitting with legs crossed OR 0.87 CI (0.791-0.958), $p= 0.004$ and being overweight OR 2.158 CI (1.217-3.827) $p = 0.009$.

Table 4-7. Multivariate logistic regression for TSK, anxiety and depression

Variable	TSK				Anxiety				Depression			
	Initial		Final		Initial		Final		Initial		Final	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No. of health co-morbidities	1.277	0.923-1.768	**1.416**	**1.068-1.876**	1.113	0.89-1.392			1.039	0.834-1.294		
No. of days of physical activity in past week	0.856	0.717-1.022	**0.818**	**0.694-0.963**					0.998	0.831-1.200		
No. of pain sites	0.977	0.835-1.142			**1.145**	**1.012-1.296**	**1.172**	**1.059-1.296**	**0.833**	**0.740-0.938**	**0.824**	**0.744-0.914**
Pain during activity												
Lying on side	1.117	0.957-1.303			0.934	0.811-1.175			1.066	0.922-1.232		
Sitting cross-legged	0.989	0.869-1.125			**1.121**	**1.003-.1253**	**1.124**	**1.026-1.230**	**0.875**	**0.784-0.977**	**0.87**	**0.791-0.958**
Walking	1.157	0.998-1.343	**1.185**	**1.040-1.349**	1.032	0.910-1.170			0.939			
Stairs	1.094	0.976-1.226										
Age group												
< 40 years old					Ref							
≥ 40 years old					0.558	0.300-1.039						
Overweight												
Yes	Ref				Ref				Ref			
No	0.505	0.225-1.130			0.695	0.363-1.331			**2.25**	**1.181-4.285**	**2.158**	**1.217-3.827**
Physical activity participation (≥ once per week)												
No	Ref				Ref				Ref			
Yes	0.72	0.245-2.114			0.663	0.306-1.439			0.723	0.324-1.612		
Physical activity (< or ≥ than 150 minutes)												
Active									Ref			
Sedentary									1.909	0.768-4.745		

Table 4-7 continued

Variable	TSK				Anxiety				Depression			
	Initial		Final		Initial		Final		Initial		Final	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Duration of symptoms												
< 3 months					Ref							
3-6 months					0.295	0.80-1.093						
6-12 months					0.729	0.199-2.768						
> 12 months					0.648	0.270-1.554						
First episode of lateral hip pain												
Yes					Ref							
No					**2.884**	**1.438-5.782**	**2.773**	**1.507-5.103**				
No. of previous episodes of lateral hip pain												
0	Ref											
1	1.380	0.361-5.280										
2	**0.098**	**0.22-0.443**	**0.086**	**0.21-0.351**								
3	1.717	0.401-7.360										
4	2.726	0.268-27.768										
5 or greater	0.919	0.433-1.948										
Sleep disturbance												
Never	Ref											
≤ once a week	**0.279**	**0.102-0.761**	**0.295**	**0.144-0.607**	**0.346**	**0.133-0.904**			2.101	0.713-6.190		
Every 2-3 nights	**0.231**	**0.074-0.725**	**0.296**	**0.136-0.646**	0.363	0.126-1.050			1.066	0.359-3.170		
Once a night	0.136	0.136-1.938			**0.181**	**0.47-0.701**			1.464	0.387-5.537		
> once a night	0.270	0.270-4.636			0.577	0.076-1.892			0.88	0.262-2.953		

Bold = statistically significant $p < 0.05$, Ref = reference category

4.4 Discussion

This was the first study to compare the clinical characteristics of i) younger individuals (< 40 years) and older individuals (≥ 40 years) and ii) sedentary individuals (< 150 minutes of physical activity) and active individuals (≥ 150 minutes of physical activity per week) with self-reported GTPS. Contrary to the first hypothesis, when divided into subgroups, younger individuals did not have fewer health co-morbidities, pain sites, lower disability, kinesiophobia or depression compared to older individuals. However, the prevalence of anxiety was higher and lower pain intensity was experienced going upstairs and running in younger individuals. As hypothesised, sedentary individuals had a greater number of health co-morbidities, pain sites, higher disability, depression and higher pain intensity during side-lying, sitting cross-legged and walking compared to active individuals. The prevalence of kinesiophobia and anxiety was similar between sedentary and active individuals. A number of clinical characteristics, including number of health co-morbidities, number of pain sites and sleep disturbance were associated with disability and psychological factors.

Previous studies have reported that GTPS is more prevalent in middle-aged and older individuals (Riel et al. 2019, Segal et al. 2007). Riel et al. (2019) analysed primary care data in Denmark and identified that patients within all age groups (0-17 years, 18-44 years, 45-64 years and 65+ years) had been previously diagnosed with lower limb tendinopathy. The mean age was 50.8 years, however the prevalence of GTPS in each age group was not reported. The prevalence of GTPS in younger populations is unknown, however, in this cross-sectional survey almost one third of respondents were < 40 years old. Due to the recruitment strategy in the current study, younger populations with GTPS could have been more aware of the survey as social media use is higher amongst younger people. Regardless, a sizeable number of younger people appear to be affected by GTPS and further research is required to investigate the true prevalence in this population. The clinical presentation of younger individuals and older individuals appears similar, but interestingly, the number of health co-morbidities was not significantly different between age groups. This was a surprising finding given that health co-morbidities typically increase with ageing (Barnett et al. 2012). Higher pain intensity when going upstairs and running was reported by the older age group. Both activities increase the loading around the hip when compared to walking (Bergmann et al. 1993, Bergmann et al. 2001). Given that ageing is associated with tendon degeneration, it is possible that the gluteal tendons of

older individuals with GTPS are less able to tolerate the demands of these activities and therefore experience more severe pain. A progressive decline in gluteal muscle strength and tendon structure has been reported with increasing age (Chi et al. 2015). Despite this, disability was similar in younger and older individuals in the current study with no significant differences in VISA-G scores between age groups.

The findings of this chapter build on previous research which has reported the prevalence of GTPS in both active and sedentary populations (Blank et al. 2012, Plinsinga et al. 2018, Plinsinga et al. 2020, Rompe et al. 2009). The World Health Organisation (WHO) currently recommends adults undertake at least 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity physical activity per week (Bull et al. 2020). Globally, about 28% of adults do not meet these recommendations (Guthold et al. 2018). Utilising the WHO guidelines, 20% of the survey respondents were classified as sedentary. Plinsinga et al. (2018) used similar criteria and 25% of individuals with gluteal tendinopathy did not achieve the recommended weekly activity level. One explanation for these results is that pain may limit an individual's ability to participate in regular physical activity. Alternatively, sedentary behaviours over a prolonged period could lead to the development of gluteal tendinopathy secondary to the metabolic factors discussed in Chapter 1.11. However, due to the cross-sectional design, causality cannot be determined from either study. In the current study, the median VISA-G score was 26 points lower in the sedentary subgroup compared to the active subgroup, implying an association between disability and physical activity level. Respondents in the sedentary subgroup also reported higher pain intensity during walking suggesting that lateral hip pain could limit physical activity in GTPS. This would support the findings of Fearon et al. (2017) who concluded that activity limitations in GTPS, which included walking, could be secondary to pain. Individuals in the sedentary group also reported an increased number of pain sites when compared to active individuals, which could further explain the lower levels of physical activity. This is one of the first studies to report the physical activity levels of a large cohort of individuals with GTPS. Physical activity level is often poorly reported in tendinopathy research, especially the duration of time spent engaging in physical activity (McAuliffe et al. 2021). Researchers are encouraged to routinely assess the physical activity level of participants in accordance with the WHO recommendations.

In the current study a number of clinical characteristics were associated with disability. For the first time, associations were identified between the VISA-G and number of health co-

morbidities, number of pain sites and sleep disturbance. Multi-variate linear regression revealed that pain intensity during walking was strongly correlated with the VISA-G, explaining 40% of the total variance. In the final regression model, eight variables were statistically significant and explained 70% of the total variance. In the study by Plinsinga et al. (2020), depression, hip abductor muscle strength and time required to complete stairs explained 26% of the variance in the VISA-G. These three variables were not investigated in the current study. However, the independent variables in the current study appear to be better able to predict disability in GTPS, at least in the population under investigation in the survey. In the current study, 39% of respondents were pre-menopausal and 35% menopausal or post-menopausal. In a clinical trial with 204 participants with gluteal tendinopathy 21% were pre-menopausal and 57% were menopausal or post-menopausal (Mellor et al. 2018). The difference between studies is likely related to the eligibility criteria in the latter study as younger individuals < 35 years old were excluded. Based on the findings of both studies, approximately 1 in every 3 females with GTPS may be either menopausal or post-menopausal. A novel finding was the lack of association between disability and hormonal status in women. A reduction in collagen tensile strength occurs during the menopause, primarily due to a reduction in oestrogen (Kjaer et al. 2009). This alteration in tendon mechanical properties however does not appear to influence pain-related disability and median VISA-G scores were similar in both pre-menopausal and menopausal or post-menopausal females.

An important finding from the current study was that anxiety and depression appear to be under-diagnosed in GTPS. Only 20% of respondents reported a previous diagnosis of anxiety or depression (Table 4-2). However, when measured with the HADS, the prevalence of anxiety and depression was 45% and 34% respectively. Using the same measure, anxiety was previously identified in 20-25% and depression 5-10% of individuals with gluteal tendinopathy (Mest al. 2020, Plinsinga et al. 2020). In both studies, the sample size was small with 11 and 40 participants respectively which could underestimate the true prevalence and explain the observed differences. In the current study, logistic regression analysis revealed that the likelihood of experiencing anxiety was more than 2.7 times greater for respondents with recurrent lateral hip pain. For each additional pain site reported there was a 17.2% increased likelihood of anxiety, which taken together provides support, albeit weak, that anxiety is secondary to pain and the recurrence of pain in this population. Prospective studies are required to determine whether anxiety experienced by individuals with GTPS is directly related to the presence and persistence of lateral hip pain or due to other factors.

Sixty-nine percent of respondents in the current study exhibited kinesiophobia. The prevalence of kinesiophobia in GTPS populations has been reported as 53-57% (Ferrer-Pena et al. 2019, Mest et al. 2020, Plinsinga et al. 2020). Thus, it appears that 1 in every 2 individuals with GTPS will likely display kinesiophobia which is comparable to the prevalence of 54% in musculoskeletal disorders (Lundberg et al. 2006). It is not entirely clear why the prevalence of kinesiophobia was higher in the current study. Kinesiophobia has been associated with pain intensity in musculoskeletal pain (Larsson et al. 2016, Luque-Suarez et al. 2019). Pain intensity (0-10) during activity (walking, stairs and running) in the current study was similar to previous findings where mean and median pain scores of between 3 and 5 points were reported (Mest al. 2020, Plinsinga et al. 2020). The prevalence of other psychological factors, including depression was also higher in the current study. Individuals with osteoarthritis and depression are more likely to exhibit kinesiophobia (Aykut Selçuk and Karakoyun 2020). The higher prevalence of kinesiophobia in the current study, affecting nearly 70% of respondents, could therefore be related to the high prevalence of co-existing depression rather than activity related pain. Interestingly, 67% of respondents in the active subgroup exhibited kinesiophobia. This suggests that fear of movement or activity does not always prevent participation in physical exercise in GTPS. Similar findings have been reported in a low back pain population (Carvalho et al. 2017). It is plausible that a number of respondents in the current study were indeed fearful about activity and as a consequence reduced their physical activity level, but were still able to meet the WHO physical activity guidelines. Multivariate logistic regression indicated that the likelihood of displaying kinesiophobia increased by 18.5% for every one-point increase in pain intensity during walking. As higher pain intensity during walking was identified in the ‘sedentary’ subgroup, it is possible that a proportion of people with GTPS do not engage in regular physical activity due to activity related pain and also due to fear of further injury.

Respondents who reported being overweight were more than twice as likely to have depression when measured with the HADS. Obesity and depression have previously been associated in chronic hip pain (Schwarze et al. 2019). Plinsinga et al. (2018) stratified participants with gluteal tendinopathy into mild, moderate and severe subgroups based on the VISA-G score. Interestingly, participants in the severe subgroup and the ‘sedentary’ subgroup in the current study share similar clinical characteristics, namely obesity, depression and lower physical activity levels. Furthermore, individuals with ‘severe’ gluteal tendinopathy had a mean VISA-G score of 42 points, which is similar to the median

VISA-G score of 39 points in the sedentary subgroup. In both studies, depression was associated with physical inactivity; although, it is unclear whether depression leads to a reduction in physical activity or physical inactivity secondary to pain contributes to depression. Physical activity can however improve mental health and decrease the symptoms of anxiety and depression (Bull et al. 2020). Anxiety, depression and kinesiophobia were all associated with worsening disability in GTPS (Plinsinga et al. 2020). Given these associations and the high prevalence of these psychological factors in the current study, investigating such factors in future GTPS research appears justified. Indeed, psychological factors have been identified as one of the nine core health-related domains in tendinopathy research and have been recommended to be measured in future clinical trials (Vicenzino et al. 2020). This illustrates that tendinopathy is now recognised as a musculoskeletal condition which requires a biopsychosocial approach to patient management.

The prevalence of single-site pain in GTPS has not been previously reported. In the current study, 14% of respondents reported pain at only one site. This is comparable with other musculoskeletal populations, where 11%-13% of people reported single-site pain (Carnes et al. 2007, Kamaleri et al. 2008). Bilateral tendinopathy is common with a prevalence of 13% - 50% in GTPS (Clifford et al. 2019, Fearon et al. 2017, Mellor et al. 2018, Plinsinga et al. 2020). The median (IQR) number of pain sites in the current study was 4 (2-5) compared to 3 (2) (Plinsinga et al. 2018). It appears therefore, that individuals with GTPS are more likely to experience multi-site pain and single-site pain is uncommon. The American College of Rheumatology (ACR) defined chronic widespread pain as 'pain present in two contralateral quadrants of the body above and below the waist and in the axial skeleton that has been present for at least three months (Wolfe et al.1990). Using these criteria, widespread pain was present in 13% of the study population which is comparable to the 10-12% reported in the general population (Mansfield et al. 2016). Gluteal tendinopathy may also be present in individuals with widespread pain. However, participants with multiple pain sites have not been included in previous clinical trials, including the pilot study (Chapter 2). As a consequence, more than 10% of people with gluteal tendinopathy may be excluded from study participation based on this single criterion alone. Osteoarthritis was reported by 17% of respondents which is comparable to 15% who reported lower limb osteoarthritis in an NHS population with GTPS (Stephens et al. 2019). Co-existing lower limb osteoarthritis appears to be a risk factor for poorer outcome, with individuals almost five times more likely to have lateral hip pain after 12

months (Lievense et al. 2005). In the current study, over 50% of respondents reported lateral hip pain for more than one year and further research is required to determine whether a 'multi-modal' management approach is required in some individuals with GTPS, addressing impairments in relation to both lateral hip pain and also osteoarthritis. As discussed in Chapter 1.11, metabolic factors and low-level systemic inflammation are believed to play a role in the development and persistence of pain in tendinopathy. Interestingly, the pathophysiology of osteoarthritis and tendinopathy may be similar (Askari et al. 2017, van den Bosch 2018). This may explain why osteoarthritis and GTPS often co-exist in some individuals with GTPS. In summary, associations were identified between the number of pain sites and disability, kinesiophobia, anxiety and depression in the current survey. The relevance of additional pain sites warrants further investigation in future GTPS research.

Over one-third of respondents reported sleep disturbance at least once per night due to lateral hip pain. Sleep quality can be significantly affected in this population affecting 40 - 60% of individuals (Lievense et al. 2005, Stephens et al. 2019). Pain intensity during side-lying was higher than walking and similar to running. Side-lying will cause direct compression of the gluteal tendons and trochanteric bursa and the high prevalence of sleep disturbance in GTPS is likely secondary to this irritation. Sleep disturbance was also associated with lower physical activity level and it is plausible that tiredness and fatigue due to a lack of sleep may affect the ability and motivation of an individual to remain active. An association has been established between poor sleep quality, disability, depression and musculoskeletal pain (Wei et al. 2018). Sleep was also found to be associated with the presence of psychological factors in the current study, illustrating the likely importance of sleep for emotional well-being and mental health in GTPS.

4.4.1 Strengths and limitations

A strength of the current study was that the prevalence of a number of clinical characteristics has been identified for the first time in a GTPS population. This study also identified that subgroups exist for this condition and should be explored further in future research studies. The main limitation of this study was that all clinical data were self-reported. Respondents were only included in the final analysis if they identified as having lateral hip pain, however in the absence of a clinical examination, it is possible that a number of respondents did not have gluteal tendinopathy. The TSK and HADS have been used in previous GTPS research but have not been validated for GTPS and cut-offs have

still to be established. Only people with access to social media platforms were able to participate in the study which introduces the possibility of selection bias. As previously discussed, results from cross sectional studies prohibits causal inferences and it is unknown whether the reported clinical characteristics are precursors to or secondary to the presence of GTPS. Further studies are required to determine whether the high prevalence of psychological factors, pain sites and health co-morbidities contribute to the poorer clinical outcome often observed following loading programmes in GTPS.

4.5 Conclusion

This was the first study to divide individuals with GTPS into subgroups based on age group and physical activity level. The clinical characteristics of younger individuals (< 40 years) and older individuals (≥ 40 years) were similar. Sedentary individuals had a greater number of health co-morbidities, pain sites, higher disability and depression. A number of clinical characteristics were identified which may contribute to disability and affect the treatment outcome. This chapter provides further evidence that a biopsychosocial approach is required in the management of GTPS.

Chapter 5

Discussion and future directions

5.1 Summary of studies

The overall aim of this thesis was to explore the clinical presentation of individuals with GTPS and to investigate the effectiveness of isometric exercise in the management of tendinopathy, with a focus on GTPS.

The aim of Chapter 2 was to evaluate and compare clinical outcomes for individuals with GTPS who completed a 12-week programme of either progressive isometric or progressive isotonic exercises. Isometric exercise and isotonic exercise have been compared in other tendinopathies but this was the first study to investigate isometric exercise in GTPS. The immediate and short-term effect of isometric exercise for pain relief has also been previously investigated but this was the first clinical trial to evaluate the effectiveness of isometric exercise beyond 4 weeks for any tendinopathy. Thirty patients with GTPS were recruited from an NHS population in Glasgow and randomised to an isometric exercise or isotonic exercise group. Both programmes were effective in reducing pain and improving function at 4 and 12-week follow-up but no difference was observed between groups. After 12 weeks, mean VISA-G scores improved by 10 points in both groups. However, over 35% of patients in both groups failed to improve. One of the limitations was the drop-out rate with seven participants not completing the study. The small sample size also limits the generalisability of the findings and in the absence of a 'no-treatment' control group, it is difficult to ascertain the true effectiveness of either programme as some participants may have improved with natural recovery. This chapter however provides further evidence that loading programmes are not always effective for GTPS with some individuals responding more favourably to exercise than others. Results of this chapter guided the development of the subsequent studies in this thesis, both the systematic review (Chapter 3) and the on-line survey (Chapter 4).

The second study, presented in Chapter 3, was a systematic review of randomised clinical trials. The aim of this chapter was to assess the effectiveness of isometric exercise in comparison with other treatment strategies, including isotonic exercise, or no treatment in the management of tendinopathy. Ten studies were identified, including participants with patellar (n=4), rotator cuff (n=2), lateral elbow (n=2), Achilles (n=1) and gluteal (n=1) tendinopathies. A number of clinical outcome measures were evaluated including pain (primary outcome), functional disability, range of movement, muscle strength, quality of life, satisfaction, structural integrity and cortical inhibition (secondary outcomes). The

most important finding of this study was that, similar to the findings of the study in Chapter 2, isometric exercise was not superior to isotonic exercise for tendinopathy either immediately following treatment or in the short term (≤ 12 weeks) for pain relief or any of the secondary outcome measures. Meta-analysis detected no significant difference between isometric exercise and isotonic exercise with regard to the immediate post intervention improvement in pain for patellar tendinopathy. Based on the findings of the pilot study specifically of GTPS (Chapter 2), and the interest generated by the 2015 study by Dr Ebonie Rio, I was intrigued to investigate the effectiveness of isometric exercise in comparison to isotonic exercise for all tendinopathies. In 2018 Lim and Wong conducted a systematic review which evaluated isometric exercise for patellar tendinopathy and concluded that isometric exercise programmes appeared effective for short-term pain relief in athletes during the competitive season. The systematic review in Chapter 3 was the first study to evaluate the effectiveness of isometric exercise in the management of all tendinopathies and included a recently published study not included in the review by Lim and Wong. The findings reported in this chapter were based on studies of either good or poor quality. The total number of participants over 10 clinical trials was 294, demonstrating that sample sizes for these studies were relatively small. In summary, the superiority of isometric exercise in providing immediate or short-term pain relief in tendinopathy was not supported by the results of this chapter.

The third study, presented in Chapter 4, was an on-line survey of 261 individuals with self-reported GTPS. The first aim was to compare clinical characteristics between i) younger individuals (< 40 years) and older individuals (≥ 40 years) and ii) sedentary individuals (< 150 minutes of physical activity per week) and active individuals (≥ 150 minutes of physical activity per week). A further aim was to identify whether any clinical characteristics were associated with, and also able to predict disability, kinesiophobia, anxiety or depression. This was the first study to divide individuals with GTPS into subgroups based on age group and physical activity level. The prevalence of clinical characteristics in younger and older individuals was found to be similar. However, sedentary individuals had a greater number of health co-morbidities and higher prevalence of psychological factors compared to active individuals. Regression analysis revealed that pain intensity during walking was strongly correlated with disability and the likelihood of exhibiting kinesiophobia. Results of the pilot study (chapter 2) and other GTPS exercise trials highlighted that 20-50% of individuals do not improve with current loading programmes. This inspired the design of this study, to investigate the prevalence of clinical

characteristics and possible associations with disability. Obesity and lower levels of physical activity are believed to affect treatment outcome for Achilles tendinopathy and psychological variables may contribute to poorer clinical outcomes in musculoskeletal pain. This raises the possibility that lifestyle and psychological factors (which are potentially modifiable) could affect the treatment outcome in GTPS. It is currently unclear whether the high prevalence of kinesiophobia, anxiety and depression identified in Chapter 4 influences long-term prognosis, clinical outcomes and effectiveness of loading programmes in GTPS. The research group led by Dr Karin Silbernagel have recently defined subgroups for Achilles tendinopathy (Hanlon et al. 2021). Subgrouping based on clinical characteristics opens up an exciting area for further research which may eventually lead to more targeted treatment approaches. The results presented in chapter 4 provide a basis for future work to evaluate the impact of addressing lifestyle and psychological factors in the management of GTPS. As with all surveys, there are limitations. All data were self-reported and the findings should be confirmed in a patient population with a clinical diagnosis of GTPS. Although associations were established, causality could not be determined due to the cross-sectional study design. The findings of this chapter highlight that GTPS is a heterogeneous musculoskeletal condition and provides further evidence that a biopsychosocial approach is required in the management of GTPS.

5.2 Recommendations for clinicians

Loading programmes are critically important in the management of GTPS and tendinopathy and are usually the first-line treatment in clinical practice. The findings of this thesis demonstrate that if the desired goal is pain relief, a rehabilitation programme does not always need to include isometric exercise. Instead, clinicians should design an individualised programme, which may consist of progressive isometric exercises and/or progressive isotonic exercises. Participants engaging in isometric exercise continue to experience improvements beyond 4 weeks, indicating that isometric exercise can also be used as part of a structured rehabilitation programme. Individuals with GTPS are a heterogeneous population with a high prevalence of kinesiophobia, anxiety and depression. Health co-morbidities, physical activity level and number of pain sites are also important considerations for clinicians. Loading programmes may not adequately address the low-levels of physical activity, psychological factors and obesity often observed in clinical practice.

Based on the findings of this thesis, the following recommendations can be made to clinicians:

- Isometric and isotonic exercise programmes can be effective in reducing pain and improving function and should be considered in the management of patients with GTPS.
- Isometric exercise is not superior to isotonic exercise for acute or short-term pain relief in tendinopathy.
- The immediate and short-term pain response to isometric exercise is variable both within and across tendinopathy populations.
- GTPS is a heterogenous musculoskeletal condition and a biopsychosocial approach to management is required.
- Psychological and lifestyle factors are prevalent in GTPS and should be considered during assessment.

5.3 Recommendations for researchers

Cross-sectional studies, including surveys, are a useful first step in describing the population characteristics of a complex condition such as GTPS. Furthermore, they can inform researchers as to what should be investigated in longitudinal studies. Chapter 4 identified that 30% of individuals with GTPS were less than 40 years old. This is a group often under-represented in clinical trials, and which requires to be further researched. As highlighted in this thesis, 20-50% of individuals with GTPS do not improve with current loading programmes and a sizeable number continue to experience chronic pain which significantly affects quality of life. Identifying further management strategies which improve clinical outcomes should therefore be a research priority. The prevalence of clinical characteristics identified in Chapter 4 also requires further investigation. Of particular importance is to identify which characteristics are likely to affect prognosis and treatment outcome. To optimise clinical outcome, it is currently unknown whether weight loss will be beneficial for individuals with obesity, whether increasing physical activity is required for sedentary individuals or whether psychological support is required for individuals with issues around mental health. Screening for such factors may be valuable, providing clinical information which can be incorporated into patient management strategies. In this thesis, individuals were divided into sub groups based on age group and physical activity level. It is likely that additional subgroups exist in GTPS and should be

explored further. Specific subgroups may not respond to current loading programmes, requiring a different management strategy to achieve a positive clinical outcome.

Based on the findings of this thesis, the following recommendations can be made to researchers:

- Gather epidemiological data on younger individuals with GTPS.
- Investigate the prevalence of clinical characteristics in a patient population with a clinical diagnosis of GTPS.
- Establish whether clinical characteristics can affect clinical outcome in GTPS.
- Identify subgroups of individuals with GTPS based on clinical characteristics.
- Evaluate how identified subgroups respond to targeted management strategies.

5.4 Conclusion

In summary, this thesis has provided evidence that isometric and isotonic exercise programmes can be effective in reducing pain and improving function in GTPS. However, no difference was observed between groups indicating that muscle contraction type may not affect the clinical outcome. Furthermore, this thesis has found no strong evidence that isometric exercise is superior for acute or short-term pain relief when compared with isotonic exercise, other treatments, or no treatment in tendinopathy. GTPS is a complex musculoskeletal condition and both lifestyle and psychological factors may contribute to the development and persistence of pain. A biopsychosocial rehabilitation approach is required in the management of this population to enhance clinical outcomes.

Chapter 6

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Appendices

West of Scotland REC 4

Attendance at Committee meeting on 2 June 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Miss Lynda Brown	Public Health Adviser	Yes	
Dr Grace Campbell	Lead Clinician, Prison Healthcare	No	
Dr Michael Fail	Consultant Geriatrician	Yes	
Dr Kay Greenshields	Account Manager for Scottish Enterprise	Yes	
Dr Ken James	Consultant Anaesthetist	Yes	
Mrs Janet Johnstone	Research Nurse	Yes	
Mrs Laura Kenicer	Prescribing Support Pharmacist	Yes	
Dr Agata Kochman	Consultant Pathologist	No	
Dr Karen Lang	Clinical Project Manager	Yes	
Dr Rachael MacIsaac	Stroke Trials Statistician	Yes	
Miss Fiona Mackelvie	Retired Administrator	No	
Dr Brian Neilly	Consultant Physician	Yes	
Ms Aileen Scullion	Retired Head Teacher	Yes	
Dr Subra Viswanathan	Consultant GI Radiologist	Yes	
Mr John Woods	Retired Project Co-ordinator	Yes	
Mr Iain Wright	Retired - Technical Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Sophie Bagnall	Assistant Coordinator
Dr Judith Godden	Scientific Adviser
Ms Rozanne Suarez	REC Manager

Appendix 2 Participant invitation letter

Participant Invitation Letter

Date: xx/xx/20xx

Dear xxxxxx

Research Study Title:
Comparing the effectiveness of two exercise programmes for pain at the side of the hip

Full Study Title:
Isometric versus Isotonic exercise for greater trochanteric pain syndrome – a pilot randomised controlled trial comparing two rehabilitation programmes

You have recently been referred to physiotherapy and are currently on the waiting list for the pain you are experiencing at the side of your hip. We are writing to let you know about a research study that is taking place within NHS Greater Glasgow and Clyde in association with the University of Glasgow.

We are conducting a study comparing two physiotherapy exercise programmes for people with lateral hip pain (pain at the side of the hip). As you are awaiting physiotherapy for your hip pain you might be interested in taking part in the study.

An information sheet about the study is included. If you wish to participate in the study or wish to discuss the study further, please contact Chris Clifford, the chief investigator directly by either telephone or email. If you do not wish to take part in the study, your referral will remain on the waiting list and you will be contacted as per usual arrangements.

Thank you.

Yours sincerely

Mr. Chris Clifford

Chief Investigator

Senior Musculoskeletal Physiotherapist

West Glasgow Ambulatory Care Hospital (Previously Yorkhill Children's Hospital)

Dalnair Street

Glasgow, G3 8SJ

Email: chris.clifford@ggc.scot.nhs.uk

Tel: 0141 201 0270

Appendix 3 Participant information sheet

Participant Information Sheet

Research Study Title:
Comparing the effectiveness of two exercise programmes for pain at the side of the hip

Full Study Title:
Isometric versus Isotonic exercise for greater trochanteric pain syndrome – a pilot randomised controlled trial comparing two rehabilitation programmes

We would like to invite you to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

The purpose of the study is to help determine which physiotherapy exercise programme is best for patients with greater trochanteric pain syndrome (GTPS), a common condition which causes pain at the side of the hip. It is being conducted as part of a PhD for the chief investigator at the University of Glasgow.

Exercise has been shown to be effective for treating this condition, however it is not known which type is better. In order to find this out we are undertaking a clinical trial involving 30 participants with GTPS. We will compare two exercise programmes. The results will help us to find out which of the two programmes is best for this condition.

Why have I been chosen?

You have been chosen because you are waiting for treatment for pain at the side of your hip which may be due to injury of the gluteal tendons and muscles. The gluteal tendons and muscles are a group of muscles located in the region of the buttocks.

Do I have to take part?

No, it is up to you to decide whether or not to take part. Participation in the study is voluntary. You can choose to withdraw your consent and drop out of the study at any time and this will not affect your medical care. If you decide to take part in the study, we will ask you to sign a written consent form.

What would taking part involve?

Before entering the study, you will have a telephone conversation with the chief investigator to assess if you are eligible to participate in the trial. If you are eligible we will invite you to attend for a 60-minute assessment with a specialist physiotherapist. They will ask you some questions about your symptoms and general health and carry out a physical examination of your hip and lower back.

You may need an X-ray of your hip to determine whether your pain is due to other causes such as osteoarthritis, 'wear and tear', of the hip joint. If you agree to enter the study you will be randomly allocated to either the isometric exercise group (Group A) or the isotonic exercise group (Group B). Isometric exercise is when the muscle length and position of the leg do not change with the leg being held in static position for a set amount of time. Isotonic exercise is when the muscle length and position of the leg do change, with the muscle both shortening and lengthening during movement. Everyone who agrees to take part in this study will receive a specific treatment for their condition. You will initially be asked to complete questionnaires about your pain and the impact it has on your quality of life.

What does each exercise programme involve?

We will ask participants in both groups to attend for an individual 60-minute appointment with the chief investigator. You will be given a booklet which contains the exercises and an exercise diary which you will be asked to complete. The exercise programme will take no longer than 10 minutes and you should do these every day for 12 weeks. Both exercise programmes specifically target the gluteal muscles and tendons. There will be the opportunity to practice your exercises under the supervision of the chief investigator and to ask any relevant questions.

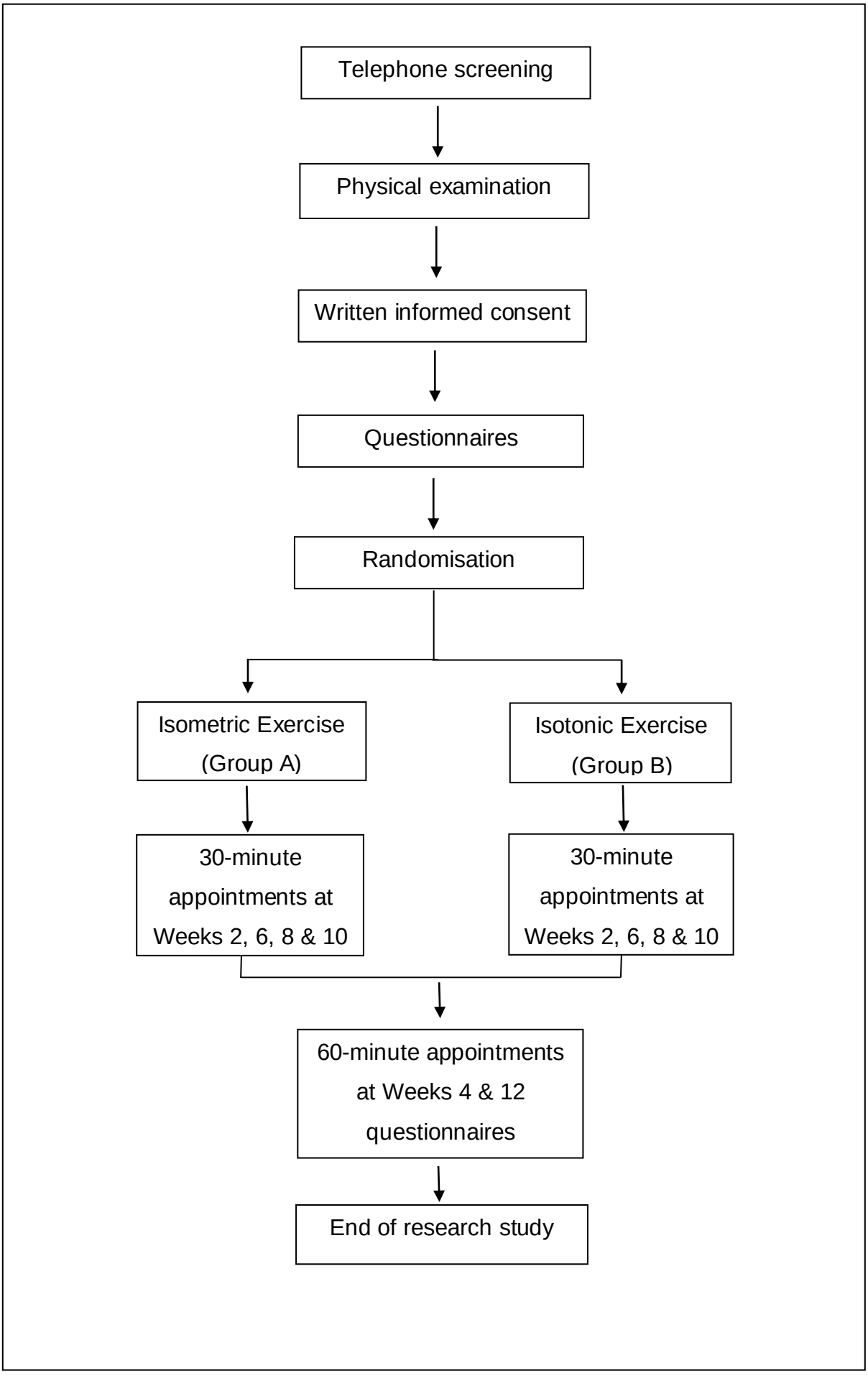
We would like you to attend for further appointments at Weeks 1, 2, 4, 6, 8, 10 and 12 so that we can review your progress and modify your exercise programme if appropriate. These appointments will last 30 minutes aside from those at Week 4 and Week 12 which will last 60 minutes as we will ask you to complete some questionnaires. All appointments will take place within the Physiotherapy Department at West Glasgow Ambulatory Care Hospital (Previously Yorkhill Children's Hospital).

What is randomisation?

The treatment you receive will be chosen by a process called randomisation. To allow us to make a fair comparison we will randomly allocate you to one of two groups. This is like making a choice by tossing a coin meaning that you have an equal chance of being allocated to either the isometric exercise group (Group A) or the isotonic exercise group (Group B). Neither you nor the chief investigator will decide on which exercise programme you will be allocated.

How long will the study last?

The study will last 12 weeks. The flow chart explains briefly what occurs if you agree to participate in the study.


Telephone screening
Physical examination
Written informed consent
Questionnaires
Randomisation
Isometric Exercise (Group A)
Isotonic Exercise (Group B)
30-minute appointments at Weeks 2, 6, 8 & 10
30-minute appointments at Weeks 2, 6, 8 & 10
60-minute appointments at Weeks 4 & 12 questionnaires
End of research study

Will my taking part in this study be kept confidential?

Yes, all information which we collect about you during the study will be kept strictly confidential. We will give each participant in the study a unique identification number to make sure you cannot be identified. Only health professionals involved directly in the study and those organising it will have access to medical records and research data. This may include representatives of the study sponsor, NHS Greater Glasgow and Clyde who may audit the study and need access to the research data.

Following completion, research data from the study may be presented at a conference or published in a scientific journal but no findings that could identify you will be made public. Research data may also be used to support other research and may be shared anonymously with other researchers. It is important that your GP is aware that you have agreed to take part in this study and we will inform them of your participation. If you agree to your GP being informed please tick the relevant box on the consent form.

What are the possible benefits of taking part in the study?

By conducting this research, we will learn more about the best possible exercise programme for this condition. We expect there to be a reduction in your hip pain regardless of which programme you are allocated to.

What are the possible risks of taking part in the study?

There are unlikely to be any serious risks but you may experience muscle soreness initially after completing the exercise programme.

What happens at the end of the study?

At the end of the research study the results may be published in a scientific journal to tell other doctors and physiotherapists in the United Kingdom about the most effective treatment for patients with GTPS. All participants will receive a summary of the results.

Who has reviewed the study?

This study protocol has been peer reviewed within the research supervisory team, the Research + Development Department and the West of Scotland Research Ethics Service.

Contacts for further information

Mr. Chris Clifford
Chief Investigator
Senior Musculoskeletal Physiotherapist
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow, G3 8SJ
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Professor Lorna Paul
Institute for Applied Health Sciences
Glasgow Caledonian University
70 Cowcaddens Road
Glasgow
Email: Lorna.Paul@gcu.ac.uk
Tel: 0141 331 8108

Thank you for taking the time to read this information leaflet.

Appendix 4 Telephone screening form

Telephone Screening Questionnaire

Name: **CHI:** **Date:**

Q1. Do you have any pain at the side of your hip? How long has it been present?

.....

Q2. Do you have any low back pain?

.....

Q3. Do you have any groin pain?

.....

Q4. Have you had any recent x-rays of your hip, pelvis or lower back? When?

.....

Q5. Have you had any steroid injections into the side of your hip? When?

.....

Q6. Have you had physiotherapy for the pain at the side of your hip? When did it finish?

.....

Q7. Have you been previously diagnosed with inflammatory arthritis such as rheumatoid arthritis?

……

Q8. Are you diabetic? If yes, is it currently well-controlled?

.....

Q9. Have you been diagnosed with any other medical conditions?

.....

Q10. Have you had any previous low back or hip surgery in past 12 months?

……

Q11. Are you pregnant or could you be pregnant?

.....

Q12. Are you involved in any other research studies at present?

……

Please bring reading glasses along to your first physiotherapy appointment. Please also bring loose trousers or shorts for the examination.

Appendix 5 Participant assessment form

Participant Assessment Form Date:

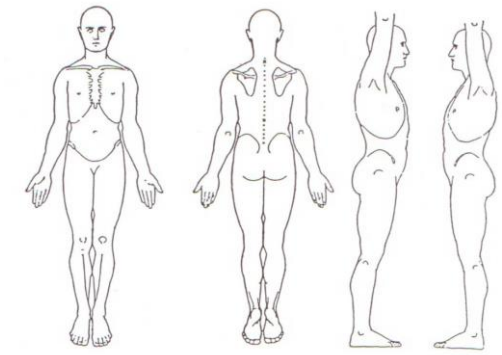
Participant ID number:

Age: …….

Gender: …….

Height: ……. Weight: …….

BMI: ……



Red Flags

	Yes	No
History of cancer	☐	☐
Recent unexplained weight loss	☐	☐
Bladder symptoms	☐	☐
Bowel symptoms	☐	☐
Recent infections/illnesses	☐	☐

Additional information: ……
……...
……

General Health

	Yes	No
Diabetes	☐	☐
Cardiovascular	☐	☐
Neurological	☐	☐
Epilepsy	☐	☐
Menopausal/post-menopausal	☐	☐
Previous corticosteroid injections for GTPS	☐	☐

Additional information: ……
……...

Current Medication

Analgesia: ……..……
Statins: ……..…….
HRT: ……..……
Other Medication: ……....

Symptom History

Duration of symptoms: …….

Constant or Intermittent? ……. NRS/10? …….

Groin pain? ……. If yes, NRS/10? …….

Low back pain? ……. If yes, NRS/10? …….

Current sports/hobbies: …….……..

Frequency p/week: ……

Relevant Investigations (Hip or Lumbar spine): ……

Aggravating Factors:

	Yes	No
Pain lying on affected side	☐	☐
Going up stairs	☐	☐
Standing on affected leg	☐	☐
Sitting	☐	☐
Cross-legged sitting	☐	☐
Sit to stand	☐	☐
Putting socks and shoes on	☐	☐
Walking	☐	☐
Running	☐	☐

24hr: EMS? …….. How long? …… Night pain? ……

Clinical Examination

	Positive	Negative
FADIR	☐	☐
<u>Pain provocation tests</u>		
Direct palpation	☐	☐
FABER	☐	☐
FADER	☐	☐
FADER + derotational test	☐	☐
Single leg stand	☐	☐
Resisted abduction at EOR adduction	☐	☐

Able to actively abduct hip in side lying? .....
Resisted hip abduction in side-lying?.....
Lumbar spine: Flexion, Extension, Side-flexion
…….....

Appendix 6 Participant consent form

CONSENT FORM

Study Number: xxx
Participant ID Number: xxxx

Research Study Title:
Comparing the effectiveness of two exercise programmes for pain at the side of the hip

Full Study Title:

Isometric versus Isotonic exercise for greater trochanteric pain syndrome – a pilot randomised controlled trial comparing two rehabilitation programmes

Name of chief investigator: Mr. Chris Clifford **please initial box**

I confirm that I have read and understood the participant information sheet dated 19th June 2017 (Version 2) for the above study. I have had the opportunity to consider the information, ask questions and have these answered to my satisfaction. ☐

I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving any reason and without my medical care or legal rights being affected. ☐

I understand that information collected about me may be used to support other research in the future and may be shared anonymously with other researchers. ☐

I agree that research data provided by me or with my permission during the project may be presented at conferences and published in journals on the condition that neither my name nor any other identifying information is used. ☐

I agree to my General Practitioner being informed of my participation in the study. ☐

I agree to take part in the above study. ☐

Name of Participant:	Signature:	Date:
Name of Person Taking Consent:	Signature:	Date:

Appendix 7 Letter to G.P.

Letter to GP – patient included in trial

Date: xx/xx/20xx

Dear Dr.

Re: Participant name (CHI:)

Research Study Title:
Isometric versus Isotonic exercise for greater trochanteric pain syndrome – a pilot randomised controlled trial comparing two rehabilitation programmes

Your patient is currently on the MSK physiotherapy waiting list and has recently agreed to participate in the above study. This will take place at West Glasgow Ambulatory Care Hospital in conjunction with the NHS Greater Glasgow & Clyde Musculoskeletal Physiotherapy Service, Department of Orthopaedics and the University of Glasgow.

The study will compare two different 12-week exercise programmes for patients with lateral hip pain and a clinical diagnosis of greater trochanteric pain syndrome. Participants are being randomised to either complete an isometric exercise programme (Group A) or an isotonic exercise programme (Group B). Your patient has been randomised to Group A.

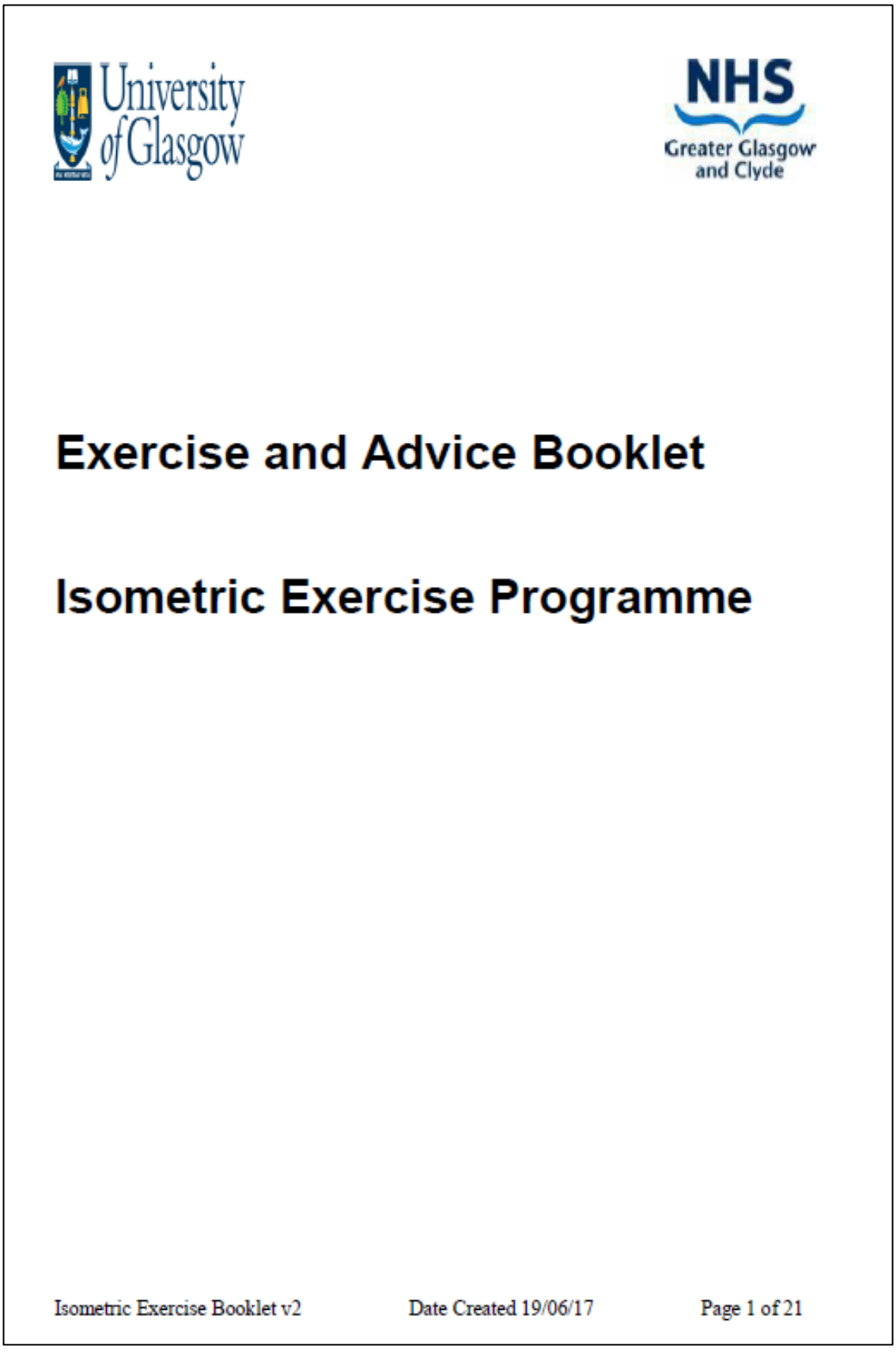
The trial will last 3 months and the final outcome measures will be taken at this time. Details of the study are outlined in the enclosed participant information leaflet.

If you have any concerns about your patient participating in this trial or require any further information about the study then please do not hesitate to contact me.

Yours sincerely

Chris Clifford
Chief Investigator
Senior Musculoskeletal Physiotherapist
Physiotherapy Department
West Glasgow Ambulatory Care Hospital, G3 8SJ
Tel: 0141 201 0270
Email: chris.clifford@ggc.scot.nhs.uk

Appendix 8 Isometric exercise programme



This booklet contains:

- Information about common postures
- The exercises that you should do each day
- An exercise diary

Background Information

The gluteal muscles are a group of muscles located in the region of the buttocks. They attach via a tendon to the bony prominence at the side of the hip. The bony prominence is called the greater trochanter.

The gluteus medius and gluteus minimus tendons are the most commonly injured tendons at the side of the hip. Compression of the gluteal tendons against the greater trochanter can occur during movements of the hip and also during certain postures and positions. This is mainly when the leg crosses the mid-line of the body.

This booklet gives advice and information on how to reduce compression of the gluteal tendons during daily activities and common postures. This is a key component of the exercise programme.

The aims of the exercise programme are to reduce pain and progressively strengthen the gluteal muscles and tendons. Initially you may need to reduce or completely stop some of your normal sports and activities, especially if your symptoms increase significantly afterwards. You can discuss this with a member of the research team.

Common Postures

Lying

When lying down or sleeping, do not lie on the affected side. If lying on the opposite side, use pillows between your knees to keep leg in parallel position. You can also lie on your back with a pillow under your knees.

Sitting

Do not cross your legs or sit with your knees together and feet apart. It may help to sit with your hips higher than your knees, you may need to use a pillow or cushion to do this or raise your chair.

Standing

Do not stand 'hanging on hip' with all your weight on one leg or stand with your legs crossed. Stand upright with weight evenly shared between both legs and feet shoulder width apart.

Rising from a chair

Keep knees apart. Do not allow knees to roll in across body, squeeze buttocks as you stand to help prevent this. Lean forward, bending at your hips and knees while keeping back straight.

Going up stairs

If going up stairs is painful, use a hand rail on the opposite side from your affected leg. Keep feet a little wider.

Stretching

Avoid stretching your leg across your body or stretching your leg by pushing your knee down while the foot is placed on the opposite knee.

Exercises

1. Isometric Side-Lying Hip Abduction

During isometric exercise the muscle length and position of the leg do not change. The leg is held in a static position for a set amount of time.

Starting position

Lie on your non-affected side. Bend the lower knee. Put 1 or 2 pillows between your knees so that your affected leg doesn't cross the mid-line of your body (Picture 1).

Picture 1

Exercise

Lift the affected leg up towards the ceiling away from the body by about 10 inches (Picture 2). This movement is called hip abduction. Do not allow this knee to bend.

Picture 2

Hold for 30 seconds then lower. Rest for 60 seconds between each repetition. You should feel the gluteal muscles at the side of your hip working.

How often?

Repeat 6 times.

Complete once a day

Progress to using a resistance band around both ankles when advised by your physiotherapist.

2. Isometric Standing Hip Abduction

Starting position

Stand on affected leg with opposite hand supported (Picture 1).

Exercise

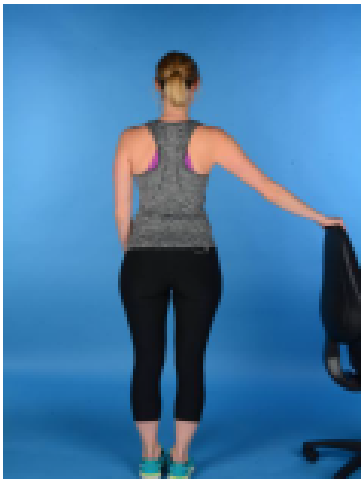
Take non-affected leg out to the side to the count of 3 seconds while keeping straight back (Picture 2). Make sure your pelvis doesn't drop on standing leg. Bring your leg back to starting position for the count of 3 seconds. Do not allow your foot to touch the floor.

How often?

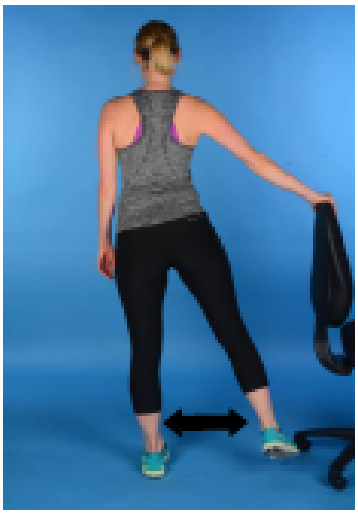
Aim to complete 3 sets of 10 repetitions. Rest for 60 seconds between sets.

Complete once a day

Progress to using a resistance band around both ankles when advised by your physiotherapist.



Picture 1



Picture 2

Pain Monitoring Model

Numerical Pain Rating Scale (NPRS)

1. The pain is allowed to reach 5 on the NPRS during the activity.
2. The pain after completion of the activity is allowed to reach 5 on the NPRS.
3. The pain the morning after the activity should not exceed a 5 on the NPRS.
4. Pain and stiffness is not allowed to increase from week to week.

Adapted from Silbernagel 2007

You can use this pain scale can be used to monitor your pain during your exercise programme. It ranges from 0 (no pain) to 10 (worse pain imaginable). The pain is allowed to reach 5 during your exercise programme. If the pain you experience during your exercise programme is more than 5, you should reduce the number of repetitions.

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Exercise Diary

This should be completed every day for 12 weeks.

Week 1	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 2	Exercise 1 Number of repetitions completed (1-8)	Exercise 2 Number of repetitions completed (1-8)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 3	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 4	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 5	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 6	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 7	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 8	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

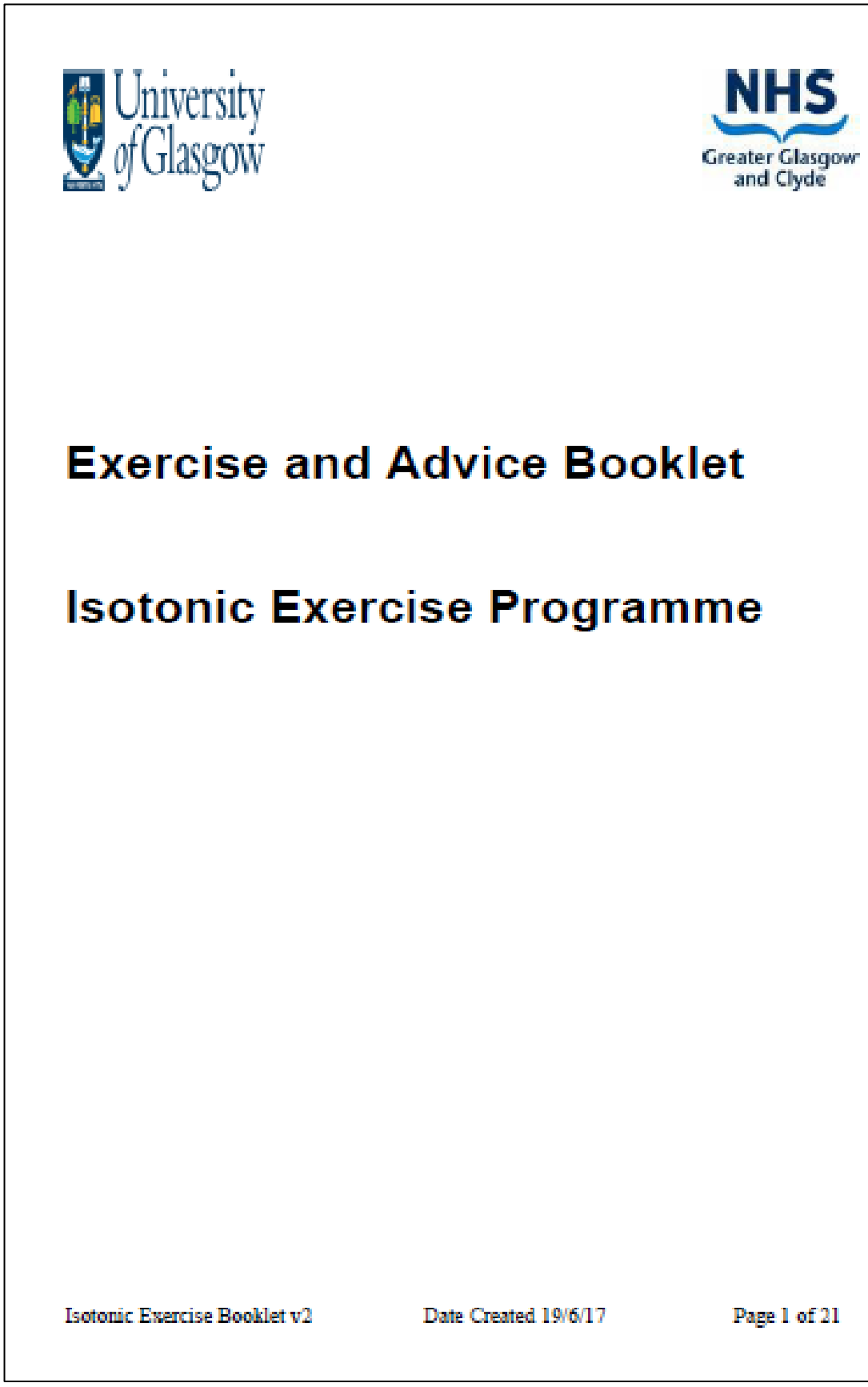
Week 9	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 10	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 11	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 12	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Appendix 9 Isotonic exercise programme



This booklet contains:

- Information about common postures
- The exercises that you should do each day
- An exercise diary

Background Information

The gluteal muscles are a group of muscles located in the region of the buttocks. They attach via a tendon to the bony prominence at the side of the hip. The bony prominence is called the greater trochanter.

The gluteus medius and gluteus minimus tendons are the most commonly injured tendons at the side of the hip. Compression of the gluteal tendons against the greater trochanter can occur during movements of the hip and also during certain postures and positions. This is mainly when the leg crosses the mid-line of the body.

This booklet gives advice and information on how to reduce compression of the gluteal tendons during daily activities and common postures. This is a key component of the exercise programme.

The aims of the exercise programme are to reduce pain and progressively strengthen the gluteal muscles and tendons. Initially you may need to reduce or completely stop some of your normal sports and activities, especially if your symptoms increase significantly afterwards. You can discuss this with a member of the research team.

Common Postures

Lying

When lying down or sleeping, do not lie on the affected side. If lying on the opposite side, use pillows between your knees to keep leg in parallel position. You can also lie on your back with a pillow under your knees.

Sitting

Do not cross your legs or sit with your knees together and feet apart. It may help to sit with your hips higher than your knees, you may need to use a pillow or cushion to do this or if you can, raise your chair.

Standing

Do not stand 'hanging on hip' with all your weight on one leg or stand with your legs crossed. Stand upright with weight evenly shared between both legs and feet shoulder width apart.

Rising from a chair

Keep knees apart. Do not allow knees to roll in across body, squeeze buttocks as you stand to help prevent this. Lean forward, bending at your hips and knees while keeping back straight.

Going up stairs

If going up stairs is painful, use a hand rail on the opposite side from your affected leg. Keep feet a little wider.

Stretching

Avoid stretching your leg across your body or stretching your leg by pushing your knee down while the foot is placed on the opposite knee.

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Exercises

1. Isotonic Side-Lying Hip Abduction

During isotonic exercise the muscle length and position of the leg change. The muscle will both shorten and lengthen during movement

Starting position

Lie on your non-affected side. Bend the lower knee. Put 1 or 2 pillows between your knees so that your affected leg doesn't cross the mid-line of your body (Picture 1).

Picture 1

Exercise

Lift the affected leg up slowly to the count of 3 seconds and then slowly lower to the count of 3 seconds (Picture 2). This movement is called hip abduction. Do not allow this knee to bend. Do not allow your pelvis to move backwards.

Picture 2

How often?

Try to complete 3 sets of 10 repetitions. Rest for 60 seconds between each set.

Complete once a day

Progress to using a resistance band around both ankles when advised by your physiotherapist.

2. Isotonic Standing Hip Abduction Slides

Starting position

Stand with feet slightly wider than shoulder width apart with hands supported on chair or table (Picture 1).

Exercise

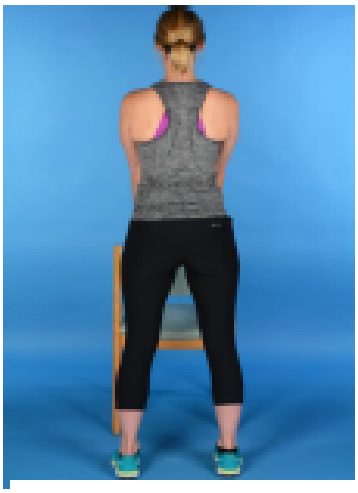
Keep your foot in contact with the floor and slide affected leg out to the side to the count of 3 seconds. You can allow the opposite knee to bend but keep your back straight (Picture 2). Slide leg back to starting position to the count of 3 seconds.

How often?

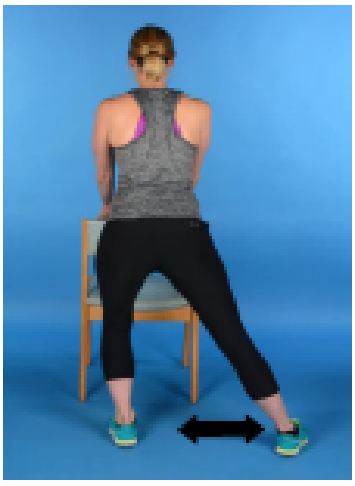
Try to complete 3 sets of 10 repetitions. Rest for 60 seconds between sets.

Complete once a day

Progress to using a resistance band around both ankles when advised by your physiotherapist.



Picture 1



Picture 2

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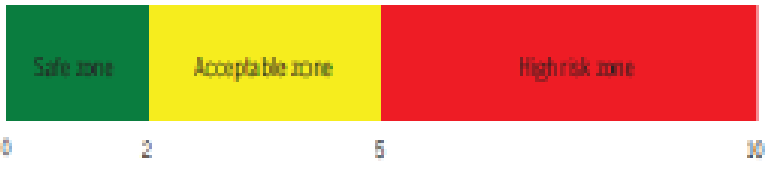
Pain Monitoring Model

Numerical Pain Rating Scale (NPRS)



No pain — Worst pain imagirable

1. The pain is allowed to reach 5 on the NPRS during the activity.
2. The pain after completion of the activity is allowed to reach 5 on the NPRS.
3. The pain the morning after the activity should not exceed a 5 on the NPRS.
4. Pain and stiffness is not allowed to increase from week to week.

Adapted from Silbernagel 2007

You can use this pain scale can be used to monitor your pain during your exercise programme. It ranges from 0 (no pain) to 10 (worse pain imaginable). The pain is allowed to reach 5 during your exercise programme. If the pain you experience during your exercise programme is more than 5, you should reduce the number of repetitions.

Exercise Diary

This should be completed every day for 12 weeks.

Week 1	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 2	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 3	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 4	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 5	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 6	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 7	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 8	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 9	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 10	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 11	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

Week 12	Exercise 1 Number of repetitions completed (1-6)	Exercise 2 Number of repetitions completed (1-6)	Maximum pain score during exercise programme (1-10)
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			

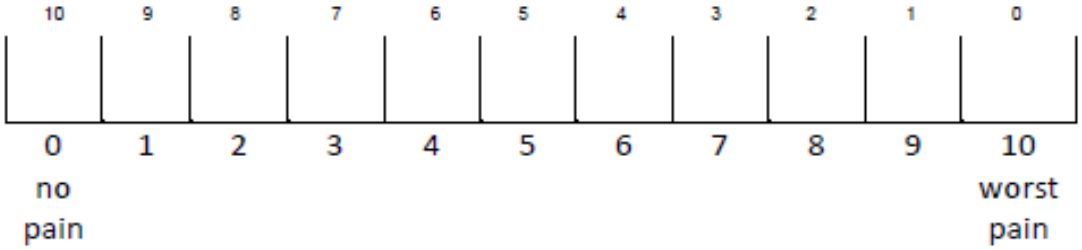
Appendix 10 VISA-G

VISA-G Questionnaire

Participant ID:

Please mark one box in each question. Choose the box that best suits you – it may not be perfect. All the questions relate to your HIP pain.

Question 1: My usual hip pain is...



Question 2: I can lie on my sore hip

10 ☐ For longer than 1 hour
7 ☐ For 30 minutes to 1 hour, then I have to move
5 ☐ For 15 to 30 minutes, then I have to move
2 ☐ For 5 to 15 minutes, then I have to move
0 ☐ I am unable to lie on my sore side at all

Question 3: Walking up or down one flight of stairs

10 ☐ I can use stairs normally with no hip pain
7 ☐ I can use stairs normally with some hip pain
5 ☐ I can use stairs normally holding onto a banister because of hip pain
2 ☐ I use stairs one step at a time and holding onto a banister because of hip pain
0 ☐ I cannot use stairs at all because of hip pain

Question 4: Walking up or down a ramp or slope

10 ☐ I can walk normally up and down a slope or ramp with no hip pain
7 ☐ I can walk normally up and down a slope or ramp with slight hip pain
5 ☐ I have some difficulty walking up and down a slope or ramp because of hip pain
2 ☐ I have significant difficulty negotiating slopes or ramps because of hip pain
0 ☐ I cannot walk up or down a slope or ramp because of hip pain

Question 5: After sitting for 30 minutes, moving to standing and then walking is...

10 ☐ Not a problem
7 ☐ Difficult for a few steps
5 ☐ I have to stand still for a moment or two before I walk
2 ☐ I have to stand still for less than 20 seconds before I walk
0 ☐ I have to stand still for more than 20 seconds before I walk

Question 6: Work about the house or garden (or similar activity)

10 ☐ I can work in my house and/or garden for an hour or more
7 ☐ Because of hip pain, I can work in my house and/or garden in 30 to 60 min bursts
5 ☐ Because of hip pain, I do very limited work in my house and garden
2 ☐ Because of hip pain, I do limited work in my house but I do not garden
0 ☐ Because of hip pain, I do not do any work in my house or garden

Question 7: Are you currently taking part in regular exercise, physical activity or sport?

10 ☐ Yes – I can exercise as I used to.
7 ☐ Somewhat less than I used to.
4 ☐ Significantly less than I used to.
0 ☐ No – I am unable to exercise, I don't want to or I don't have time.

Question 8 has *Three* sections. Please answer section A, B or C ONLY.
Does your current hip pain affect your ability to undertake weight bearing activities? (e.g. walking, shopping, running, squats, lunges).

Section A: My hip pain is so severe that it will stop me from walking, shopping, running or other weight bearing exercise.
If this is so, how much of this activity do you do each day?

0 ☐ I do not undertake any extra activity on my legs - I only move about the house.
2 ☐ I do less than 10 minutes.
5 ☐ I do 10 – 19 minutes.
7 ☐ I do 20 – 29 minutes.
10 ☐ I do more than 30 minutes.

Section B: My hip pain is present with exercise, but it does not stop me from walking, shopping, running or other weight bearing type exercise.
If this is so, how much of this activity do you do each day?

0 ☐ I do not undertake any extra activity on my legs - I only move about the house.
5 ☐ I do less than 10 minutes.
10 ☐ I do 10 – 19 minutes.
15 ☐ I do 20 – 29 minutes.
20 ☐ I do more than 30 minutes.

Section C: If you have no pain while you undertake walking, shopping, running or other weight bearing type exercise.
If this is so, how much of this activity do you do each day?

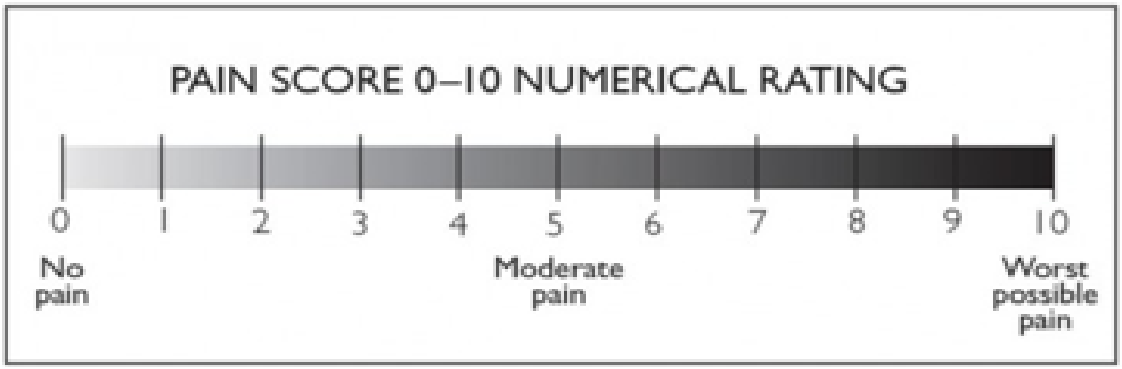
6 ☐ I do not undertake any extra activity on my legs - I only move about the house.
12 ☐ I do less than 10 minutes.
18 ☐ I do 10 – 19 minutes.
24 ☐ I do 20 – 29 minutes.
30 ☐ I do more than 30 minutes

TOTAL SCORE = /100

Appendix 11 Numeric Pain Rating Scale

Numeric Pain Rating Scale

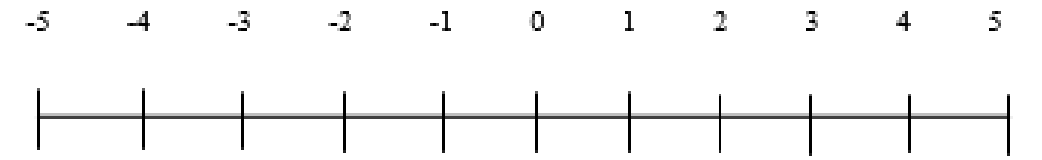
Q. With respect to your hip pain, what has been your average pain score in the past week? Please circle one number.



Appendix 12 Global Rating of Change Scale

Global Rating of ChangeScale

Q. With respect to your hip pain, how would you describe your condition now compared to the start of the research study? Please circle one number.



Very much worse

Unchanged

Completely Recovered

Appendix 13 Pain Catastrophising Scale

Pain Catastrophizing Scale

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feeling that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

Appendix 14 Hip Disability and Osteoarthritis Outcome Score

Hip dysfunction and Osteoarthritis Outcome Score (HOOS), English version LK 2.0

HOOS HIP SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your hip. This information will help us keep track of how you feel about your hip and how well you are able to do your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are uncertain about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your hip symptoms and difficulties during the last week.

S1. Do you feel grinding, hear clicking or any other type of noise from your hip?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Difficulties spreading legs wide apart

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S3. Difficulties to stride out when walking

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the last week in your hip. Stiffness is a sensation of restriction or slowness in the ease with which you move your hip joint.

S4. How severe is your hip joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S5. How severe is your hip stiffness after sitting, lying or resting later in the day?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often is your hip painful?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of hip pain have you experienced the last week during the following activities?

P2. Straightening your hip fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

What amount of hip pain have you experienced the last week during the following activities?

P3. Bending your hip fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Walking on a flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Walking on a hard surface (asphalt, concrete, etc.)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P10. Walking on an uneven surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your hip.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Hip dysfunction and Osteoarthritis Outcome Score (HOOS), English version LK 2.0

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your hip.

A5. Bending to the floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on a flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining hip position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the last week due to your hip.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Twisting/pivoting on loaded leg

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Walking on uneven surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your hip problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid activities potentially damaging to your hip?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your hip?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your hip?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

Appendix 15 EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

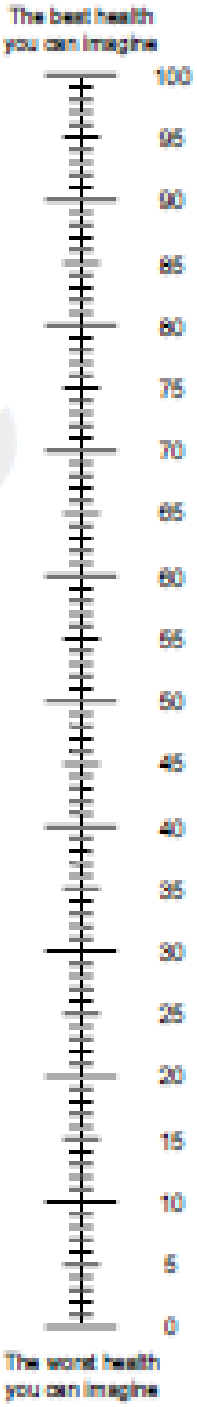
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Appendix 16 International Physical Activity Questionnaire Short Form

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Appendix 17 PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Chris Clifford, Dimitris Challoumas, Lorna Paul, Grant Syme, Neal Millar. Effectiveness of isometric exercise for pain relief in tendinopathy – a systematic review. PROSPERO 2019 CRD42019147179 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019147179

Review question

Is isometric exercise effective in reducing pain in patients with tendinopathy?

Searches

Trials published from database inception up to August 2019 will be included. The search strategy will include Ovid MEDLINE, Ovid EMBASE, CINAHL Plus and Cochrane Library

The search terms included 'Tendinopathy' OR 'Tendinitis' OR 'Tendinosis' OR 'Rotator cuff' OR 'Shoulder' OR 'Lateral Elbow' OR 'Tennis Elbow' OR 'Gluteal' Or 'Greater Trochanteric' OR Patellar' OR 'Achilles' AND 'Isometric' or 'Static'

Studies will only be included if published in English.

We will re-run the search prior to final analysis.

Types of study to be included

Randomised controlled trials will be included if an isometric loading programme was used to treat tendinopathy. Prospective cohort/observational studies, case reports/series, clinical observations and systematic reviews will be excluded.

Condition or domain being studied

Tendinopathy. Exercise in Tendinopathy

Participants/population

Inclusion: Adults (16 years and above) with a clinical diagnosis of tendinopathy with or without radiological signs,
Exclusion: Children (under 16 years), previous tendon rupture or surgery

Intervention(s), exposure(s)

Isometric exercise loading programmes.

Comparator(s)/control

Any other treatment non-pharmacological or pharmacological (e.g. other forms of exercise, shockwave therapy, analgesia or injections) or no treatments.

Context

Studies in both primary care and sports setting will be eligible as tendinopathy affects sporting/active and sedentary adults of all ages.

Main outcome(s)

Pain as measured by any valid and reliable patient reported outcome measure e.g Visual Analogue Scale or

Numeric Pain Rating Scale.

Change in pain score from baseline assessment to end of treatment will be analysed.

Measures of effect

In relation to length of follow-up we will measure immediate, short-term (up to 6 weeks), medium (6 weeks to 6 months) and long-term effects (> 6 months) of isometric exercise for pain relief in comparison to other treatments or no treatment in patients with tendinopathy.

Additional outcome(s)

Tenderness, function, range of motion (ROM), strength, quality of life (QoL), structural integrity and cortical inhibition are the secondary outcome measures

Measures of effect

In relation to length of follow-up we will measure immediate, short-term (up to 6 weeks), medium (6 weeks to 6 months) and long-term effects (> 6 months) of isometric exercise for pain relief in comparison to other treatments or no treatment in patients with tendinopathy.

Data extraction (selection and coding)

Two researchers will independently be involved in screening records for inclusion and extracting data for analysis. A third researcher will resolve any discrepancies. The main data that will be extracted will include: Study design, Tendon affected, Sample characteristics, symptom duration, intervention, treatment duration and follow-up, outcome measures, eligibility criteria and allocation concealment.
If relevant data is found to be missing we will contact the lead authors directly
Data will be recorded on an Excel Spreadsheet

Risk of bias (quality) assessment

Two researchers will assess risk of bias. A third researcher will resolve any discrepancies.

The Cochrane Risk of Bias Tool will be used to assess risk of bias

Strategy for data synthesis

Data will be aggregated and presented in tables. A systematic narrative synthesis will be provided to summarise and explain the characteristics and findings of the studies in line with the review question. Differences on the primary outcome measure (Pain) between isometric exercise and the comparator group will be defined as treatment effects. We will group outcomes in relation to length of follow-up, up to 6 weeks (short-term), 6 weeks to 6 months (medium term) and > 6 months (long-term). Studies will be graded on level of evidence, Level 1 (strong) to Level 4 (no evidence) based on the classification by Van Tulder.

Analysis of subgroups or subsets

Not applicable

Contact details for further information

Chris Clifford
c.clifford.1@research.gla.ac.uk

Organisational affiliation of the review

University of Glasgow

Review team members and their organisational affiliations

Mr Chris Clifford. University of Glasgow
Dr Dimitris Challoumas. University of Glasgow
Professor Lorna Paul. Glasgow Caledonian University
Dr Grant Syme. NHS Fife
Mr Neal Millar. University of Glasgow

Type and method of review
Intervention, Narrative synthesis, Systematic review

Anticipated or actual start date
01 August 2019

Anticipated completion date
31 December 2019

Funding sources/sponsors
None

Conflicts of interest
None known

Language
English

Country
Scotland

Stage of review
Review Completed published

Details of final report/publication(s) or preprints if available
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7406028/pdf/bmjsem-2020-000760.pdf

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Exercise; Humans; Pain; Pain Management; Tendinopathy

Date of registration in PROSPERO
10 October 2019

Date of first submission
13 September 2019

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note
We decided to include a number of secondary outcome measures, tenderness, function, range of motion (ROM), strength, quality of life (QoL), structural integrity and cortical inhibition

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.
The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

10 October 2019
12 November 2019
10 June 2021

Appendix 18 Advert for on-line survey

Do you have pain at the side of your hip?

- Is the side of your hip painful to touch?
- Is it painful when you lie on your side?
- Have you been diagnosed with Trochanteric bursitis, Gluteal tendinopathy or Greater Trochanteric Pain Syndrome (GTPS)?
- Does the pain at the side of your hip affect your daily activities and quality of life?

- If you have answered 'Yes' to any of these four questions then you may be eligible to participate in an on-line survey.
- We are conducting research to learn more about the experience of living with pain at the side of your hip.
- To participate you must be aged 18 years or over.

For further information please contact:
Chris Clifford (email: c.clifford.1@research.gla.ac.uk)

University of Glasgow

Appendix 19 Online survey

University of Glasgow

Lateral Hip Pain Survey

Page 1

Research Study Title

The experience of living with lateral hip pain – an on-line survey

Background to the study

Thank you for your interest in this on-line survey. Before deciding whether you wish to participate in this study, it is important for you to understand why the research is taking place and what it involves. Please spend some time reading the information.

My name is Chris Clifford, and I am a physiotherapist and PhD student at the University of Glasgow. Our research team are currently conducting research investigating lateral hip pain (pain at the side of the hip). Lateral hip pain is common and normally caused by injury to the gluteal muscles and tendons as they join the side of the hip. The gluteal muscles are a group of muscles located in the region of the buttocks. This condition was previously diagnosed as Trochanteric bursitis but is now called Gluteal tendinopathy or Greater Trochanteric Pain Syndrome (GTPS). It can affect people of all ages and is common in both active and less active individuals. The pain is often worse at night, especially while lying on the affected side. It may also be aggravated by sitting with your legs crossed, walking, running or stairs.

What is the purpose of the study?

This survey will allow us to gain a better understanding of how your hip pain affects your function, quality of life and daily activities. Recent research has found that factors such as stress, emotional wellbeing and a person's beliefs and feelings about their hip pain can also be important. We are also interested to see how lateral hip pain affects different age groups.

Why should I take part?

We would like to learn more about lateral hip pain and how it affects you. Your contribution to this study will help us understand more about this condition and may lead to improvements in how this it is treated.

Do I have to take part?

No, it is up to you to decide whether you wish to take part. You are free to withdraw at any time without giving a reason. If you do not complete the survey, your responses will not be included in the research findings. Once you have completed the survey, it will not be possible to either identify you or remove the data.

What would taking part involve?

If you agree to take part, you will be asked to complete a one-off, on-line survey. You will be asked for your consent to participate in the research study. All responses are anonymous. No information you provide will be used that could lead to you being identified personally. By completing and submitting the survey you agree that any information you provide can be used for research purposes only. Please answer all questions and do not leave any blank. It should take approximately 10-15 minutes to complete.

What are the possible benefits of taking part?

There will be no direct benefits to you for taking part. The findings of this study will be used to inform future research for individuals with this condition.

What are the possible risks of taking part?

There are no known or anticipated risks to you completing this survey.

Do I have to provide you with my name and email address?

You will not be asked to provide us with your name or contact details.

Who will have access to this data?

Only the chief investigator (Chris Clifford) and the direct research team will have access to this data.

What will happen to the results of this survey?

The information that you provide is confidential and will be used solely for the purpose of

this study. All digital questionnaires will be permanently deleted once the data is submitted to the University of Glasgow secure platform. Research data will be stored securely for 10 years and may be used to support other research in the future. If you would like a copy of the findings once the research is complete, please contact the research team (details below). The results will be written up as part of a PhD and are likely to be published in a peer reviewed scientific journal.

Who has reviewed the study?

This survey has been reviewed and ethical approval granted by the University of Glasgow Research Ethics Committee.

Research team contact details

For further information about this study, please contact the chief investigator:

Chris Clifford (email:c.clifford.1@research.gla.ac.uk). Alternatively you can contact one of the academic supervisors, Dr. Neal Millar (Neal.Millar@glasgow.ac.uk) or Professor Lorna Paul (Lorna.Paul@gcu.ac.uk).

Thank you for agreeing to complete this survey.

1. I consent to participate in this study * *Required*

- ○ Yes
- ○ No

Section 1 - Personal details

2. **Gender:**

- ○ Male
- ○ Female
- ○ Transperson
- ○ Prefer not to say

3. **Age:**

- ○ 18-29
- ○ 30-39
- ○ 40-49
- ○ 50-59
- ○ 60-69
- ○ 70-79
- ○ 80 or older

4. **Country of residence:**

5. **Employment status:**

- ○ Employed
- ○ Self-employed
- ○ Non-paid work
- ○ Off work due to hip pain
- ○ Unemployed (other health reasons)
- ○ Unemployed (other reasons)
- ○ Homemaker
- ○ Student
- ○ Retired
- ○ Carer
- ○ Other

5.a. If you selected Other, please specify:

Section 2 - General health and physical activity

6. **Do you have any of the following conditions? (tick all that apply)**

- [ ] Hypertension (high blood pressure)
- [ ] Raised cholesterol
- [ ] Asthma
- [ ] Chronic bronchitis or emphysema
- [ ] Diabetes
- [ ] Thyroid disorder
- [ ] Osteoarthritis
- [ ] Rheumatoid arthritis
- [ ] Back pain or sciatic pain
- [ ] Osteoporosis
- [ ] Tendonitis
- [ ] Reflux, heartburn or a peptic ulcer
- [ ] Intestinal problem (e.g. irritable bowel, Chrohns disease)
- [ ] Circulatory problem in legs
- [ ] Hearing problem (hard of hearing)
- [ ] Visual problem
- [ ] Cardiac illness (e.g. angina, heart attack, artery bypass, stents)
- [ ] Previous stroke
- [ ] Heart failure (diagnosis confirmed by doctor)
- [ ] Cancer in the past 5 years
- [ ] Depression or anxiety problems (diagnosed)
- [ ] None of the above

7. Do you consider yourself overweight?

- Yes
- No

8. What is your current hormonal status? (if male, tick not applicable)

- Pre menopause
- Menopausal
- Post menopause
- Unknown
- Not applicable

9. Do you regularly participate in sports or activity i.e. at least once per week?

- Yes
- No

9.a. What sports or activity do you participate in at least one per week?

10 - In the past week, on how many days have you been physically active for a total of 30 minutes or more? (Physical activity may include walking or cycling for recreation or to get to and from places, gardening, and exercise or sport which lasts for at least 10 minutes).

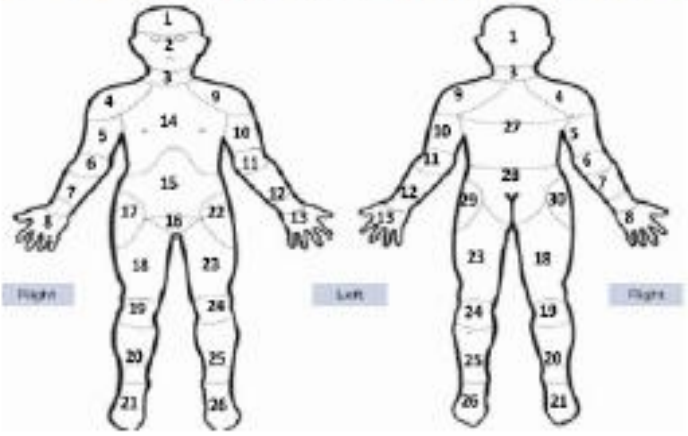
0
1
2
3
4
5
6
7

10.a. If four days or less, have you been physically active for at least two and a half hours (150 minutes) over the course of the past week?

- Yes
- No

Section 3 - Symptoms

11. **Please identify all areas where you currently have pain.**



- [ ] 1 - Head
- [ ] 2 - Face
- [ ] 3 - Neck
- [ ] 4 - Right shoulder
- [ ] 5 - Right upper arm
- [ ] 6 - Right elbow
- [ ] 7 - Right forearm
- [ ] 8 - Right hand/wrist
- [ ] 9 - Left shoulder
- [ ] 10 - Left upper arm
- [ ] 11 - Left elbow
- [ ] 12 - Left forearm
- [ ] 13 - Left hand/wrist
- [ ] 14 - Chest
- [ ] 15 - Abdomen
- [ ] 16 - Pelvis
- [ ] 17 - Right front of hip
- [ ] 18 - Right thigh
- [ ] 19 - Right knee
- [ ] 20 - Right lower leg
- [ ] 21 - Right foot/ankle
- [ ] 22 - Left front of hip
- [ ] 23 - Left thigh
- [ ] 24 - Left knee
- [ ] 25 - Left lower leg
- [ ] 26 - Left foot/ankle
- [ ] 27 - Thorax
- [ ] 28 - Lower back
- [ ] 29 - Left lateral hip
- [ ] 30 - Right lateral hip

12. Is this your first episode of pain at the side of the hip?

- [ ] Yes

12.a. If no, how many previous episodes have you had?

- [ ] 1
- [ ] 2
- [ ] 3
- [ ] 4
- [ ] 5 or greater

13. How long have you been experiencing pain at the side of the hip?

- less than 3 months
- 3 - 6 months
- more than 6 months, but less than 12 months
- 12 months or more

What is your usual hip pain, (where 0 is 'no pain' and 10 is 'pain as bad as it could be'), during each of these activities?

14. Lying on sore hip

14.a. Sitting with legs crossed

14.b. Walking

14.c. Going up stairs

14.d. Running

15 - How often is your sleep affected by hip pain?

Never
Once per week or less
Every 2 to 3 nights

Once a night
More than once a night

Section 4 - Function and activity

16 - My usual hip pain is, (where 0 is 'no pain' and 10 is 'pain as bad as it could be').

0
1
2
3
4
5
6
7
8
9
10

17. I can lie on my sore hip:

- For longer than 1 hour
- For 30 minutes to 1 hour, then I have to move
- For 15 to 30 minutes, then I have to move
- For 5 to 15 minutes, then I have to move
- I am unable to lie on my sore side at all

18. Walking up or down one flight of stairs:

- I can use stairs normally with no hip pain
- I can use stairs normally with some hip pain
- I can use stairs normally holding onto a bannister because of hip pain
- I use stairs one step at a time and holding onto a bannister because of hip pain
- I cannot use stairs because of hip pain

19. Walking up or down a ramp or slope:

- I can walk normally up and down a slope with no hip pain
- I can walk normally up and down a slope or ramp with slight hip pain
- I have some difficulty walking up and down a slope or ramp because of hip pain
- I have significant difficulty negotiating slopes or ramps because of hip pain
- I cannot walk up or down a slope or ramp because of hip pain

20. After sitting for 30 minutes, moving to standing and then walking is:

- Not a problem
- Difficult for a few steps
- I have to stand still for a moment or two before I walk
- I have to stand still for less than 20 seconds before I walk
- I have to stand still for more than 20 seconds before I walk

21. Work about the house or garden (or similar activity):

- Not a problem
- Difficult for a few steps
- I have to stand still for a moment or two before I walk
- I have to stand still for less than 20 seconds before I walk
- I have to stand still for more than 20 seconds before I walk

22. Are you currently taking part in regular exercise, physical activity or sport?

- Yes - I can exercise as I used to
- Somewhat less than I used to
- Significantly less than I used to
- No - I am unable to exercise, I don't want to or I don't have time

The next question has three sections. **Please only answer one Section**, either A, B **or** C. The remaining two sections should be left as 'Please select'

Does your current hip pain affect your ability to undertake weight bearing activities? (e.g. walking, shopping, running, squats, lunges)

23. **Section A**: My hip pain is so severe that it will stop me from walking, shopping, running or other weight bearing exercise. If this is so, how much of this activity do you do each day?

23.a. **Section B:** My hip pain is present with exercise, but it does not stop me from walking, shopping, running or other weight bearing type exercise If this is so, how much of this activity do you do each day?

23.b. **Section C:** If you have no hip pain while you undertake walking, shopping, running or other weight bearing type exercise If this is so, how much of this activity do you do each day?

Section 5 - Thoughts and beliefs about activity and exercise

24. I'm afraid I might injure myself if I exercise.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

25. If I were to try to overcome it, my pain would increase.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

26. My body is telling me that I have something dangerously wrong.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

27. My pain would probably be relieved if I were to exercise.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

28. People aren't taking my condition seriously enough.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

29. My injury has put my body at risk for the rest of my life.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

30. Pain always means I have injured my body.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

31. Just because something aggravates my pain does not mean it is dangerous.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

32. I am afraid that I might injure myself accidentally.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

33. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

34. I wouldn't have this much pain if there wasn't something potentially dangerous going on in my body.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

35. Although my condition is painful I would be better off if I were physically active.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

36. Pain lets me know when to stop exercising so that I do not injure myself.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

37. It's really not safe for a person with a condition like mine to be physically active.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

38. I can't do all the things normal people do because it's too easy for me to get injured.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

39. Even though something is causing me a lot of pain, I don't think it's actually dangerous.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

40. No one should have to exercise when he/she is in pain.

- Strongly disagree
- Disagree
- Agree
- Strongly agree

Section 6 - Emotional wellbeing

These questions are to help assess mental wellbeing. Tick the box that is closest to how you have been feeling in the past week:

41. I feel tense or 'wound up'

- ○ Most of the time
- ○ A lot of the time
- ○ From time to time, occasionally
- ○ Not at all

42. I still enjoy the things I used to enjoy

- ○ Definitely as much
- ○ Not quite as much
- ○ Only a little
- ○ Hardly at all

43. I get a sort of frightened feeling like something awful is about to happen

- ○ Very definitely and quite badly
- ○ Yes, but not too badly
- ○ A little, but it doesn't worry me
- ○ Not at all

44. I can laugh and see the funny side of things

- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

45. Worrying thoughts go through my mind

- A great deal of the time
- A lot of the time
- From time to time, but not too often
- Only occasionally

46. I feel cheerful

- Not at all
- Not often
- Sometimes
- Most of the time

47. I can sit at ease and feel relaxed

- Definitely
- Usually
- Not often
- Not at all

48. I feel as if I am slowed down

- Nearly all the time
- Very often
- Sometimes
- Not at all

49. I get a sort of frightened feeling like 'butterflies' in the stomach

- Not at all
- Occasionally
- Quite often
- Very often

50. I have lost interest in my appearance

- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

51. I feel restless as I have to be on the move

- Very much indeed
- Quite a lot
- Not very much
- Not at all

52. I look forward with enjoyment to things

- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

53. I get sudden feelings of panic

- Very often indeed
- Quite often
- Not very often
- Not at all

54. I can enjoy a good book or radio or TV programme

- Often
- Sometimes
- Not often
- Very seldom

Thank you for completing the survey.

Appendix 20 Ethical approval for on-line survey

University of Glasgow

10th December 2020

MVLS College Ethics Committee

Project Title: The experience of living with lateral hip pain ¿ an on-line survey

Project No: 200200037

Dear Dr Miller,

The College Ethics Committee has reviewed your application and has agreed that there is no objection on ethical grounds to the proposed study. It is happy therefore to approve the project.

- Project end date: As stated in application.
- The data should be held securely for a period of ten years after the completion of the research project, or for longer if specified by the research funder or sponsor, in accordance with the University's Code of Good Practice in Research: (http://www.gla.ac.uk/media/media_227599_en.pdf)
- The research should be carried out only on the sites, and/or with the groups defined in the application.
- Any proposed changes in the protocol should be submitted for reassessment, except when it is necessary to change the protocol to eliminate hazard to the subjects or where the change involves only the administrative aspects of the project. The Ethics Committee should be informed of any such changes.
- You should submit a short end of study report to the Ethics Committee within 3 months of completion.

Yours sincerely,

Jesse Dawson
MD, BSc (Hons), FRCP, FESO
Professor of Stroke Medicine
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Clinical Lead Scottish Stroke Research Network / NRS Stroke Research Champion
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